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: **Statistical Analysis Plan, 24 Aug 2021**

STATISTICAL ANALYSIS PLAN
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:	Vutrisiran (ALN-TTRSC02)
EudraCT Number:	2018-002098-23
IND Number:	139086
Protocol Version and Date:	Original: 11 October 2018
Analysis Plan Version and Date:	Original: 30 January 2019
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted] [redacted]

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without expressed written authorization of Alnylam Pharmaceuticals, Inc.

APPROVAL SIGNATURE PAGE

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)

Protocol:	ALN-TTRSC02-002
Analysis Plan Version and Date:	Original: 30 January 2019

This document has been authored by the following:

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

This document has been approved and signed electronically on the final page by the following:

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

AMENDMENT HISTORY

Amendment 1: Not applicable

Section	Description	Rationale

TABLE OF CONTENTS

APPROVAL SIGNATURE PAGE 2
AMENDMENT HISTORY 3
TABLE OF CONTENTS 4
LIST OF TABLES 7
LIST OF FIGURES 7
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 8
1. INTRODUCTION 11
1.1. Study Design 11
1.2. Study Objectives and Endpoints 13
1.3. Study Hypotheses 14
1.3.1. Multiple Comparisons Procedure 14
1.4. Sample Size Determination 15
2. PATIENT POPULATIONS 16
3. GENERAL CONSIDERATIONS 17
3.1. Computing Environment 17
3.2. General Methods 17
3.3. Baseline Definitions 17
3.4. Randomization Stratification Factors 18
3.5. Initiation of Local Standard Treatment for hATTR Amyloidosis 18
3.6. Missing Data with Efficacy Endpoints 18
3.6.1. Missing Subcomponents within Co-primary and Secondary Efficacy Endpoints 19
3.6.2. Summary of Missing Data 19
3.7. Visit Windows 19
3.8. Interim Analyses 19
4. STUDY ANALYSES 20
4.1. Patient Disposition 20
4.2. Protocol Deviations 20
4.3. Demographics and Baseline Characteristics 21
4.4. Efficacy Evaluation 22
4.4.1. General Efficacy Methods 22
4.4.1.1. ANCOVA/MI 22

4.4.1.2. MMRM 23
4.4.2. Primary Efficacy Evaluations 23
4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis 24
4.4.2.2. Sensitivity Analysis: Propensity Score 24
4.4.2.3. Other Analysis: Binary Endpoint 24
4.4.2.4. Overview of Co-primary Endpoint Analyses 24
4.4.3. Secondary Efficacy Evaluations 25
4.4.3.1. 10-meter Walk Test Speed, mBMI, and R-ODS 25
4.4.3.2. TTR Percent Reduction 25
4.4.3.3. Composite Endpoint of All-cause Deaths and/or All-cause Hospitalizations 25
4.4.3.4. Overview of Secondary Endpoint Analyses 26
4.4.4. Exploratory Efficacy Evaluations 26
4.4.5. Subgroup Analyses 27
4.4.6. Component/Domain Analyses 28
4.5. Pharmacodynamic Analyses 28
4.6. Pharmacokinetic Analyses 28
4.6.1. Study Variables 28
4.6.1.1. Concentration Data 28
4.6.1.2. Plasma Pharmacokinetic Parameters 28
4.6.2. Statistical Methods 29
4.7. Safety Analyses 29
4.7.1. Study Drug Exposure 29
4.7.2. Adverse Events 30
4.7.3. Laboratory Data 31
4.7.4. Vital Signs and Physical Examination 32
4.7.5. Electrocardiogram 32
4.7.6. Premedication 33
4.7.7. Prior and Concomitant Medications 33
4.7.8. Suicidality Questionnaire 33
4.8. Anti-Drug Antibody 34
5. CHANGES TO PLANNED ANALYSES 35
6. REFERENCES 36

7. APPENDICES 37
7.1. Questionnaire/Scoring 37
7.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS) 37
7.1.1.1. Modified Neuropathy Impairment Score (mNIS+7) 37
7.1.1.2. Neuropathy Impairment Score (NIS)...39
7.1.1.3. Algorithms for Setting Normal Deviates and Points 39
7.1.2. Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN).................................45
7.1.3. EuroQOL-5-Dimension 5-Level (EQ-5D-5L)..46
7.1.4. 10-Meter Walk Test (10-MWT)...46
7.1.5. Modified Body Mass Index (mBMI)...46
7.1.6. Rasch-Built Overall Disability Scale (R-ODS) 47

LIST OF TABLES

Table 1: Multiple Comparisons Procedure 14
Table 2: Postbaseline TTR Assessment Requirements by Treatment Group 16
Table 3: Analysis of Co-primary Endpoints mNIS+7 and Norfolk 25
Table 4: Analysis of Secondary Endpoints 26
Table 5: QTc Derivation 32
Table 6: All Percentiles Table 41
Table 7: Extended Percentiles Table 45
Table 8: 10-MWT Derivation Scenarios 46

LIST OF FIGURES

Figure 1: Study Design 12

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	**Definition**
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATTR	Amyloid transthyretin
BMI	Body mass index
CI	Confidence Interval
CMAP	Compound muscle action potential
C_{max}	Observed peak concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQoL 5-Dimensions 5-Levels
EQ-VAS	EuroQoL visual analogue scale
FAP	Familial amyloidotic polyneuropathy, also known as hATTR amyloidosis with polyneuropathy
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
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
LLN	Lower limit of normal
LS	Least-squares
LV	Left ventricle
mBMI	Modified body mass index

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
10-MWT	10-meter walk test
mNIS+7	Modified Neurologic Impairment Score +7
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
PD	Pharmacodynamics
PK	Pharmacokinetics
PND	Polyneuropathy Disability
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
QTcB	QT obtained using Bazett’s formula
QTcF	QT obtained using Fridericia's formula
RBC	Red blood cell
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
siRNA	Small interfering ribonucleic acid

Abbreviation	Definition
SMQ	Standardized MedDRA query
SNAP	Sensory nerve action potential
SOC	System organ class
t_{max}	Time of observed maximum concentration
TTR	Transthyretin
ULN	Upper limit of normal
V30M	Valine to methionine mutation at position 30
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan details comprehensive, technical specifications of the statistical analyses of the efficacy/safety data outlined and/or specified in the final protocol of Study ALN-TTRSC02-002. This document focuses on 18-month Treatment Period analyses; Treatment Extension Period descriptive analyses will be specified in an amendment to this document. Specifications of tables, figures, and data listings are documented separately.

1.1. Study Design

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

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 to vutrisiran treatment, and up to a 1-year Follow-up Period after the last dose of study drug as shown in Figure 1.

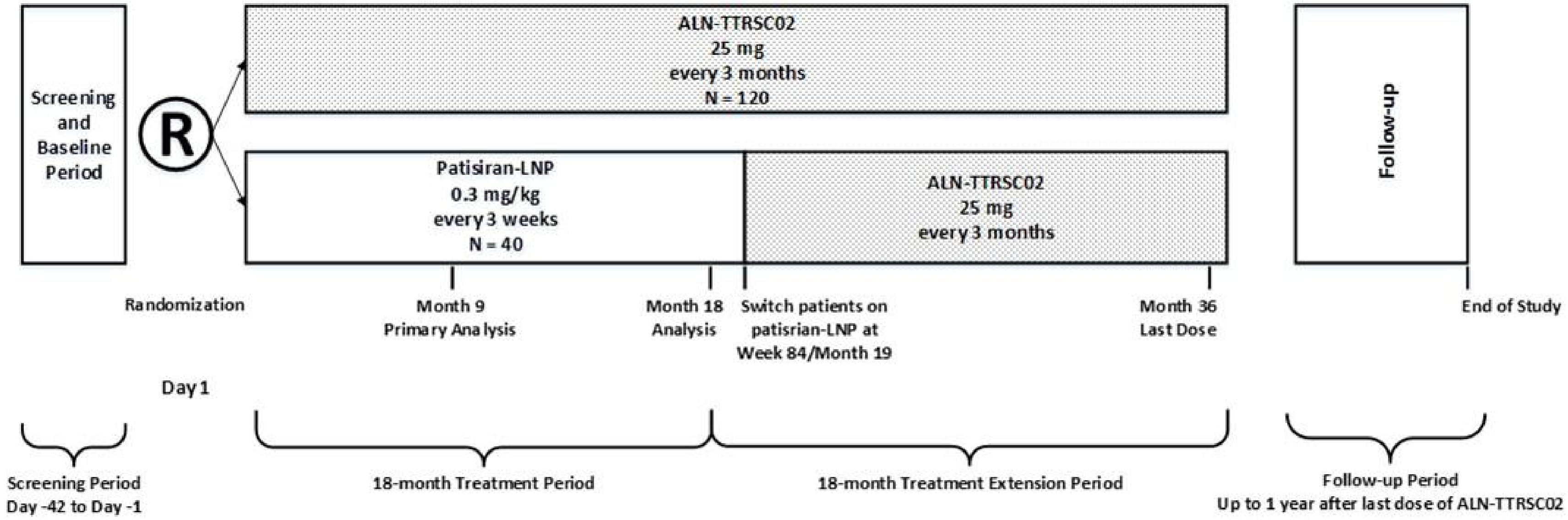
After the Screening period, and at the start of the Treatment Period, eligible patients will be randomized 3:1 on Day 1 to receive 25 mg of vutrisiran administered as a subcutaneous (SC) injection once every 3 months (q3M) or patisiran administered as an intravenous (IV) infusion once every 3 weeks (q3w). 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 group will switch to treatment with vutrisiran (first dose) and remain on vutrisiran 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 vutrisiran 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 will undergo a follow-up visit 30 days after the last dose of study drug.

The placebo group of the APOLLO (ALN-TTR02-004) 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.

Figure 1: Study Design


Screening and Baseline Period
R
ALN-TTRSC02
25 mg
every 3 months
N = 120
Patisiran-LNP
0.3 mg/kg
every 3 weeks
N = 40
ALN-TTRSC02
25 mg
every 3 months
Follow-up
Randomization
Month 9
Primary Analysis
Month 18
Analysis
Switch patients on patisrian-LNP at Week 84/Month 19
Month 36
Last Dose
End of Study
Day 1
Screening Period
Day -42 to Day -1
18-month Treatment Period
18-month Treatment Extension Period
Follow-up Period
Up to 1 year after last dose of ALN-TTRSC02

1.2. Study Objectives and Endpoints

The co-primary, and most secondary and exploratory efficacy endpoints are in comparison to the placebo group of the Phase 3 pivotal patisiran-LNP study (APOLLO study) as specified in the statistical analysis section of the ALN-TTRSC02-002 (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 vutrisiran 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 group of the APOLLO study • Change from baseline in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score compared to the placebo group of the APOLLO study
Secondary	
• To determine the efficacy of vutrisiran on gait speed, nutritional status, and disability • To characterize the effect of vutrisiran on serum TTR levels • To evaluate the effect of vutrisiran on patient mortality and hospitalization	• Change from baseline in the following parameters compared to the placebo group 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 vutrisiran group compared to the within-study patisiran group • Composite events of all-cause deaths and/or all-cause hospitalizations in the overall population (over 18 months) compared to the placebo group 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 group of the APOLLO study
Exploratory	
• To determine the effect of vutrisiran on: – 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 group 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)

Objectives	Endpoints
- To characterize the pharmacodynamic (PD) effect of vutrisiran and patisiran on vitamin A levels - To characterize plasma pharmacokinetics (PK) of vutrisiran and patisiran - To assess presence of antidrug antibodies (ADA) to vutrisiran and patisiran	– 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 vutrisiran and patisiran - Incidence and titers of ADA to vutrisiran and patisiran
Safety	
- To determine the safety and tolerability of vutrisiran in patients with hATTR amyloidosis	- Frequency of adverse events (AE)

1.3. Study Hypotheses

For most inferentially-evaluated efficacy endpoints, the null hypothesis for the comparison of vutrisiran vs placebo is defined as follows:

H_0: No difference between vutrisiran and placebo (APOLLO): difference (vutrisiran – placebo) = 0 or ratio (vutrisiran/placebo) = 1

For TTR percent reduction endpoints, the null hypothesis for the comparison of vutrisiran vs patisiran is defined as follows:

H_0: Vutrisiran is inferior to patisiran: difference in median TTR reduction (vutrisiran – patisiran) ≤ -10%

1.3.1. Multiple Comparisons Procedure

The overall familywise error rate will be controlled at α=0.05 for the co-primary and secondary endpoint hypothesis tests as follows:

Table 1: Multiple Comparisons Procedure

MCP Step[a]	Endpoint	Vutrisiran comparator	MCP Criteria
1	Modified Neurologic Impairment Score +7 (mNIS+7) change from baseline at Month 9	Placebo (APOLLO)	Intersection-union test (Both nominal P values ≤ α
	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score) change from baseline at Month 9	Placebo (APOLLO)	
2	10-MWT gait speed change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
3	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α

MCP Step[a]	Endpoint	Vutrisiran comparator	MCP Criteria
4	R-ODS change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
5	TTR percent reduction through Month 9	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%
6[b]	Incidence of composite events of all-cause deaths and/or all-cause hospitalizations over 18 months (overall population)	Placebo (APOLLO)	Nominal P value ≤ α
7[b]	Incidence of composite events of all-cause deaths and/or all-cause hospitalizations over 18 months (patients with cardiac involvement)	Placebo (APOLLO)	Nominal P value ≤ α

[a] Per serial gatekeeping MCP, if the MCP criteria are satisfied in a given step, all hypothesis tests in the given step are deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.
[b] Will be evaluated at the Month 18 analysis timepoint.
LCB=lower confidence bound; MCP=multiple comparisons procedure.

1.4. Sample Size Determination

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

The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of vutrisiran in this patient population. For the co-primary efficacy endpoints mNIS+7 and Norfolk QoL-DN total scores, the vutrisiran group in the Phase 3 study will be compared to the placebo group 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 group from the APOLLO study. Assuming a mean change of 0 points for the vutrisiran group, 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 group from the APOLLO study. Assuming a mean change of -4 points for the vutrisiran group, 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 vutrisiran 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 baseline NT-proBNP values greater than 3000 ng/L.

2. PATIENT POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data in this study, and for applicable analyses, relevant data from the APOLLO study.

- Modified Intent-to-Treat (mITT) population: All randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment to which they were randomized.
- Per-protocol (PP) Population: All mITT population patients with a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment between Months 6 (Week 24) and the analysis timepoint (Month 9 [Week 36] or Month 18 [Week 72]) that meets the requirements described in Table 2. Patients will be analyzed according to the treatment to which they were randomized.
- Cardiac Subpopulation: All mITT population patients who had preexisting evidence of cardiac amyloid involvement, defined as patients with baseline left ventricular (LV) wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history. Patients will be analyzed according to the treatment to which they were randomized.
- Safety population: All patients who received any amount of study drug. Patients will be analyzed according to the treatment received.
- Pharmacokinetic (PK) population: All randomized patients who received any amount of study drug and have at least 1 postdose blood sample for PK parameters and have evaluable PK data. Patients will be analyzed according to the treatment received.

Efficacy analyses (except TTR) and PD summaries will be conducted in the mITT population unless otherwise specified. The noninferiority of TTR will be assessed using the PP population applicable to the analysis timepoint. Safety analyses will be conducted in the Safety population. PK analyses will be conducted in the PK population.

Table 2: Postbaseline TTR Assessment Requirements by Treatment Group

Treatment Group	Postbaseline TTR Assessment Requirements
Vutrisiran or Patisiran	• Assessment must be before administration of study drug at the current visit • Assessment after initiation of local standard treatment for hATTR amyloidosis excluded (Section 3.5)
Vutrisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 12 weeks before the TTR assessment • Patient must receive planned, complete administration of study drug at 2 consecutive planned treatment visits at any time before the TTR assessment visit to ensure steady state
Patisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 3 weeks before the TTR assessment

3. GENERAL CONSIDERATIONS

3.1. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software version 9.3 (or later), unless otherwise noted. Figures may be generated using R version 3.4 (or later).

3.2. General Methods

All data listings that contain an evaluation date will contain a study day relative to the day of the first dose of study drug, which is designated as Day 1. On-treatment study days will be calculated as evaluation date – first dose date +1 and pretreatment days will be calculated as evaluation date – first dose date. There is no Day 0.

Categorical descriptives will include the count and percentage of patients (or events, if applicable) within each category (with a category for missing data) of the parameter. Continuous descriptives will include the number of patients, mean, median, standard deviation (SD), standard error (SE), minimum, and maximum values.

Laboratory data (including vitamin A) collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

For assessments that are repeated multiple times for the study visit, the average will be calculated unless otherwise noted.

All summaries will be presented by treatment group. Unless otherwise specified, treatment groups in the treatment period will be presented using the following labels:

- Placebo (APOLLO)
- Vutrisiran (HELIOS-A)
- Patisiran (HELIOS-A)
- Patisiran (HELIOS-A + APOLLO)
    - for TTR sensitivity analyses only
- Total (HELIOS-A)
    - patient disposition, protocol deviations, and baseline summaries only

3.3. Baseline Definitions

For the mNIS+7/NIS individual components, total scores and related endpoints, the 2 baseline assessments are performed on separate days. Baseline will be calculated as the mean of the nonmissing replicate measures.

For 10-MWT, 2 baseline assessments are performed on separate days. Baseline will be calculated as described in Section 7.1.4.

For PD parameters (TTR, Vitamin A), baseline will be defined as the average of all records, including those from any unscheduled visits, before the date and time of first dose.

For all other parameters, unless noted otherwise, baseline will be defined as the last nonmissing measurement on or before the first dose date.

3.4. Randomization Stratification Factors

Stratification factors for randomization include TTR genotype (V30M vs. non-V30M) and baseline NIS score (< 50 vs. ≥ 50).

Stratification factors are recorded in both the Interactive Response System (IRS) and the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database. In the presence of stratification errors, the stratification used in analysis may not match that in the IRS.

3.5. Initiation of Local Standard Treatment for hATTR Amyloidosis

In the APOLLO study, there were placebo patients who discontinued study drug, but remained on study and received local standard treatment. For the primary analysis of mNIS+7 and Norfolk QoL-DN, assessments were censored (excluded from analysis) after initiation of any of the following:

- Orthotopic liver transplant
- Use of TTR stabilizing agents (eg, tafamidis, diflunisal) for >14 days

For consistency of data handling, the placebo group from the APOLLO study will follow the same censoring rule as the APOLLO study.

For this study, APOLLO censoring rules will be applied. Additionally, assessments will be censored after initiation of any of the following recently approved treatments:

- Any use of TTR-targeting anti-sense oligonucleotides (eg, inotersen)
- Any use for patisiran (applicable for the vutrisiran treatment group only)

This data will be included and flagged in efficacy listings. These assessments from either study will be included in sensitivity analyses as specified.

For TTR percent reduction, TTR assessments collected after initiation of local standard treatment for hATTR amyloidosis will be excluded from the analysis. For all other efficacy endpoints, data from either study collected after initiation of local standard treatment for hATTR amyloidosis will be included in analyses.

A separate listing will be provided for patients who initiate local standard treatment for hATTR amyloidosis while on study.

3.6. Missing Data with Efficacy Endpoints

All efficacy data collected during study, regardless of whether before or after treatment discontinuation, will be included for analyses, with the exception of mNIS+7/Norfolk QOL collected post local standard treatment for hATTR amyloidosis (discussed in Section 3.5).

3.6.1. Missing Subcomponents within Co-primary and Secondary Efficacy Endpoints

For each patient, missing subcomponents within the primary mNIS+7 endpoint and secondary efficacy endpoints will be imputed whenever possible according to the algorithms specified in Section 7.1. When this "partial imputation" is successful (ie, complete mNIS+7 values are produced), these values will be used in all statistical analyses. When partial imputation is unsuccessful, the efficacy endpoint will be treated as completely missing.

3.6.2. Summary of Missing Data

For each of the co-primary and secondary efficacy endpoints, the number and percentage of missing data (completely missing) at each visit (Baseline, Month 9, and Month 18) will be summarized by study group.

3.7. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window.

For efficacy assessments, if the scheduled visit (eg, Month 9) is not performed, the unscheduled and/or discontinuation visits performed within a ± 3-month window will be grouped with the scheduled visit. The derived visits will be used for all analyses.

Unless otherwise specified above, data collected at unscheduled visits will be included in by-patient data listings and figures, but no assignment to a study visit will be made for the purpose of by-visit summary tabulations. However, unscheduled visits may be used in the calculation of baseline values (as discussed in Section 3.3) and for inclusion in any categorical shift summaries (e.g., shift from baseline to "worst" postbaseline value).

3.8. Interim Analyses

No interim analysis is planned for this study.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated for all randomized patients and will include categorical descriptives for the following parameters:

- Patients in each analysis population
- Patients randomized
- Patients treated
- Patients who complete treatment through Month 9
- Patients who discontinue treatment before Month 9
  - Primary reasons for treatment discontinuation
- Patients who complete treatment (18-month Treatment Period)
- Patients who discontinue treatment
  - Primary reasons for treatment discontinuation
- Patients who complete extension treatment
- Patients who discontinue extension treatment
  - Primary reasons for extension treatment discontinuation
- Patients who complete the study
- Patients who stop study participation
  - Primary reasons for stopping study participation

The number and percent of patients enrolled by country and site will be summarized by randomized treatment group and overall. The number and percent of patients in each randomization stratification factor recorded in IRS, and a comparison of the number and percent of patients in each randomization stratification factor in IRS versus the clinical database will be summarized by randomized treatment group and in total.

Data listings of treatment/study completion information including the reason for treatment discontinuation and/or stopping participation in the study will be presented.

Time to treatment discontinuation will be estimated descriptively using Kaplan-Meier method by treatment group. Patients completing study treatment will be censored at the last dose of study drug.

4.2. Protocol Deviations

Protocol deviations will be defined in a separate document, including the process for major/minor classification.

All protocol deviations and major protocol deviations will be presented in data listings.

4.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics, baseline disease characteristics, baseline efficacy parameters, and medical history information will be summarized by treatment group and overall.

Age [years; at informed consent], height [cm], weight [kg], and body mass index (BMI) [kg/m^2] will be summarized using continuous descriptives. Age group [<65; ≥65 to <75, ≥ 75], sex, race, ethnicity, and region [North America; Western Europe; Rest of World (Asia; Central and South America; Eastern Europe; Australia)] will be summarized using categorical descriptives.

The following baseline disease characteristics will be summarized by presenting categorical descriptives:

- Age at hATTR Symptom onset [< 50; ≥ 50]
- Neuropathy Impairment Score (NIS) [< 50; ≥ 50 & < 100; ≥ 100]
- Genotype [V30M; non-V30M]
- Early onset V30M [< 50 years of age at onset] vs. all other mutations [including late onset V30M]
- Previous tetramer stabilizer use [tafamidis or diflunisal] vs. no previous tetramer stabilizer use
- Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
- New York Heart Association (NYHA) Classification [I; II; III; IV]
- NT-proBNP [≤ 3000 ng/L; > 3000 ng/L]
- Cardiac Subpopulation

Time (years) since diagnosis with hATTR will be summarized using descriptive statistics. For those who previously used tetramer stabilizers, the time from discontinuation of these previous therapies to the start of study drug will be summarized using descriptive statistics.

Continuous efficacy parameters will be summarized using continuous descriptives. Categorical descriptives for PND score (I, II, IIIA, IIIB, IV) and FAP stage (I, II, III) will also be summarized.

Medical history will be coded using the MedDRA coding system (version 21.1 or later) and will be summarized by system organ class (SOC), high level term (HLT), and preferred term. A patient contributes only once to the count for a given condition (overall, by SOC, by HLT, by preferred term).

All demographic and baseline data for each patient will be provided in data listings. Medical history data, including baseline cardiac and ophthalmology history, prior surgeries/procedures, and pregnancy test results, will be presented in a data listing. Screening test results will also be presented in data listings.

4.4. Efficacy Evaluation

This Phase 3 study will use 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.

Except for TTR endpoints, analysis models will include only the 2 treatment groups compared, vutrisiran and placebo (APOLLO), and only simple descriptives will be presented for patisiran (HELIOS-A). For TTR endpoints, vutrisiran and patisiran (HELIOS-A) will be compared unless otherwise specified.

For efficacy endpoints, 2-sided 95% confidence intervals and 2-sided nominal P values will be presented if applicable unless otherwise specified. Formal multiplicity-controlled hypothesis testing will be conducted as described in Section 1.3.1; all other P values presented will be considered descriptive.

At the primary analysis timepoint after all Month 9 data has been collected, Month 9 analyses will be conducted. After all Month 18 data has been collected, Month 18 analyses will be conducted.

4.4.1. General Efficacy Methods

Most continuous efficacy endpoints will be evaluated using an analysis of covariance (ANCOVA) model incorporating multiple imputation (MI) or a mixed-effects model for repeated measures (MMRM).

4.4.1.1. ANCOVA/MI

ANCOVA incorporating MI will be the default analysis for most continuous endpoints at Month 9.

MI is a broadly applicable technique for handling missing data. Missing data are imputed multiple times using a regression method. Each imputed data set is analyzed using the same analysis model, and the point estimates and standard errors are combined to provide inferences that reflect the uncertainty about the missing values. MI assumes the data are missing at random (MAR).

For a given endpoint, missing endpoint values will be multiply imputed separately for each treatment group using a regression procedure, with baseline information including baseline score as covariate and genotype, age at hATTR symptom onset, prior tetramer stabilizer use, region, KPS, FAP stage (I vs. II/III), Cardiac subpopulation, sex, and baseline NIS (<50 vs. ≥50) as factors. For NIS-related endpoints, the categorical baseline NIS score will not be included in the regression procedure.

One hundred imputed datasets (per treatment group) will be generated from the MI regression procedure using SAS PROC MI. Each of the imputed datasets will then be analyzed using an ANCOVA model, including a covariate (baseline value) and factors (treatment group; genotype; age of disease onset, baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

The resulting estimates (LS mean differences and standard errors) from the 100 imputed datasets will be combined using SAS PROC MIANALYZE to produce inferential results (difference in LS means, 95% CI for the difference, and the P value from the test that the difference is zero). Combined LS mean estimates will be calculated as the average of the 100 complete-data estimates. A total variance estimate will be calculated as a weighted sum of within-imputation variance, which is the average of the complete-data variance estimates, and a between-imputation variance term. Complete details may be found in the SAS documentation for the MIANALYZE procedure (see Combining Inferences from Imputed Data Sets under Details: http://support.sas.com/documentation/onlinedoc/stat/131/mianalyze.pdf.)

4.4.1.2. MMRM

MMRM will be the default analysis for most continuous endpoints at Month 18. MMRM makes use of fully and partially observed data sequences from individual patients by estimating the covariance between data from different time points. The MMRM will be implemented using an unstructured approach to modeling both the treatment-by-time means and the (co)variances, leading to what is essentially a multivariate normal model wherein treatment group means at the primary time point are adjusted to reflect both the actually observed data and the projected outcomes from the patients with missing data. MMRM also assumes data are missing at random (MAR).

For most endpoints, the MMRM will include a covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), and an interaction term (treatment group by visit), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

LS mean and mean difference estimates, SEs, 95% CIs, and p-values at Month 9 and Month 18 will be presented at each respective analysis timepoint.

An unstructured covariance structure will be used to model the within-patient errors. If the model fails to converge, the following covariance structures will be specified in sequence and the first to converge will be used:

1. Toeplitz
2. Autoregressive (1)
3. Compound symmetry

The Satterthwaite approximation will be used to estimate the degrees of freedom.

4.4.2. Primary Efficacy Evaluations

The co-primary endpoints are change from baseline at Month 9 for mNIS+7 (Section 7.1.1) and Norfolk-DN QoL total scores (Section 7.1.2). 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 (Section 1.3.1). The primary comparison will be conducted at Month 9. The co-primary endpoints will be analyzed using the general ANCOVA/MI methods.

Additionally, the co-primary endpoints will be analyzed at Month 18 using the general MMRM methods, and Month 9 and 18 LS mean estimates from this MMRM will be presented graphically as well.

4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis

The primary analysis will not include assessments performed after the initiation of local standard treatment for hATTR amyloidosis (Section 3.5). Sensitivity analysis including data post local standard treatment for hATTR amyloidosis from either study will be conducted using the same ANCOVA/MI method at Month 9 and MMRM method at Month 18 for the each co-primary endpoint.

4.4.2.2. Sensitivity Analysis: Propensity Score

To allow some control of more factors and covariates without saturating the model, a propensity score approach will be used to reduce the predictors to a single propensity score. The propensity score is defined as the probability of being treated with vutrisiran as obtained from a logistic regression model of treatment group [vutrisiran; placebo (APOLLO)]. The logistic regression model will include covariate (baseline NT-proBNP) and baseline factors:

- Previous tetramer stabilizer use [tafamidis or diflunisal] [yes vs. no]
- Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
- New York Heart Association (NYHA) Classification [I; II/III/IV]
- Cardiac Subpopulation [yes vs no]
- PND score [I, II, IIIA, IIIB/IV]

The co-primary endpoints will be analyzed in this sensitivity analysis using the same ANCOVA/MI method at Month 9 and MMRM method at Month 18, including the propensity score covariate in addition to the default model factors and covariates.

4.4.2.3. Other Analysis: Binary Endpoint

The number and percentage of patients with a decrease (change from baseline < 0) in total score of mNIS+7 and Norfolk from baseline to Month 9 and to Month 18 will be summarized. The endpoints will be analyzed using Cochran-Mantel-Haenszel (CMH) test with Mantel-Haenszel odds ratios and associated CIs presented, stratified by genotype (V30M vs. non-V30M). Patients with missing change from baseline values will be considered non-responders.

4.4.2.4. Overview of Co-primary Endpoint Analyses

The planned analyses of the co-primary endpoints mNIS+7 and Norfolk-DN QoL total scores are summarized in Table 3.

Table 3: Analysis of Co-primary Endpoints mNIS+7 and Norfolk

Statistical Method
Month 9: ANCOVA/MI
Month 18: MMRM
Sensitivity analysis: Including data post local standard treatment for hATTR amyloidosis (Month 9: ANCOVA/MI; Month 18: MMRM)
Sensitivity analysis: Propensity score (Month 9: propensity-adjusted ANCOVA/MI; Month 18: propensity-adjusted MMRM)
Other analysis: Binary endpoint analysis using stratified CMH

4.4.3. Secondary Efficacy Evaluations

4.4.3.1. 10-meter Walk Test Speed, mBMI, and R-ODS

For 10-meter walk test speed (Section 7.1.4), mBMI (Section 7.1.5), and R-ODS (Section 7.1.6), change from baseline will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18.

4.4.3.2. TTR Percent Reduction

TTR percent reduction through Month 9 is defined as the average trough (ie, predose) TTR percent reduction from Month 6 to 9, which is the steady state period for both vutrisiran and patisiran. Only trough TTR assessments meeting requirements described in the PP population definition (Section 2; Table 2) will be included. The Hodges-Lehmann method (Hodges and Lehmann 1962), stratified by previous TTR stabilizer use (yes vs no), where values within each stratum are first aligned by the within-stratum 1-sample Hodges-Lehmann median, will be used to estimate the 95% CI for the median difference between the vutrisiran and patisiran groups in this study. Non-inferiority of vutrisiran (versus patisiran) will be declared if the lower limit of the 95% CI for the median treatment difference in TTR percent reduction (vutrisiran - patisiran) in this study is greater than –10%.

TTR percent reduction through Month 18, defined as the average trough TTR percent reduction from Month 6 to 18, will also be analyzed at the Month 18 analysis timepoint using the same analysis method.

Sensitivity analyses using the same analysis method will be conducted to compare the TTR percent reduction through Month 9 and Month 18 between the vutrisiran group from this study and the pooled patisiran group from this study and the APOLLO study.

4.4.3.3. Composite Endpoint of All-cause Deaths and/or All-cause Hospitalizations

Given the advanced disease setting where patients may experience recurrent hospitalizations, an analysis of time to first hospitalization or death does not characterize disease burden sufficiently. As such, the composite endpoint of all-cause deaths and/or all-cause hospitalizations over 18 months will be analyzed using the Andersen-Gill model, a survival analysis method accounting for recurrent events with covariate (baseline KPS) and factors (treatment group; age group; genotype). The endpoint will be analyzed for both the mITT population and the Cardiac Subpopulation.

4.4.3.4. Overview of Secondary Endpoint Analyses

The planned analyses of the secondary endpoints are summarized in Table 4.

Table 4: Analysis of Secondary Endpoints

Endpoint	Statistical Method	Analysis Population	Special Notes
10-meter walk test speed	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.4
mBMI	Month 9: ANCOVA/MI Month 18: MMRM	mITT	In APOLLO study, mBMI was not assessed at Months 9 or 18. The average values of Day 189 and Day 357 will be derived as Month 9. Day 546 will be used as Month 18.
R-ODS	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.6
TTR percent reduction through Month 9 and Month 18	Stratified Hodges-Lehmann	PP applicable to analysis timepoint	Sensitivity analysis comparing against patisiran (HELIOS-A + APOLLO)
All-cause deaths and/or all-cause hospitalizations over 18 months	Andersen-Gill model	mITT; Cardiac Subpopulation	

4.4.4. Exploratory Efficacy Evaluations

The exploratory continuous endpoints, including change from baseline in NIS (Section 7.1.1.2), EQ-5D-5L index (Section 7.1.3), and EQ VAS, will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. For EQ-5D-5L, categorical descriptives for ordinal response within each EQ-5D domain will be presented at each visit.

The exploratory categorical endpoints, PND score, FAP stage, NYHA class and KPS, will be descriptively summarized by presenting categorical descriptives for each visit. Categorical descriptives for patients with improving, no change, and worsening in PND/FAP at each postbaseline visit will also be summarized.

Cardiac structure and function will be assessed for all patients through echocardiograms. Cardiac stress and injury will be measured using serum levels of the cardiac biomarkers NT-proBNP, troponin I, and troponin T. Quantification of these biomarkers will be performed at a central laboratory. Descriptive statistics will be provided for actual values, changes, and percentage changes from baseline in echocardiogram parameters and serum levels of troponin I, troponin T, and NT-proBNP by treatment group at each visit.

For the mITT Population and Cardiac Subpopulation, select echocardiographic parameters will be analyzed using an MMRM at Month 18, including:

- Mean left ventricular (LV) wall thickness
- LV mass
- Global longitudinal strain
- LV end-diastolic volume
- Cardiac output

Cardiac biomarker NT-proBNP will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18, for both the mITT population and cardiac subpopulation. A logarithmic transformation will be applied to both baseline and change from baselines values to normalize the data before fitting the MMRM. The adjusted geometric mean fold-change and the ratio of the fold-change (vutrisiran/placebo) from baseline will be presented.

For the mITT Population and Cardiac Subpopulation, change from baseline in heart-contralateral lung ratio as assessed by technetium scintigraphy will be summarized at Month 18.

All echocardiogram, cardiac, and technetium scintigraphy data will be presented in data listings.

4.4.5. Subgroup Analyses

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Region [North America; Western Europe; Rest of World]
  - Region groups may be adjusted if <20 patients included in any category
- NIS [< 50; ≥ 50]
- Previous tetramer Use [Yes; No]
- Genotype [V30M; non-V30M]
- FAP stage [I; II & III]
- NYHA Classification [I; II]
- Cardiac Subpopulation

Subgroup analyses will be performed for the co-primary endpoints mNIS+7 and Norfolk QOL-DN using separate ANCOVA/MI models with covariate (baseline value) and factor (genotype [not applicable to genotype subgroup analyses). A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

4.4.6. Component/Domain Analyses

Component analyses will be conducted to assess the consistency of treatment effect on the change from baseline at Month 9 for each component of mNIS+7 (Section 7.1.1) and Norfolk QoL-DN domains (Section 7.1.2). The analyses will be performed using the ANCOVA/MI model used for the corresponding endpoint. A forest plot will be generated to illustrate the estimated treatment effect along with 95% CIs for each component/domain.

4.5. Pharmacodynamic Analyses

The PD parameters include serum TTR and vitamin A. All summary tables and figures will be based on assessments within 21 days after last dose of patisiran or within 84 days after last dose of vutrisiran. Assessments more than 21 days after last dose of patisiran or more than 84 days after last dose of vutrisiran will be presented in listings and individual patient plots only.

Summary tables will be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group for TTR and vitamin A.

In addition to TTR percent reduction analyses specified in Section 4.4.3, the serum TTR maximum percentage reduction and mean percentage reduction over 9 months will be summarized using descriptive statistics. Subgroup analysis will be provided for age (≥ 65 vs. <65), sex (male vs. female), genotype (V30M vs. Non-V30M), and previous tetramer stabilizer use (yes vs. no). The summary will also be provided for over 18 months.

Summary of TTR levels over time for patients in the patisiran group before and after the switch to vutrisiran will be presented to evaluate maintenance of serum TTR levels following switch from patisiran to vutrisiran.

All PD data will be displayed in data listings.

4.6. Pharmacokinetic Analyses

4.6.1. Study Variables

4.6.1.1. Concentration Data

For vutrisiran, plasma concentrations of ALN-65492(siRNA) will be obtained. For patisiran, plasma concentrations of ALN-18328(siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG will be obtained. Concentration values that are below the limit of quantification (LLOQ or BLQ) will be set to zero for analysis.

4.6.1.2. Plasma Pharmacokinetic Parameters

Model independent PK parameters to be calculated include:

- Study days 1 and 253:
  - Observed concentration 3-hour, 6-hour, 24-hour postdose (Cp [3 hr, 6 hr, 24hr]) for vutrisiran and 30-min, 6 hour, 24-hour postdose (Cp [30 min, 6 hr, 24 hr]) for patisiran
  - AUC0-24 for vutrisiran

  - Observed trough concentration (Ctrough)
  - Observed maximum concentration (Cmax)
  - Time of observed maximum concentration (Tmax)
- All other visits:
  - Predose levels for vutrisiran and patisiran
  - Observed concentration 3-hour postdose (Cp [3 hr]) for vutrisiran and 30-min, postdose (Cp [30 min]) for patisiran

4.6.2. Statistical Methods

Descriptive statistics for plasma concentration will include the number of patients, mean, SD, coefficient of variation (CV), median, minimum, and maximum.

The plasma Cmax, AUC, Cp (3 hr, 6hr, 24 hr), C_{trough} and Tmax of vutrisiran will be summarized by nominal sampling day as well as the plasma Cmax, Cp (30 min, 6 hr, 24 hr), C_{trough} and Tmax of ALN-18328 (siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG for patisiran. Mean concentrations (+/- SE) as well as individual concentrations will be plotted versus nominal sampling time.

Plasma concentration data will be presented in by-patient listings.

The PK-PD relationship between the plasma concentration and the percent change from baseline in TTR protein, vitamin A and RBP will be explored graphically for vutrisiran and ALN-18328 (siRNA) of patisiran separately

The PK exposure-response relationships for primary endpoint (mNIS+7) and incidence of relevant AEs may also be explored. These may be summarized by exposure quartiles at 9-months for vutrisiran and ALN-18328, DLin-MC3-DMA and PEG_{2000}-C-DMG PK for patisiran.

Population PK and exposure-response modeling will be reported separately.

4.7. Safety Analyses

Safety analyses will be conducted using the Safety population. All safety summaries will be descriptive and will be presented by treatment group.

4.7.1. Study Drug Exposure

Duration of drug exposure will be defined as:

- minimum of (the last dose of study drug – the first dose of study drug + 84, survival time)/30.44 months for vutrisiran group
- minimum of (the last dose of study drug – the first dose of study drug + 21, survival time)/30.44 months for patisiran group.

Duration of drug exposure, the total number of doses received, and total amount of study drug received will be summarized by descriptive statistics. Summaries of the numbers and percentages of patients with missing dose, and the number of missing doses per patient will also be provided. For patisiran group, the total volume infused will be summarized as well.

Study drug exposure data collected in the CRFs of study drug administration will also be summarized for each dose or infusion. For the patisiran group, the number of patients who experienced interruptions of infusions for any reason will be tabulated, as well as the number of patients with infusion interruptions due to an infusion-related reaction (IRR). For the vutrisiran group, the number of patients who experienced interruptions of injections for any reason will be tabulated, as well as the number of patients with injection interruptions due to an injection site reaction (ISR).

Duration of follow-up will also be summarized. It is defined as last date on study – date of first dose + 1.

Dosing information for each patient will be presented in a data listing.

4.7.2. Adverse Events

AEs will be coded using the MedDRA coding system (version 21.1 or later) and displayed in tables and data listings using SOC and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, defined as any AE with onset during or after the administration of study drug through 28 days following the last dose of patisiran or 84 days following the last dose of vutrisiran. In addition, any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study will be considered treatment-emergent. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first administration of study drug.

Adverse events will be summarized by the numbers and percentages of patients reporting a given AE. A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Overall event counts and frequencies may also be summarized.

An overall summary of AEs will include the number and percentage of patients with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any serious AE (SAE), any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths.

Tabulations by SOC and preferred term will be produced for the following: all AEs; AEs related to treatment; severe AEs; AEs leading to infusion interruption; AEs leading to drug delay; AEs leading to treatment discontinuation; AEs leading to study withdrawal; and SAEs. Adverse events and AEs related to treatment will also be tabulated by preferred term in decreasing order in frequency in the vutrisiran group. Adverse events and SAEs will also be summarized by SOC and preferred term for the cardiac subpopulation.

Separate tables will present AE incidence rates by maximum relationship to study drug and by maximum severity. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

AEs mapping to the standardized MedDRA queries (SMQs) Depression and Suicide/Self-injury, Torsade de pointes/QT prolongation, and Cardiac failure will be summarized by preferred term.

Adverse events mapping to the SMQ Drug Related Hepatic Disorder will be summarized by SOC and preferred term. Adverse events mapping to the SMQ Malignant or Unspecified Tumors will be summarized by high level term and preferred term. Other SMQs or AE groupings may be evaluated.

Separate tables will be provided summarizing signs and symptoms of IRRs (overall and by premedication regimen) and AEs related to premedication (overall and by premedication regimen) by SOC and preferred term for the patisiran group. Injection site reactions will be summarized for the vutrisiran group. The incidence and frequency of AEs and IRRs over time will also be summarized by SOC and preferred term.

All AEs will be presented in patient data listings. Separate listings will be provided for death, SAEs, AEs leading to treatment discontinuation, AEs leading to study withdrawal, AEs related to study procedures, and AEs mapping to the SMQ as described above. Listing of IRRs, AEs related to premedications will also be provided for patisiran group. A listing of patients who underwent liver transplant will also be provided.

4.7.3. Laboratory Data

Clinical laboratory values will be expressed in SI units. Central laboratory data will be summarized; local laboratory data will be included in the derivation of “worst” or potentially clinically significant values as applicable.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and liver function tests). Descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Shift tables will be employed to summarize the baseline category versus the “worst” postbaseline category, where the “worst” postbaseline category is evaluated for worst high and worst low separately as applicable for each parameter.

A listing will be produced for all patients with abnormal liver function tests defined as an ALT > 3×ULN, AST > 3×ULN, and total bilirubin > 2×ULN at any time point.

A table will be produced to summarize the number and percentage of patients in each of the below categories at any postbaseline time point.

- ALT > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- AST > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- ALT or AST > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- ALP > 1.5 ×ULN,
- Total Bilirubin > 1.5 & ≤ 2, > 2 & ≤ 3, > 3 & ≤ 5 and > 5 ×ULN,
- Total Bilirubin > 2 ×ULN concurrent with ALT or AST > 3 ×ULN.

A shift table from baseline to worst postbaseline for ALT, AST, and total bilirubin will also be provided. In separate figures, the peak total bilirubin (at any time postbaseline) will be plotted against the peak AST, the peak ALT, and the peak AST or ALT levels at any time postbaseline.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities will be provided. The results may also be graded according to the NCI CTCAE Version 4.0 or above. A shift summary of baseline to maximum postbaseline CTCAE grade may be presented, as appropriate.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) will be categorized as below: ≥ 90; 60-89; 30-59; 15-29 and < 15. A shift summary of baseline to worst postbaseline eGFR category will be presented.

All laboratory data will be provided in data listings. Out-of-range laboratory results will be identified in the listings.

4.7.4. Vital Signs and Physical Examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. Summary tables of potentially clinically significant vital signs will be provided

Vital sign measurements will be presented for each patient in a data listing.

4.7.5. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, and QTc interval. Baseline values will be the average of measurements from the baseline triplicate ECGs for each patient recorded. Descriptive statistics will be provided for each measure over time. Change from predose to each postdose assessment will also be summarized. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each study visit will also be summarized.

Corrected QT interval (QTc) will be calculated using both Fridericia's (QTcF) and Bazett's (QTcB) correction formula, derived as follows:

Table 5: QTc Derivation

	Derivation	
Parameter	**If RR available**	**If RR unavailable**
QTcB	$\frac{\text{QT (msec)}}{\text{Square root of RR (sec)}}$ [a]	$\frac{\text{QT (msec)}}{\text{Square root of 60/HR (bpm)}}$
QTcF	$\frac{\text{QT (msec)}}{\text{Cubic root of RR (sec)}}$ [a]	$\frac{\text{QT (msec)}}{\text{Cubic root of 60/HR (bpm)}}$

[a] RR (sec)=RR(msec)/1000.

QTcB=QTc Bazett; QTcF=QTc Fridericia; HR = heart (ventricular) rate.

Categorical analyses of the QTc data will be conducted and summarized as follows:

- The number and percentage of patients with maximum increase from baseline in QTc (< 30, 30 – 60, > 60 ms)
- The number and percentage of patients with maximum postbaseline QTc (< 450, 450 – < 480, 480 – 500, > 500 ms)

All ECG data for each patient will be provided in a data listing. A separate listing will be provided for patients with any QTc postbaseline value > 500ms or an increase from baseline > 60 ms.

4.7.6. Premedication

Patisiran 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 histamine 1 (H1) blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous histamine 1 (H2) blocker (ranitidine 50 mg, or equivalent)

Premedications will be coded using the WHO Drug Dictionary (September 2018 or later). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Premedication data will be listed.

4.7.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (September 2018 or later). Results will be tabulated by ATC and preferred term.

When there are partial or missing dates, imputed dates will be used to determine 1) if a medication is prior or concomitant, and 2) duration of exposure of local standard treatment for hATTR amyloidosis. Imputed dates will not be presented in the listings.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug; medications will be classified as prior, concomitant or both depending on the medication stop dates. For medications with a completely missing stop date, the end of study date will be imputed.

For patients who receive local standard treatment (including liver transplant) for hATTR amyloidosis during the study, the type of treatment will be summarized categorically.

Prior and concomitant medications will be presented in data listings.

4.7.8. Suicidality Questionnaire

The number and percentage of patients experiencing the suicidal ideation, suicidal behavior, or self-injurious behavior composite outcomes (and individual components) will be summarized by visit. A shift table will be employed to summarize the baseline C-SSRS category versus the worst postbaseline C-SSRS category; the categories are defined as 1) no suicidal ideation or behavior, 2) suicidal ideation, and 3) suicidal behavior. Patients experiencing both suicidal ideation and suicidal behavior are included in the suicidal behavior category.

Data from the C-SSRS questionnaire will be provided in a data listing.

4.8. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at any time point during study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will also be summarized using descriptive statistics.

For patients with confirmed positive ADA results, spaghetti plots for the serum TTR (ELISA) over time and the plasma concentration of vutrisiran and ALN-18328, DLin-MC3-DMA, and PEG2000-C-DMG for patisiran over time will be presented. Effect of positive ADA on efficacy and safety may also be explored.

ADA data and patients with confirmed positive ADA results will be presented in data listings.

5. CHANGES TO PLANNED ANALYSES

Modifications to planned analysis specifications from the protocol are documented below:

1. Section 2: The Safety population definition was modified to include all patients who received any amount of study drug, regardless of randomization status. The updated definition is consistent with the APOLLO study.

6. REFERENCES

Rubin, DB. Multiple Imputation after 18+ Years. Journal of the American Statistical Association, 1996; 91:473–489.

Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Inf J*. 2008;7:303–319.

Collins, L.M., Schafer, J.L., and Kam, C.M. (2001). A comparison of inclusive and restrictive missing-data strategies in modern missing-data procedures. Psychological Methods, 6, 330-351.

Barnes, S. A., Kallin, C., David, S. R., Mallinckrodt, C. H (2008). The impact of missing data and how it is handled on the rate of false positive results in drug development. Pharmaceutical Statistics 7:215–225.

Siddiqui, O. (2011). MMRM versus MI in Dealing with Missing Data – A Comparison Based on 25 NDA Data Sets, Journal of Biopharmaceutical Statistics, 21: 423–436, 2011.

Hodges Jr, JL and Lehmann, EL (1962). Rank methods for combination of independent experiments in analysis of variance. The Annals of Mathematical Statistics 33(2): 482-497.

7. APPENDICES

7.1. Questionnaire/Scoring

In questionnaires, if multiple responses are provided to a single-response question, the question is deemed as missing.

7.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS)

Note: the mNIS+7 and NIS measurements are conducted in duplicate per time point. The average of 2 complete duplicate values will be reported, except in cases of missing or partially missing data as described in the table below.

Assessment Tool	Total Points	Components (maximum points)
Modified NIS+7	304	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • Quantitative sensory testing by body surface area including touch pressure (TP) and heat as pain (HP): QST-BSA$_{TP+HP5}$ (80) • ∑5 nerve conduction studies (10) – Ulnar compound muscle action potential (ulnar CMAP) – Ulnar sensory nerve action potential (ulnar SNAP) – Sural sensory nerve action potential (sural SNAP) – Tibial compound muscle action potential (tibial CMAP) – Peroneal compound muscle action potential (peroneal CMAP) • Postural blood pressure (BP) (2)
NIS	244	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • NIS-S: Sensation (32)

7.1.1.1. Modified Neuropathy Impairment Score (mNIS+7)

There are 5 components within mNIS+7 total score including NIS-W, NIS-R, QST, ∑5 NC, and postural BP, as described in details below.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

7.1.1.2. Neuropathy Impairment Score (NIS)

The components of NIS include the following:

1. NIS-W as described in previous section.
2. NIS-R as described in previous section.
3. NIS-S is the sum of the finger and toe sensation components (touch pressure, pin-prick, vibration, joint position). Assessments are performed separately for the right- and left-hand side of the body. Scoring for the sensory assessment is 0 (normal), 1 (decreased) and 2 (absent). The maximum total score for NIS-S is 32.

[redacted]

[redacted] [redacted] [redacted]

[redacted] [redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

7.1.1.3. Algorithms for Setting Normal Deviates and Points

[redacted]

[redacted]

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

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

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

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

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

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

[redacted]

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

7.1.2. Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN)

QOL-DN is a tool for assessing patients' perception of the effects of diabetes and diabetic neuropathy. There are 35 questions divided into 5 domains. The range of possible total scores is -4 to 136.

Part I: Symptoms

Items 1-7 (Part I) are a simple inventory of symptoms of neuropathy. The presence of the symptom is checked in whichever box applies, and an absence of a symptom is checked under "none." Positive responses are scored as 1; and negative responses, as 0.

Part II: Activities of Daily Life

Items 8-35 (Part II) pertain to Activities of Daily Life, and most of these are scaled on a 5-point Likert scale ranging from 0 ("Not a problem") to 4 ("Severe problem"). However, Questions 31 and 32 are scored differently. In Question 31, "Good", the middle item, is scored as 0. "Very Good" is scored as –1, "Excellent" is scored as –2. "Fair" is scored as 1, and "Poor" is scored as 2. In Question 32, "About the Same," the middle item, is scored as 0. "Somewhat better" is scored as –1, "Much better" is scored as -2. "Somewhat worse" is scored as 1, and "Much worse" is scored as 2.

Subscales and Scoring Algorithm

The Total QOL and 5 domains should be summed as follows:

- Total QOL (35 items)	[redacted]
- Physical Functioning/Large Fiber (15 items)	[redacted]
- Activities of Daily Living (ADLs) (5 items)	[redacted]
- Symptoms (8 items)	[redacted]
- Small Fiber (4 items)	[redacted]
- Autonomic (3 items)	[redacted]

The total score and domain scores are calculated without weighting of any kind, and reported as the integer sum of the listed questionnaire items.

[redacted]

[redacted]

7.1.3. EuroQOL-5-Dimension 5-Level (EQ-5D-5L)

Each of the 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) is scored on a 5-point Likert scale from 1 (“I have no problems/pain/anxiety”) to 5 (“I am unable to…,” “I have extreme anxiety/depression”).

The 5 scores are concatenated together (in the order of Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) to create an EQ-5D-5L profile (e.g., 11111, 55555). The profile is then used to obtain an index value using the United States value set. The index values range from –0.109, associated with a profile of 55555, to 1.0, associated with a profile of 11111. Smaller index values indicate greater impairment.

Missing values are handled as follows:

- Missing items are coded as “9” in creating patient profiles.
- The index value is deemed as missing when responses are missing for 1 or more of the 5 dimensions.
- If the entire instrument is missing, the EQ-5D-5L index value is considered as missing.

7.1.4. 10-Meter Walk Test (10-MWT)

Two replicate assessments are expected to be performed approximately 24 hours apart and no more than 7 days apart per protocol. At baseline and for each postbaseline visit, the walk speed (m/s) analysis value is derived as follows:

Table 8: 10-MWT Derivation Scenarios

Scenario	Derivation
Both replicate assessments nonmissing	
Patient able to walk for both assessments	10/mean(time 1, time 2)
Patient unable to walk for 1 of the 2 assessments	mean(0, 10/assessable time)
Patient unable to walk for both assessments	0
One replicate assessment nonmissing	
Patient able to walk	10/assessable time
Patient unable to walk	0

7.1.5. Modified Body Mass Index (mBMI)

In the APOLLO study, mBMI was not assessed at Months 9 or 18. For the placebo (APOLLO) group, these assessments are derived as follows:

- Month 9 = mean of Day 189 (Week 27) and Day 357 (Week 51) assessments
- Month 18 = Day 546 (Week 78) assessment

7.1.6. Rasch-Built Overall Disability Scale (R-ODS)

The R-ODS consists of 24 items scored on a scale of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty). A total score will be calculated as the average of all nonmissing items multiplied by 24 if at least 90% of the items are nonmissing. The total score will be deemed as missing if more than 10% of the items (3 or more items) are missing.

Approval	[redacted] 2019 18:22:47 GMT+0000

Approval	[redacted] 2019 21:56:42 GMT+0000

STATISTICAL ANALYSIS PLAN
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:	Vutrisiran (ALN-TTRSC02)
EudraCT Number:	2018-002098-23
IND Number:	139086
Protocol Version and Date:	Original: 11 October 2018 Amendment 3: 17 July 2020
Analysis Plan Version and Date:	Original: 30 January 2019 Amendment 1: 20 July 2020
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted] [redacted]

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without expressed written authorization of Alnylam Pharmaceuticals, Inc.

APPROVAL SIGNATURE PAGE

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)

Protocol:	ALN-TTRSC02-002
Analysis Plan Version and Date:	Amendment 1: 20 July 2020

This document has been authored by the following:

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

This document has been approved and signed electronically on the final page by the following:

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

TABLE OF CONTENTS

APPROVAL SIGNATURE PAGE 2
TABLE OF CONTENTS 3
LIST OF TABLES 6
LIST OF FIGURES 6
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 7
1. INTRODUCTION 10
1.1. Study Design 10
1.2. Study Objectives and Endpoints 13
1.3. Study Hypotheses 14
1.3.1. Multiple Comparisons Procedure (US/Japan/Brazil) 14
1.3.2. Multiple Comparisons Procedure (EU/Other Regions) 15
1.4. Sample Size Determination 16
2. PATIENT POPULATIONS 17
3. GENERAL CONSIDERATIONS 19
3.1. Computing Environment 19
3.2. General Methods 19
3.3. Baseline Definitions 19
3.4. Randomization Stratification Factors 20
3.5. Efficacy Censoring Rules 20
3.5.1. Initiation of Local Standard Treatment for hATTR Amyloidosis 20
3.5.2. Onset of Serious COVID-19 Adverse Events 21
3.6. Missing Data with Efficacy Endpoints 21
3.6.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints 21
3.6.2. Summary of Missing Data 21
3.7. Visit Windows 21
3.8. Interim Analyses 22
4. STUDY ANALYSES 23
4.1. Patient Disposition 23
4.2. Protocol Deviations 24
4.3. Demographics and Baseline Characteristics 24
4.4. Efficacy Evaluation 25

4.4.1. General Efficacy Methods 25
4.4.1.1. ANCOVA/MI 25
4.4.1.2. MMRM 26
4.4.1.3. ANCOVA 27
4.4.2. Primary Efficacy Evaluations 27
4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis or Post Serious COVID-19 AE 27
4.4.2.2. Sensitivity Analysis: Propensity Score 27
4.4.2.3. Sensitivity Analysis: Pattern-Mixture Model 28
4.4.2.4. Other Analysis: Binary Endpoint....................29
4.4.2.5. Other Analysis: Efficacy PP Population....................29
4.4.2.6. Overview of Primary Endpoint Analyses 29
4.4.3. Secondary Efficacy Evaluations 30
4.4.3.1. Key secondary endpoint: Norfolk QoL-DN Total Score....................30
4.4.3.2. 10-meter Walk Test Speed, mBMI, and R-ODS 30
4.4.3.3. TTR Percent Reduction 30
4.4.3.4. Overview of Secondary Endpoint Analyses 30
4.4.4. Exploratory Efficacy Evaluations....................31
4.4.5. Subgroup Analyses 32
4.4.6. Component/Domain Analyses 33
4.5. Pharmacodynamic Analyses....................33
4.6. Pharmacokinetic Analyses....................33
4.6.1. Study Variables....................33
4.6.1.1. Concentration Data 33
4.6.1.2. Plasma Pharmacokinetic Parameters 33
4.6.2. Statistical Methods....................34
4.7. Safety Analyses 34
4.7.1. Study Drug Exposure....................34
4.7.2. Adverse Events 35
4.7.3. Laboratory Data 36
4.7.4. Vital Signs and Physical Examination....................37
4.7.5. Electrocardiogram....................37
4.7.6. Premedication 38

4.7.7. Prior and Concomitant Medications 38
4.7.8. Suicidality Questionnaire 39
4.8. Anti-Drug Antibody 39
4.9. Summaries of Treatment Extension Period Data 39
4.9.1. Summaries over the Duration of the Entire Study 40
4.9.2. Summaries During Vutrisiran Treatment 40
4.10. COVID-19 Pandemic Impact Analyses 40
4.10.1. General impact 40
4.10.2. Impact on Efficacy 41
4.10.3. Impact on Adverse Events 41
4.10.4. Other Impacts 42
5. CHANGES TO PLANNED ANALYSES 43
6. REFERENCES 44
7. APPENDICES 45
7.1. Questionnaire/Scoring 45
7.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS) 45
7.1.1.1. Modified Neuropathy Impairment Score (mNIS+7) 45
7.1.1.2. Neuropathy Impairment Score (NIS) 47
7.1.1.3. Algorithms for Setting Normal Deviates and Points 47
7.1.2. Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) 53
7.1.3. EuroQol-5-Dimension 5-Level (EQ-5D-5L) 54
7.1.4. 10-Meter Walk Test (10-MWT) 54
7.1.5. Modified Body Mass Index (mBMI) 55
7.1.6. Rasch-Built Overall Disability Scale (R-ODS) 55
7.2. Pattern-Mixture Model Details 55
7.3. Pandemic Phase Start Dates by Country 57
8. AMENDMENT HISTORY 59

LIST OF TABLES

Table 1: Multiple Comparisons Procedure (US/Japan/Brazil) 14
Table 2: Multiple Comparisons Procedure (EU/Other Regions) 15
Table 3: Postbaseline TTR Assessment Requirements by Treatment Group 18
Table 4: Analysis of Primary Endpoint mNIS+7 29
Table 5: Analysis of Secondary Endpoints 30
Table 6: QTc Derivation 38
Table 7: All Percentiles Table 49
Table 8: Extended Percentiles Table 53
Table 9: 10-MWT Derivation Scenarios 55
Table 10: Pattern-Mixture Model Intermediate Dataset 55

LIST OF FIGURES

Figure 1: Study Design 12

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	**Definition**
10-MWT	10-meter walk test
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATTR	Amyloid transthyretin
BMI	Body mass index
CI	Confidence Interval
CMAP	Compound muscle action potential
C_{max}	Observed peak concentration
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EQ-VAS	EuroQol visual analogue scale
FAP	Familial amyloidotic polyneuropathy, also known as hATTR amyloidosis with polyneuropathy
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
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
LLN	Lower limit of normal

Abbreviation	**Definition**
LS	Least-squares
LV	Left ventricle
mBMI	Modified body mass index
MCP	Multiple comparisons procedure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MNAR	Missing not at random
mNIS+7	Modified Neurologic Impairment Score +7
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
PD	Pharmacodynamics
PK	Pharmacokinetics
PMM	Pattern-mixture model
PND	Polyneuropathy Disability
q3M	Once every 3 months
q3w	Once every 3 weeks
QoL or QOL	Quality of life
QST	Quantitative sensory testing
$\text{QST-BSA}_{\text{HP}}$	QST heat pain by body surface area
$\text{QST-BSA}_{\text{TP}}$	QST touch pressure by body surface area
QTc	Corrected QT interval
QTcF	QT obtained using Fridericia's formula
RBC	Red blood cell
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event

Abbreviation	Definition
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
siRNA	Small interfering ribonucleic acid
SMQ	Standardized MedDRA query
SNAP	Sensory nerve action potential
SOC	System organ class
t_{max}	Time of observed maximum concentration
TTR	Transthyretin
ULN	Upper limit of normal
V30M	Valine to methionine mutation at position 30
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan details comprehensive, technical specifications of the statistical analyses of the efficacy/safety data outlined and/or specified in the final protocol of Study ALN-TTRSC02-002. Specifications of tables, figures, and data listings are documented separately.

1.1. Study Design

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

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 to vutrisiran 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 vutrisiran administered as a subcutaneous (SC) injection once every 3 months (q3M) or patisiran 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.

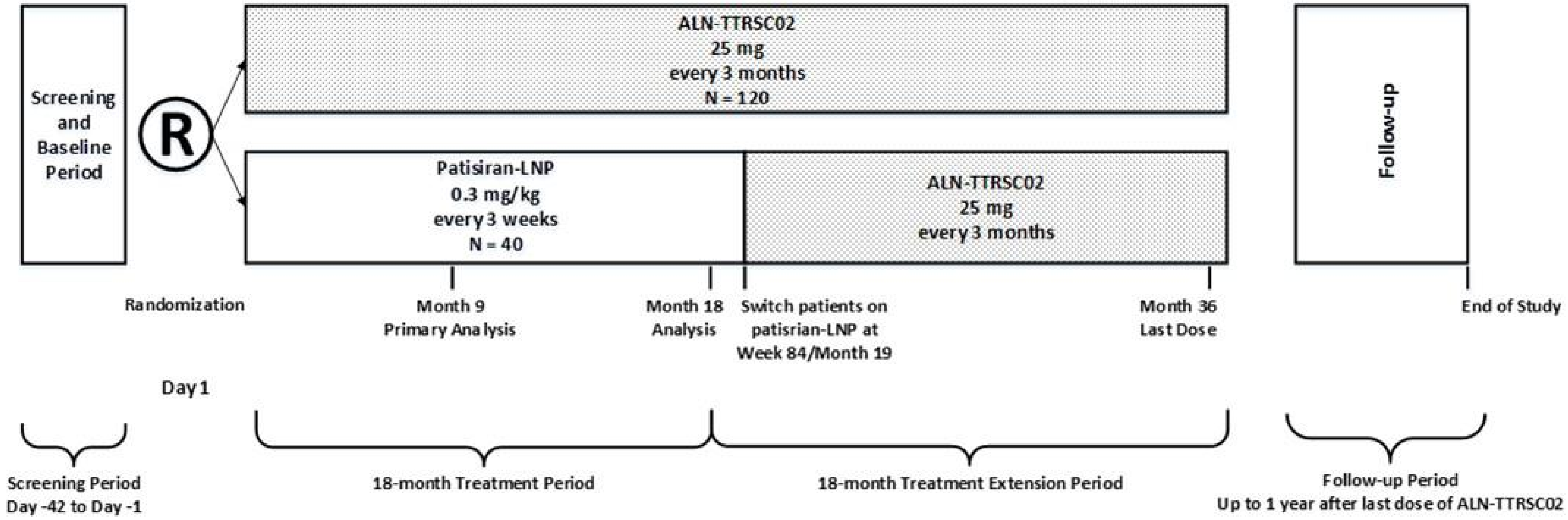
All efficacy visits must be conducted at the clinic (Month 9, Month 18, Month 27, Month 36, and modified efficacy visits). In situations in which a Month 9 or Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness 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 Study Month 15 or Month 24, respectively).

During the Treatment Extension Period, starting at Week 84/Month 19, all patients on the patisiran group will switch to treatment with vutrisiran (first dose) and remain on vutrisiran 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 vutrisiran 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 will undergo a follow-up visit 30 days after the last dose of study drug.

The placebo group of the APOLLO (ALN-TTR02-004) 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, and percent TTR reduction. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

Figure 1: Study Design


Screening and Baseline Period
R
ALN-TTRSC02
25 mg
every 3 months
N = 120
Patisiran-LNP
0.3 mg/kg
every 3 weeks
N = 40
ALN-TTRSC02
25 mg
every 3 months
Follow-up
Randomization
Month 9
Primary Analysis
Month 18
Analysis
Switch patients on
patisrian-LNP at
Week 84/Month 19
Month 36
Last Dose
End of Study
Day 1
Screening Period
Day -42 to Day -1
18-month Treatment Period
18-month Treatment Extension Period
Follow-up Period
Up to 1 year after last dose of ALN-TTRSC02

1.2. Study Objectives and Endpoints

The primary and most secondary and exploratory efficacy endpoints are in comparison to the placebo group of the Phase 3 pivotal patisiran-LNP study (APOLLO study) as specified in the statistical analysis section of the ALN-TTRSC02-002 (HELIOS-A) protocol.

Objectives	**Endpoints**
Primary	
• To determine the efficacy of vutrisiran 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 group of the APOLLO study at Month 9
Secondary	
• To determine the efficacy of vutrisiran on quality of life, gait speed, neurologic impairment, nutritional status, and disability • To demonstrate the noninferiority of vutrisiran compared to patisiran with respect to serum TTR levels	• Change from baseline in the following parameters compared to the placebo group 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 vutrisiran group compared to the within-study patisiran group through Month 18
Exploratory	
• To determine the effect of vutrisiran 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 vutrisiran and patisiran on serum TTR and vitamin A levels • To characterize plasma pharmacokinetics (PK) of vutrisiran and patisiran • To assess presence of antidrug antibodies (ADA) to vutrisiran and patisiran	• Change from baseline in the following parameters compared to the placebo group of the APOLLO study at Month 9: – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R ODS) • 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)

Objectives	**Endpoints**
	– 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 vutrisiran and patisiran • Incidence and titers of ADA to vutrisiran and patisiran
Safety	
• To determine the safety and tolerability of vutrisiran in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

1.3. Study Hypotheses

For most inferentially-evaluated efficacy endpoints, the null hypothesis for the superiority comparison of vutrisiran vs placebo is defined as follows:

H_0: No difference between vutrisiran and placebo (APOLLO): difference (vutrisiran – placebo) = 0

For TTR percent reduction endpoints, the null hypothesis for the noninferiority comparison of vutrisiran vs patisiran is defined as follows:

H_0: Vutrisiran is inferior to patisiran: difference in median TTR reduction (vutrisiran – patisiran) ≤ -10%

1.3.1. Multiple Comparisons Procedure (US/Japan/Brazil)

In the US, Japan, and Brazil, the overall familywise error rate will be controlled at α=0.05 for the primary and secondary endpoint hypothesis tests as follows:

Table 1: Multiple Comparisons Procedure (US/Japan/Brazil)

MCP Step[a]	**Endpoint**	**Comparison Group vs Vutrisiran**	**MCP Criteria**
Evaluated at the Month 9 analysis timepoint			
1	Modified Neurologic Impairment Score +7 (mNIS+7) change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score) change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
3	10-MWT gait speed change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
Evaluated at the Month 18 analysis timepoint			

MCP Step[a]	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
4	Modified Neurologic Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
5	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
6	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
7	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
8	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
9	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%

[a] Per serial gatekeeping MCP, if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.

LCB=lower confidence bound; MCP=multiple comparisons procedure.

1.3.2. Multiple Comparisons Procedure (EU/Other Regions)

In the EU, during its scientific advice procedure, the EMA/CHMP/SAWP indicated a preference for a marketing authorization application based upon 18 months data. Therefore, the Month 9 endpoints included in the US/Japan/Brazil multiple comparisons procedure (MCP) will not be included in the MCP for the EU and other regions, where instead mNIS+7 change from baseline at Month 18 will be considered the primary endpoint. The overall familywise error rate in the EU and other regions will be controlled at α=0.05 for the primary and secondary endpoint hypothesis tests as follows:

Table 2: Multiple Comparisons Procedure (EU/Other Regions)

MCP Step[a]	Endpoint	Comparison group vs Vutrisiran	MCP Criteria
Evaluated at the Month 18 analysis timepoint			
1	Modified Neurologic Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
3	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
4	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α

MCP Step[a]	**Endpoint**	**Comparison group vs Vutrisiran**	**MCP Criteria**
5	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
6	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%

[a] Per serial gatekeeping MCP, if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.

LCB=lower confidence bound; MCP=multiple comparisons procedure.

References to the primary and secondary endpoints in the remainder of this document refer to those endpoints defined in the study objectives and endpoints (Section 1.2), corresponding to the US/Japan/Brazil MCP (Section 1.3.1).

1.4. Sample Size Determination

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

The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of vutrisiran in this patient population. For the primary efficacy endpoint of mNIS+7 and the secondary endpoint of Norfolk QoL-DN total score, the vutrisiran group in the Phase 3 study will be compared to the placebo group 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 group from the APOLLO study. Assuming a mean change of 0 points for the vutrisiran group, 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 group from the APOLLO study. Assuming a mean change of -4 points for the vutrisiran group, 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 vutrisiran 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 baseline NT-proBNP values greater than 3000 ng/L.

2. PATIENT POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data in this study, and for applicable analyses, relevant data from the APOLLO study.

- Modified Intent-to-Treat (mITT) population: All randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment to which they were randomized.
- TTR Per-protocol (PP) Population: All mITT population patients with a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment between Months 6 (Week 24) and Month 18 [Week 72]) that meets the requirements described in Table 3. Patients will be analyzed according to the treatment to which they were randomized.
- Month 9 Efficacy PP Population: All mITT population patients treated with vutrisiran or placebo meeting the following criteria:
  - Month 9 efficacy visit date within 3 calendar months of protocol-planned Month 9 efficacy visit window
  - No serious or severe COVID-19 custom query AE terms or reported on or before Month 9 efficacy visit date
  - For vutrisiran-treated patients, received all planned vutrisiran doses up to and including Week 36 with ≤ 28 day delay

  Patients will be analyzed according to the treatment to which they were randomized.
- Month 18 Efficacy PP Population: All mITT population patients treated with vutrisiran or placebo meeting the following criteria:
  - Month 18 efficacy visit date within 3 calendar months of protocol-planned Month 18 efficacy visit window
  - No serious or severe COVID-19 custom query AE terms reported on or before Month 18 efficacy visit date
  - For vutrisiran-treated patients, received all planned vutrisiran doses up to and including Week 72 with ≤ 28 day delay

  Patients will be analyzed according to the treatment to which they were randomized.
- Cardiac Subpopulation: All mITT population patients who had preexisting evidence of cardiac amyloid involvement, defined as patients with baseline left ventricular (LV) wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history. Patients will be analyzed according to the treatment to which they were randomized.
- Safety population: All patients who received any amount of study drug. Patients will be analyzed according to the treatment received.
- Pharmacokinetic (PK) population: All randomized patients who received at least one full dose of study drug and have at least 1 postdose blood sample for PK parameters

and have evaluable PK data. Patients will be analyzed according to the treatment received.

- All vutrisiran-treated population: All randomized patients who received any amount of vutrisiran treatment, including patients who took vutrisiran during the 18-month treatment period and patients who first receive vutrisiran during the 18-month treatment extension period.

Efficacy analyses (except TTR) and PD summaries will be conducted in the mITT population unless otherwise specified. The noninferiority of TTR will be assessed using the TTR PP population. Safety analyses will be conducted in the Safety population. PK analyses will be conducted in the PK population. The All vutrisiran-treated population will be used to summarize long-term efficacy and safety data during vutrisiran treatment.

Table 3: Postbaseline TTR Assessment Requirements by Treatment Group

Treatment Group	**Postbaseline TTR Assessment Requirements**
Vutrisiran or Patisiran	• Assessment must be before administration of study drug at the current visit • Assessment after initiation of local standard treatment for hATTR amyloidosis excluded (Section 3.5)
Vutrisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 12 weeks before the TTR assessment • Patient must receive planned, complete administration of study drug at 2 consecutive planned treatment visits at any time before the TTR assessment visit to ensure steady state
Patisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 3 weeks before the TTR assessment

3. GENERAL CONSIDERATIONS

3.1. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software version 9.4 (or later), unless otherwise noted. Figures may be generated using R version 3.6 (or later).

3.2. General Methods

All data listings that contain an evaluation date will contain a study day relative to the day of the first dose of study drug, which is designated as Day 1. On-treatment study days will be calculated as evaluation date – first dose date +1 and pretreatment days will be calculated as evaluation date – first dose date. There is no Day 0.

Categorical descriptives will include the count and percentage of patients (or events, if applicable) within each category (with a category for missing data) of the parameter. Continuous descriptives will include the number of patients, mean, median, standard deviation (SD), standard error (SE), minimum, and maximum values.

Laboratory data (including vitamin A) collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

For assessments that are repeated multiple times for the study visit, the average will be calculated unless otherwise noted.

All summaries will be presented by treatment group. Unless otherwise specified, treatment groups in the treatment period will be presented using the following labels:

- Placebo (APOLLO)
    - Presented primarily for efficacy (except TTR) analyses and most AE and baseline summaries
- Vutrisiran (HELIOS-A)
- Patisiran (HELIOS-A)
- Total (HELIOS-A)
    - Presented primarily for patient disposition, protocol deviations, and baseline summaries

In addition, for TTR sensitivity analyses, the following treatment groups will be presented:

- Patisiran (HELIOS-A + APOLLO)
- Patisiran (APOLLO)

3.3. Baseline Definitions

For the mNIS+7/NIS individual components, total scores and related endpoints, the 2 baseline assessments are performed on separate days. Baseline will be calculated as the mean of the nonmissing replicate measures.

For 10-MWT, 2 baseline assessments are performed on separate days. Baseline will be calculated as described in Section 7.1.4.

For PD parameters (TTR, Vitamin A), baseline will be defined as the average of all records, including those from any unscheduled visits, before the date and time of first dose.

For all other parameters, unless noted otherwise, baseline will be defined as the last nonmissing measurement on or before the first dose date.

3.4. Randomization Stratification Factors

Stratification factors for randomization include TTR genotype (V30M vs. non-V30M) and baseline NIS score (< 50 vs. ≥ 50).

Stratification factors are recorded in both the Interactive Response System (IRS) and the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database. In the presence of stratification errors, the stratification used in analysis may not match that in the IRS.

3.5. Efficacy Censoring Rules

3.5.1. Initiation of Local Standard Treatment for hATTR Amyloidosis

In the APOLLO study, there were placebo-treated patients who discontinued study drug, but remained on study and received local standard treatment. For the primary analysis of mNIS+7 and Norfolk QoL-DN, assessments were censored (excluded from analysis) after initiation of any of the following:

- Orthotopic liver transplant
- Use of TTR stabilizing agents (eg, tafamidis, diflunisal) for >14 days

For consistency of data handling, the placebo group from the APOLLO study will follow the same censoring rule as the APOLLO study.

For this study, APOLLO censoring rules will be applied. Additionally, assessments will be censored after initiation of any of the following recently approved treatments:

- Any use of TTR-targeting anti-sense oligonucleotides (eg, inotersen)
- Any use for patisiran (applicable for the vutrisiran treatment group only)

This data will be included and flagged in efficacy listings. These assessments from either study will be included in sensitivity analyses as specified.

For TTR percent reduction, TTR assessments collected after initiation of local standard treatment for hATTR amyloidosis will be excluded from the analysis. For all other efficacy endpoints, data from either study collected after initiation of local standard treatment for hATTR amyloidosis will be included in analyses.

A separate listing will be provided for patients who initiate local standard treatment for hATTR amyloidosis while on study.

3.5.2. Onset of Serious COVID-19 Adverse Events

Patients who experience a serious COVID-19 AE may have worsening in general health and wellbeing unassociated with the natural course of hATTR amyloidosis or with study drug. Assessments will be censored on or after the onset of a serious COVID-19 AE for all analyses of mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS, and any associated component/domain scores. This will reflect a hypothetical estimand of interest where the COVID-19 pandemic did not occur, as was the case for placebo group from the APOLLO study.

3.6. Missing Data with Efficacy Endpoints

All efficacy data collected during study, regardless of whether before or after treatment discontinuation, will be included for analyses, with the exception of mNIS+7 and Norfolk QoL-DN collected post local standard treatment for hATTR amyloidosis (discussed in Section 3.5), and mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS on or after the onset of a serious COVID-19 AE (Section 3.5.2).

3.6.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints

For each patient, missing subcomponents within the primary mNIS+7 endpoint and secondary efficacy endpoints will be imputed whenever possible according to the algorithms specified in Section 7.1. When this "partial imputation" is successful (ie, complete mNIS+7 values are produced), these values will be used in all statistical analyses. When partial imputation is unsuccessful, the efficacy endpoint will be treated as completely missing.

3.6.2. Summary of Missing Data

For each of the primary and secondary efficacy endpoints, the number and percentage of missing data (completely missing), including due to COVID-19, at each visit (Baseline, Month 9, and Month 18) will be summarized by study group.

3.7. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window.

For efficacy assessments, if the scheduled visit (eg, Month 9) is not performed, the unscheduled and/or discontinuation visits performed within a ± 3-month window will be grouped with the scheduled visit. 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, Month 9 and Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15 or Month 24, respectively). For patients impacted by the COVID-19 pandemic, efficacy visits delayed up to 6 months after the end of the protocol-defined efficacy visit window will be included in the analysis. The derived visits will be used for all analyses.

Unless otherwise specified above, data collected at unscheduled visits will be included in by-patient data listings and figures, but no assignment to a study visit will be made for the purpose of by-visit summary tabulations. However, unscheduled visits may be used in the calculation of baseline values (as discussed in Section 3.3) and for inclusion in any categorical shift summaries (e.g., shift from baseline to “worst” postbaseline value).

3.8. Interim Analyses

No interim analysis is planned for this study.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated for all randomized patients and will include categorical descriptives for the following parameters:

- Patients in each analysis population
- Patients randomized
- Patients treated
- Patients who complete or discontinue treatment
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete treatment through Month 9
- Patients who discontinue treatment before Month 9
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete treatment through Month 18
- Patients who discontinue treatment between Month 9 and Month 18 or through Month 18
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete treatment through Month 36
- Patients who discontinue treatment between Month 18 and Month 36
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete study participation
- Patients who stop study participation
  - Primary reasons for stopping study participation and stopping study participation due to COVID-19

Patient disposition by country and site will be summarized by randomized treatment group and overall. The number and percent of patients in each randomization stratification factor recorded in IRS, and a comparison of the number and percent of patients in each randomization stratification factor in IRS versus the clinical database will be summarized by randomized treatment group and in total.

Data listings of treatment/study completion information including the reason for treatment discontinuation and/or stopping participation in the study will be presented.

4.2. Protocol Deviations

Protocol deviations, including those related to COVID-19, will be defined in a separate document, including the process for major/minor classification.

All protocol deviations, COVID-19-related protocol deviations, and major protocol deviations will be summarized.

4.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics, baseline disease characteristics, baseline efficacy parameters, and medical history information will be summarized by treatment group and overall.

Age [years; at informed consent], height [cm], weight [kg], and body mass index (BMI) [kg/m^2] will be summarized using continuous descriptives. Age group [<65; ≥65 to <75, ≥ 75], sex, race, ethnicity, and region [North America; Western Europe; Rest of World (Asia; Central and South America; Eastern Europe; Australia)] will be summarized using categorical descriptives.

The following baseline disease characteristics will be summarized by presenting categorical descriptives:

- Age at hATTR Symptom onset [< 50; ≥ 50]
- Neuropathy Impairment Score (NIS) [< 50; ≥ 50 & < 100; ≥ 100]
- Genotype [V30M; non-V30M]
- Early onset V30M [< 50 years of age at onset] vs. all other mutations [including late onset V30M]
- Previous tetramer stabilizer use [tafamidis or diflunisal] vs. no previous tetramer stabilizer use
- Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
- New York Heart Association (NYHA) Classification [No heart failure; I; II; III; IV]
- NT-proBNP [≤ 3000 ng/L; > 3000 ng/L]
- Cardiac Subpopulation [Yes; No]

Time (years) since diagnosis with hATTR will be summarized using descriptive statistics. For those who previously used tetramer stabilizers (tafamidis or diflunisal), the time from discontinuation of these previous therapies to the start of study drug will be summarized using descriptive statistics. Genotype by country will be summarized using categorical descriptives.

Continuous baseline efficacy parameters will be summarized using continuous descriptives. Categorical descriptives for baseline PND score (I, II, IIIA, IIIB, IV) and FAP stage (I, II, III) will also be summarized.

Medical history will be coded using the MedDRA coding system (version 23.0 or later) and will be summarized by system organ class (SOC), high level term (HLT), and preferred term. A patient contributes only once to the count for a given condition (overall, by SOC, by HLT, by preferred term).

All demographic and baseline data for each patient will be provided in data listings. Medical history data, including baseline cardiac and ophthalmology history, prior surgeries/procedures, and pregnancy test results, will be presented in a data listing. Screening test results will also be presented in data listings.

4.4. Efficacy Evaluation

This Phase 3 study will use 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.

Except for TTR endpoints, analysis models will include only the 2 treatment groups compared, vutrisiran and placebo (APOLLO), and only simple descriptives will be presented for patisiran (HELIOS-A). For TTR endpoints, vutrisiran and patisiran (HELIOS-A) will be compared unless otherwise specified.

For efficacy endpoints, 2-sided 95% confidence intervals and 2-sided nominal P values will be presented if applicable unless otherwise specified. Formal multiplicity-controlled hypothesis testing will be conducted as described in Section 1.3.1; all other P values presented will be considered descriptive.

As this study will be ongoing at the time of the primary analysis at Month 9 and the additional analysis at Month 18, the study database will undergo an interim database lock at the Month 9 and Month 18 data cutoff dates (ie, data in EDC will be cleaned, frozen and electronically signed by investigators; external laboratory data will be cleaned and will undergo quality assurance). The cutoff dates are defined as the dates when the last patient completes the Month 9 and Month 18 efficacy visit, respectively. Additional details regarding the interim database locks will be documented in the study Data Management Plan.

The Month 9 and Month 18 analyses will include all data on or before the respective data cutoff date. For assessments with start and end dates (eg, AEs, medications, medical history), data records with start dates after the specified data cutoff date will be excluded.

After the study is completed (ie, all patients complete the Treatment Extension Period and/or required follow-up visits), the database will undergo a final database lock, and all data will be summarized in a final CSR.

4.4.1. General Efficacy Methods

Most continuous efficacy endpoints will be evaluated using an analysis of covariance (ANCOVA) model incorporating multiple imputation (MI) or a mixed-effects model for repeated measures (MMRM).

4.4.1.1. ANCOVA/MI

ANCOVA incorporating MI will be the default analysis for most continuous efficacy endpoints at Month 9.

MI is a broadly applicable technique for handling missing data. Missing data are imputed multiple times using a regression method. Each imputed data set is analyzed using the same analysis model, and the point estimates and standard errors are combined to provide inferences that reflect the uncertainty about the missing values. MI assumes the data are missing at random (MAR).

For a given endpoint, missing endpoint values will be multiply imputed separately for each treatment group using a regression procedure, with baseline information including baseline score and KPS as covariates and genotype, age at hATTR symptom onset, prior tetramer stabilizer use, region, FAP stage (I vs. II/III), Cardiac subpopulation, sex, and baseline NIS (<50 vs. ≥50) as factors. For NIS-related endpoints, the categorical baseline NIS score will not be included in the regression procedure.

One hundred imputed datasets (per treatment group) will be generated from the MI regression procedure using SAS PROC MI. Each of the imputed datasets will then be analyzed using an ANCOVA model, including a covariate (baseline value) and factors (treatment group; genotype; age of disease onset, baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

The resulting estimates (LS mean differences and standard errors) from the 100 imputed datasets will be combined using SAS PROC MIANALYZE to produce inferential results (difference in LS means, 95% CI for the difference, and the P value from the test that the difference is zero).[Rubin 1996] Combined LS mean estimates will be calculated as the average of the 100 complete-data estimates. A total variance estimate will be calculated as a weighted sum of within-imputation variance, which is the average of the complete-data variance estimates, and a between-imputation variance term. Complete details may be found in the SAS documentation for the MIANALYZE procedure (see Combining Inferences from Imputed Data Sets under Details: http://support.sas.com/documentation/onlinedoc/stat/131/mianalyze.pdf).

4.4.1.2. MMRM

MMRM will be the default analysis for most continuous efficacy endpoints at Month 18. MMRM makes use of fully and partially observed data sequences from individual patients by estimating the covariance between data from different time points. The MMRM will be implemented using an unstructured approach to modeling both the treatment-by-time means and the (co)variances, leading to what is essentially a multivariate normal model wherein treatment group means at the primary time point are adjusted to reflect both the actually observed data and the projected outcomes from the patients with missing data. MMRM also assumes data are missing at random (MAR).

For most endpoints, the MMRM will include a covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), and an interaction term (treatment group by visit), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

LS mean and mean difference estimates, SEs, 95% CIs, and p-values at Month 9 and Month 18 will be presented.

An unstructured covariance structure will be used to model the within-patient errors. If the model fails to converge, the following covariance structures will be specified in sequence and the first to converge will be used:

1. Toeplitz

2. First order autoregressive
3. Compound symmetry

The Satterthwaite approximation will be used to estimate the degrees of freedom.

4.4.1.3. ANCOVA

ANCOVA, without incorporating MI, will be the default Month 9 sensitivity and subgroup analyses unless otherwise specified. Patients who complete both baseline and Month 9 will be included in the analysis. For most endpoints, the ANCOVA will include a covariate (baseline value), and factors (treatment group; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

4.4.2. Primary Efficacy Evaluations

The primary endpoint is change from baseline at Month 9 for mNIS+7 (Section 7.1.1). The primary endpoint will be tested at a significance level of 0.05, and must be significant to declare a positive trial (Section 1.3.1; Section 1.3.2). The primary comparison will be conducted at Month 9. The primary endpoint will be analyzed using the general ANCOVA/MI methods.

Additionally, change from baseline at Month 18 for mNIS+7 will be analyzed as a secondary endpoint using the general MMRM methods, and Month 9 and 18 LS mean estimates from this MMRM will be presented graphically as well.

4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis or Post Serious COVID-19 AE

The primary analysis will not include assessments performed after the initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE (Section 3.5). Sensitivity analysis of mNIS+7 change from baseline including data post local standard treatment for hATTR amyloidosis or post serious COVID-19 AE from either study will be conducted using the ANCOVA method at Month 9 and MMRM method at Month 18.

4.4.2.2. Sensitivity Analysis: Propensity Score

To allow some control of more factors and covariates without saturating the model, a propensity score approach will be used to reduce the predictors to a single propensity score. The propensity score is defined as the probability of being treated with vutrisiran as obtained from a logistic regression model of treatment group [vutrisiran; placebo (APOLLO)]. The logistic regression model will include the following baseline variables:

- Continuous variables
  - NT-proBNP (log-transformed)
  - mNIS+7
  - Norfolk QoL-DN total score
- Categorical variables
  - Previous tetramer stabilizer use (tafamidis/diflunisal) [Yes; No]

- Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
- Cardiac Subpopulation [Yes; No]
- PND score [I; II; IIIA; IIIB/IV]
- Age at hATTR Symptom onset [< 50; ≥ 50]
- Neuropathy Impairment Score (NIS) [< 50; ≥ 50]
- Genotype [V30M; non-V30M]
- FAP stage [I; II/III]

The primary endpoint will be analyzed in this sensitivity analysis using the ANCOVA method at Month 9 and MMRM method at Month 18, including the propensity score covariate in addition to the default model factors and covariates.

4.4.2.3. Sensitivity Analysis: Pattern-Mixture Model

The primary analysis ANCOVA/MI method addresses data under missing at random (MAR) assumptions. To assess the robustness of the primary analysis results under missing not at random (MNAR) assumptions, a sensitivity analysis using a pattern-mixture model (PMM) will be conducted at Month 9 using a modified ANCOVA/MI method.

The model will be based on the following assumptions:

1. Patients who have missing data due to COVID-19, including patients who have missing assessments, who have data censored because a serious COVID-19 AE was reported before Month 9, or who die due to COVID-19:
   a. Under the hypothetical estimand of interest where the COVID-19 pandemic did not occur, these assessments should have been obtained with no COVID-19 impact. Therefore, for patients meeting either of these criteria, assessments will be considered MAR, and will be imputed using MI estimated from all nonmissing data collected on treatment from the vutrisiran group.
2. Patients who have missing data unrelated to COVID-19 and are alive before Month 9:
   a. Placebo-treated patients who have missing data: The missing data are considered MAR and will be imputed using MI estimated from placebo-treated patients. The imputation is done regardless of whether a patient was on-treatment or discontinued treatment before the scheduled Month 9 efficacy assessment.
   b. Vutrisiran-treated patients who have missing data while on treatment: Patients are expected to continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, missing data during the on-treatment period (within 126 days of the patient's last dose before the scheduled Month 9 efficacy assessment) are considered MAR and will be imputed using MI estimated from all nonmissing data collected on treatment from the vutrisiran group. The 126-day window was selected given the long PD effect of vutrisiran.
   c. Vutrisiran-treated patients who have missing data after stopping their study treatment: Patients will no longer benefit from treatment in the future and will have trajectory similar to placebo-treated patients. Therefore, missing data after treatment

discontinuation (more than 126 days after the patient's last dose of study drug before the scheduled Month 9 efficacy assessment) will be imputed using the data from placebo-treated patients.

3. Patients who have missing data and who die before Month 9 unrelated to COVID-19:
    a. Assuming deaths observed in the study will likely be related to worsening of disease, the missing data will be imputed by taking random samples from the worst 10% mNIS+7 change from baseline scores among vutrisiran- and placebo-treated patients at Month 9. The imputation will be done for patients from both vutrisiran and placebo groups.

Following the procedure describe above, 100 imputed datasets will be generated, and each imputed dataset will be analyzed and estimates combined following the same ANCOVA/MI model as the primary analysis.

More details on the implementation of PMM are discussed in Section 7.2.

4.4.2.4. Other Analysis: Binary Endpoint

The number and percentage of patients with a decrease (change from baseline < 0) in total score of mNIS+7 from baseline to Month 9 and to Month 18 will be summarized. The endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) test with Mantel-Haenszel odds ratios and associated CIs presented, stratified by genotype (V30M vs. non-V30M). Patients with missing change from baseline values due to COVID-19 will be excluded; all other patients with missing change from baseline values will be considered non-responders.

4.4.2.5. Other Analysis: Efficacy PP Population

To mitigate for the impact of the COVID-19 pandemic, mNIS+7 will also be analyzed using the Efficacy PP population; full details are provided in Section 4.10.2.

4.4.2.6. Overview of Primary Endpoint Analyses

The planned analyses of the primary endpoint mNIS+7 are summarized in Table 4.

Table 4: Analysis of Primary Endpoint mNIS+7

Statistical Method
Month 9: ANCOVA/MI
Month 18: MMRM
Sensitivity analysis: Including data post local standard treatment for hATTR amyloidosis or post serious COVID-19 AE (Month 9: ANCOVA; Month 18: MMRM)
Sensitivity analysis: Propensity score (Month 9: propensity-adjusted ANCOVA; Month 18: propensity-adjusted MMRM)
Sensitivity analysis: Pattern-mixture model with ANCOVA/MI at Month 9
Other analysis: Binary endpoint analysis using stratified CMH
Other analysis: Efficacy PP Population (Month 9: ANCOVA; Month 18: MMRM)

4.4.3. Secondary Efficacy Evaluations

4.4.3.1. Key secondary endpoint: Norfolk QoL-DN Total Score

Change from baseline in Norfolk QoL-DN total score (primary analysis incorporating COVID-19 pandemic impact questions, described in Section 7.1.2) will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. Sensitivity, binary, and Efficacy PP Population analyses for Norfolk QoL-DN total score will also be conducted as described for mNIS+7 in Section 4.4.2.

An additional sensitivity analysis of change from baseline in Norfolk QoL-DN total score (without incorporating COVID-19 impact questions, described in Section 7.1.2) will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18.

4.4.3.2. 10-meter Walk Test Speed, mBMI, and R-ODS

For 10-meter walk test speed (Section 7.1.4), mBMI (Section 7.1.5), and R-ODS (Section 7.1.6), change from baseline will be analyzed using an ANCOVA/MI model at Month 9 (with mBMI and R-ODS analyzed at Month 9 as exploratory endpoints), and using an MMRM at Month 18. Binary analyses for 10-meter walk test speed will also be conducted as described for mNIS+7 in Section 4.4.2.4.

4.4.3.3. TTR Percent Reduction

TTR percent reduction through Month 18 is defined as the average trough (ie, predose) TTR percent reduction from Month 6 to 18, which is the steady state period for both vutrisiran and patisiran. Only trough TTR assessments meeting requirements described in the TTR PP population definition (Section 2; Table 3) will be included. The Hodges-Lehmann method [Hodges and Lehmann 1962], stratified by previous TTR stabilizer use (yes vs no), where values within each stratum are first aligned by the within-stratum 1-sample Hodges-Lehmann median, will be used to estimate the 95% CI for the median difference between the vutrisiran and patisiran groups in this study. Non-inferiority of vutrisiran (versus patisiran) will be declared if the lower limit of the 95% CI for the median treatment difference in TTR percent reduction (vutrisiran - patisiran) in this study is greater than –10%.

Sensitivity analyses using the same analysis method will be conducted to compare the TTR percent reduction through Month 18 between the vutrisiran group from this study and the pooled patisiran group from this study and the APOLLO study.

4.4.3.4. Overview of Secondary Endpoint Analyses

The planned analyses of the secondary endpoints are summarized in Table 5 .

Table 5: Analysis of Secondary Endpoints

Endpoint	Statistical Method	Analysis Population	Special Notes
Norfolk QoL-DN total score	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.2 Sensitivity and binary analyses described in Section 4.4.2

Endpoint	Statistical Method	Analysis Population	Special Notes
10-meter walk test speed	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.4 Binary analyses described in Section 4.4.2.3
mBMI	Month 9 (exploratory endpoint): ANCOVA/MI Month 18: MMRM	mITT	In APOLLO study, mBMI was not assessed at Months 9 or 18. The average values of Day 189 and Day 357 will be derived as Month 9. Day 546 will be used as Month 18.
R-ODS	Month 9 (exploratory endpoint): ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.6
TTR percent reduction through Month 18	Stratified Hodges-Lehmann	TTR PP	Sensitivity analysis comparing against patisiran (HELIOS-A + APOLLO)

4.4.4. Exploratory Efficacy Evaluations

The exploratory continuous endpoints, including change from baseline in NIS (Section 7.1.1.2), EQ-5D-5L index (Section 7.1.3), and EQ VAS, will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. For EQ-5D-5L, categorical descriptives for ordinal response within each EQ-5D domain will be presented at each visit.

The exploratory categorical endpoints, PND score, FAP stage, NYHA class and KPS, will be descriptively summarized by presenting categorical descriptives for each visit. Categorical descriptives for patients with improving, no change, and worsening in PND/FAP at each postbaseline visit will also be summarized.

Cardiac structure and function will be assessed for all patients through echocardiograms. Cardiac stress and injury will be measured using serum levels of the cardiac biomarkers NT-proBNP, troponin I, and troponin T. Quantification of these biomarkers will be performed at a central laboratory. Descriptive statistics will be provided for actual values, changes, and percentage changes from baseline in echocardiogram parameters and serum levels of troponin I, troponin T, and NT-proBNP by treatment group at each visit.

For the mITT Population, select echocardiographic parameters will be analyzed using an MMRM at Month 18, including:

- Mean left ventricular (LV) wall thickness
- LV mass
- Global longitudinal strain
- LV end-diastolic volume
- Cardiac output

Additionally, these select echocardiographic parameters will be analyzed at Month 18 for the Cardiac Subpopulation using an MMRM with covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]), and an interaction term (treatment group by visit).

Cardiac biomarker NT-proBNP will be analyzed for the mITT population using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. Additionally, NT-proBNP will be analyzed at Month 18 for the Cardiac Subpopulation using an MMRM with covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]), and an interaction term (treatment group by visit). A logarithmic transformation will be applied to both baseline and change from baselines values to normalize the data before fitting the MMRM. The adjusted geometric mean fold-change and the ratio of the fold-change (vutrisiran/placebo) from baseline will be presented.

For the mITT Population and Cardiac Subpopulation, change from baseline in heart-contralateral lung ratio as assessed by technetium scintigraphy will be summarized at Month 18.

All echocardiogram, cardiac, and technetium scintigraphy data will be presented in data listings.

Given the advanced disease setting where patients may experience recurrent hospitalizations, an analysis of time to first hospitalization or death does not characterize disease burden sufficiently. As such, the composite endpoint of all-cause deaths and/or all-cause hospitalizations over 18 months will be analyzed using the Andersen-Gill model, a survival analysis method accounting for recurrent events with covariate (baseline KPS) and factors (treatment group; age group; genotype). The endpoint will be analyzed for the mITT population.

4.4.5. Subgroup Analyses

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Region [North America; Western Europe; Rest of World]
  - Region groups may be adjusted if <20 patients included in any category
- NIS [< 50; ≥ 50]
- Previous tetramer stabilizer use [Yes; No]
- Genotype [V30M; non-V30M]
- FAP stage [I; II & III]
- Cardiac Subpopulation [Yes; No]

Subgroup analyses will be performed for the primary endpoint, mNIS+7, and key secondary endpoint, Norfolk QoL-DN, at Month 9 using separate ANCOVA models with covariate (baseline value) and factors (treatment group; genotype [not applicable to genotype subgroup analyses]), and at Month 18 using an MMRM with covariate (baseline value), factors (treatment group; visit; genotype [not applicable to genotype subgroup analyses]), and an interaction term (treatment group by visit). A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

4.4.6. Component/Domain Analyses

Component analyses will be conducted to assess the consistency of treatment effect on the change from baseline at Month 9 for each component of mNIS+7 (Section 7.1.1) and Norfolk QoL-DN domains (Section 7.1.2). The analyses will be performed at Month 9 using the ANCOVA/MI model used for the corresponding endpoint, and at Month 18 using the MMRM used for the corresponding endpoint . A forest plot will be generated to illustrate the estimated treatment effect along with 95% CIs for each component/domain.

4.5. Pharmacodynamic Analyses

The PD parameters include serum TTR and vitamin A. All summary tables and figures will be based on assessments within 21 days after last dose of patisiran or within 84 days after last dose of vutrisiran. Assessments more than 21 days after last dose of patisiran or more than 84 days after last dose of vutrisiran will be presented in listings and individual patient plots only.

Summary tables will be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group for TTR and vitamin A.

In addition to TTR percent reduction analyses specified in Section 4.4.3.3, the serum TTR maximum percentage reduction and mean percentage reduction over 9 months will be summarized using descriptive statistics. Subgroup analysis will be provided for age (≥ 65 vs. <65), sex (male vs. female), genotype (V30M vs. Non-V30M), and previous tetramer stabilizer use (yes vs. no). The summary will also be provided for over 18 months.

Summary of TTR levels over time for patients in the patisiran group before and after the switch to vutrisiran will be presented to evaluate maintenance of serum TTR levels following switch from patisiran to vutrisiran.

All PD data will be displayed in data listings.

4.6. Pharmacokinetic Analyses

4.6.1. Study Variables

4.6.1.1. Concentration Data

For vutrisiran, plasma concentrations of ALN-TTRSC02(siRNA) will be obtained. For patisiran, plasma concentrations of ALN-18328(siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG will be obtained. Concentration values that are below the limit of quantification (LLOQ or BLQ) will be set to zero for analysis.

4.6.1.2. Plasma Pharmacokinetic Parameters

Model independent PK parameters to be calculated and summarized descriptively include:

- Study days 1 and 253:

  - Observed concentration 3-hour, 6-hour, 24-hour postdose (Cp [3 hr, 6 hr, 24hr]) for vutrisiran and 30-min, 6 hour, 24-hour postdose (Cp [30 min, 6 hr, 24 hr]) for patisiran
  - AUC0-24 for vutrisiran
  - Observed trough concentration (Ctrough)
  - Observed maximum concentration (Cmax)
  - Time of observed maximum concentration (Tmax)
- All other visits:
  - Predose levels for vutrisiran and patisiran
  - Observed concentration 3-hour postdose (Cp [3 hr]) for vutrisiran and 30-min, postdose (Cp [30 min]) for patisiran

4.6.2. Statistical Methods

Descriptive statistics for plasma concentration will include the number of patients, mean, SD, coefficient of variation (CV), geometric mean, geometric mean CV, median, minimum, and maximum.

The plasma Cmax, AUC, Cp (3 hr, 6hr, 24 hr), C_{trough} and Tmax of vutrisiran will be summarized by nominal sampling day as well as the plasma Cmax, Cp (30 min, 6 hr, 24 hr), C_{trough} and Tmax of ALN-18328 (siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG for patisiran. Mean concentrations (+SD) as well as individual concentrations will be plotted versus nominal sampling time.

Plasma concentration data will be presented in by-patient listings.

The PK-PD relationship between the plasma concentration and the percent change from baseline in TTR protein and vitamin A will be explored graphically for vutrisiran and ALN-18328 (siRNA) of patisiran separately

The PK exposure-response relationships for primary endpoint (mNIS+7) and incidence of relevant AEs may also be explored. These may be summarized by exposure quartiles at 9-months for vutrisiran and ALN-18328, DLin-MC3-DMA and PEG_{2000}-C-DMG PK for patisiran.

Population PK and exposure-response modeling will be reported separately.

4.7. Safety Analyses

Safety analyses will be conducted using the Safety population. All safety summaries will be descriptive and will be presented by treatment group.

4.7.1. Study Drug Exposure

Duration of drug exposure will be defined as:

- minimum of (the last dose of study drug – the first dose of study drug + 84, survival time)/30.4375 months for vutrisiran group

- minimum of (the last dose of study drug – the first dose of study drug + 21, survival time)/30.4375 months for patisiran group.

Duration of drug exposure, the total number of doses received, and total amount of study drug received will be summarized by descriptive statistics. Summaries of the numbers and percentages of patients with no missing dose, and the number of missing doses per patient will also be provided. The total volume infused or injected will be summarized as well.

Study drug exposure data collected in the CRFs of study drug administration will also be summarized for each dose or infusion. The numbers and percentages of patients with complete, partial, and missing dose administrations will be summarized. Complete and partial administration is defined as follows:

- Patisiran:
  - Complete: ≥80% (≥160 mL) of the planned infusion volume (200 mL)
  - Partial: >0% to <80% (>0 to <160 mL) of the planned infusion volume (200 mL)
- Vutrisiran:
  - Complete: 100% administered
  - Partial: >0% to <100% administered

For the patisiran group, the number of patients who experienced interruptions of infusions for any reason will be tabulated, as well as the number of patients with infusion interruptions due to an infusion-related reaction (IRR).

For the vutrisiran group, the above drug exposure summaries applicable to vutrisiran will also be provided by vial vs prefilled syringe dose presentations. Vutrisiran doses with missing dose presentation information before the date of first prefilled syringe administration to any patient will be treated as vial dose presentations.

Dosing information for each patient will be presented in a data listing.

4.7.2. Adverse Events

This Phase 3 study will use the APOLLO study as an external control. Patient-level data from this study will be compared with patient-level data from APOLLO for relevant AE summaries only.

AEs will be coded using the MedDRA coding system (version 23.0 or later) and displayed in tables and data listings using SOC and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, defined as any AE with onset during or after the administration of study drug through 28 days following the last dose of patisiran or 84 days following the last dose of vutrisiran. In addition, any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study will be considered treatment-emergent. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first administration of study drug.

Adverse events will be summarized by the numbers and percentages of patients reporting a given AE. A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Overall event counts and event rates may also be summarized.

An overall summary of AEs will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any serious AE (SAE), any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths.

Tabulations by SOC and preferred term will be produced for the following: all AEs; AEs related to treatment; severe AEs; AEs leading to infusion interruption; AEs leading to drug delay; AEs leading to treatment discontinuation; AEs leading to stopping study participation; and SAEs. Adverse events and AEs related to treatment will also be tabulated by preferred term in decreasing order in frequency in the vutrisiran group. Adverse events and SAEs will also be summarized by SOC and preferred term for the cardiac subpopulation.

Separate tables will present the number and percentage of AEs by maximum relationship to study drug and by maximum severity. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

AEs mapping to the standardized MedDRA queries (SMQs) Depression and Suicide/Self-injury, Torsade de pointes/QT prolongation, and Cardiac failure will be summarized by preferred term. Adverse events mapping to the SMQ Drug Related Hepatic Disorder and SMQ Acute Renal Failure will be summarized by SOC and preferred term. Adverse events mapping to Cardiac Arrhythmias high level group term and the SMQ Malignant or Unspecified Tumors will be summarized by high level term and preferred term. Other SMQs or AE groupings may be evaluated.

Separate tables will be provided summarizing signs and symptoms of IRRs (overall and by premedication regimen) and AEs related to premedication by SOC and preferred term for the patisiran group. Injection site reactions will be summarized for the vutrisiran group by presentation (vial vs prefilled syringe) and in total. The number and percentage of patients with AEs, ISRs, and IRRs over time will also be summarized by SOC and preferred term.

All AEs will be presented in patient data listings. Separate listings will be provided for death, SAEs, AEs leading to treatment discontinuation, AEs leading to stopping study participation, and AEs mapping to the SMQ as described above. A listing of ISRs will be provided for the vutrisiran group. Listing of IRRs and AEs related to premedications will also be provided for patisiran group. A listing of patients who underwent liver transplant will also be provided.

4.7.3. Laboratory Data

Clinical laboratory values will be expressed in SI units. Central laboratory data will be summarized; local laboratory data will be included in the derivation of "worst" or potentially clinically significant values as applicable.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and liver function tests). Descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit.

A listing will be produced for all patients with abnormal liver function tests defined as an ALT > 3×ULN, AST > 3×ULN, and total bilirubin > 2×ULN at any time point.

A table will be produced to summarize the number and percentage of patients in each of the below categories at any postbaseline time point.

- ALT ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- AST ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- Maximum ALT or AST ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- ALP > 1.5 ×ULN,
- Total Bilirubin ≤ 1, > 1 & ≤ 1.5, > 1.5 & ≤ 2, > 2 & ≤ 3, > 3 & ≤ 5 and > 5 ×ULN,
- Total Bilirubin > 2 ×ULN concurrent with ALT or AST > 3 ×ULN.

A shift table from baseline to worst postbaseline for ALT, AST, and total bilirubin will also be provided. In separate figures, the peak total bilirubin (at any time postbaseline) will be plotted against the peak AST, the peak ALT, and the peak AST or ALT levels at any time postbaseline.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities will be provided. The results may also be graded according to the NCI CTCAE Version 4.0 or above. A shift summary of baseline to maximum postbaseline CTCAE grade may be presented, as appropriate.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) will be categorized as below: ≥ 90; 60-89; 30-59; 15-29 and < 15. A shift summary of baseline to worst postbaseline eGFR category will be presented.

All laboratory data will be provided in data listings. Out-of-range laboratory results will be identified in the listings.

4.7.4. Vital Signs and Physical Examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. Summary tables of potentially clinically significant vital signs will be provided.

Vital sign measurements will be presented for each patient in a data listing.

4.7.5. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, and QTc interval. Baseline values will be the average of measurements from the baseline triplicate ECGs for each patient recorded. Descriptive statistics will be provided for each measure over time. Change from predose to each postdose assessment will also be summarized. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each study visit will also be summarized.

Corrected QT interval (QTc) will be calculated using the Fridericia's (QTcF) correction formula, derived as follows:

Table 6: QTc Derivation

	Derivation	
Parameter	**If RR available**	**If RR unavailable**
QTcF	$\frac{\text{QT (msec)}}{\text{Cubic root of RR (sec)}^{a}}$	$\frac{\text{QT (msec)}}{\text{Cubic root of 60/HR (bpm)}}$

[a] RR (sec)=RR(msec)/1000.
QTcF=QTc Fridericia; HR = heart (ventricular) rate.

Categorical analyses of the QTc data will be conducted and summarized as follows:

- The number and percentage of patients with maximum increase from baseline in QTc (< 30, 30 – 60, >30, > 60 ms)
- The number and percentage of patients with maximum postbaseline QTc (< 450, 450 – < 480, 480 – 500, >480, > 500 ms)

All ECG data for each patient will be provided in a data listing. A separate listing will be provided for patients with any QTc postbaseline value > 500ms or an increase from baseline > 60 ms.

4.7.6. Premedication

Patisiran 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 histamine 1 (H1) blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous histamine 1 (H2) blocker (ranitidine 50 mg, or equivalent)

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

Premedications will be coded using the WHO Drug Dictionary (March 2020 or later). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Premedication data will be listed.

4.7.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (March 2020 or later). Prior medications include medications taken ≥ 1 time before the first dose of study drug, regardless of medication end date. Concomitant medications include medications taken ≥ 1 time on or after the first dose of study drug, regardless of medication start date. Results will be tabulated by ATC and preferred term.

When there are partial or missing dates, imputed dates will be used to determine 1) if a medication is prior or concomitant, and 2) duration of exposure of local standard treatment for hATTR amyloidosis. Imputed dates will not be presented in the listings.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug; medications will be classified as prior, concomitant or both depending on the medication stop dates. For medications with a completely missing stop date, the end of study date will be imputed.

For patients who receive local standard treatment (including liver transplant) for hATTR amyloidosis during the study, the type of treatment will be summarized categorically.

Prior and concomitant medications will be presented in data listings.

4.7.8. Suicidality Questionnaire

The number and percentage of patients experiencing the suicidal ideation, suicidal behavior, or self-injurious behavior composite outcomes (and individual components) will be summarized by visit. A shift table will be employed to summarize the baseline C-SSRS category versus the worst postbaseline C-SSRS category; the categories are defined as 1) no suicidal ideation or behavior, 2) suicidal ideation, and 3) suicidal behavior. Patients experiencing both suicidal ideation and suicidal behavior are included in the suicidal behavior category.

Data from the C-SSRS questionnaire will be provided in a data listing.

4.8. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at any time point during study as well as at each scheduled visit will be summarized. The titer results for patients with confirmed positive ADA results will also be summarized using descriptive statistics.

For patients with confirmed positive ADA results, spaghetti plots for the serum TTR (ELISA) over time and the plasma concentration of vutrisiran and ALN-18328, DLin-MC3-DMA, and PEG2000-C-DMG for patisiran over time will be presented. Effect of positive ADA on efficacy and safety may also be explored.

ADA data and patients with confirmed positive ADA results will be presented in data listings.

4.9. Summaries of Treatment Extension Period Data

The study design includes an 18-month Treatment Period, where patients will be randomized to either vutrisiran or patisiran treatment, followed by an 18-month Treatment Extension Period, where all patients will receive vutrisiran treatment. The primary objective is to evaluate the efficacy and safety of vutrisiran during the initial 18-month Treatment Period; most analyses described in this SAP focus on this objective. Additionally, the long-term visit-based efficacy and safety of vutrisiran will be characterized over the entire study including the Treatment Extension Period, and the long-term period-based safety of vutrisiran will be characterized for the All vutrisiran-treated population.

4.9.1. Summaries over the Duration of the Entire Study

Descriptive summaries for visit-based parameters throughout the study, including the Treatment Extension period, will be conducted to characterize effect of vutrisiran following patisiran treatment relative to sustained vutrisiran treatment. Efficacy endpoints will be summarized by visit on the mITT population and safety parameters (labs, ECGs, vital signs) will be summarized by visit on the Safety population. Baseline definitions will remain as previously defined.

4.9.2. Summaries During Vutrisiran Treatment

Data in the vutrisiran-treatment period will consist of all data on or after the first administration of vutrisiran treatment:

- For patients randomized to vutrisiran, all data in the Treatment and Treatment Extension periods will be included
- For patients randomized to patisiran, all data in the Treatment Extension period will be included; data in the Treatment Period while on patisiran treatment will be excluded

Adverse events, concomitant medications, overall study drug exposure, and ADAs during the vutrisiran-treatment period will be summarized on the All vutrisiran-treated population. AE and ISR summaries described in Section 4.7.2 will also be provided for vutrisiran-emergent adverse events, defined as treatment-emergent adverse events occurring on or after the first dose of vutrisiran treatment.

4.10. COVID-19 Pandemic Impact Analyses

Additional data were collected to characterize the impact of the COVID-19 pandemic on general study conduct, disposition, and quality of life, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidances (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

4.10.1. General impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries as described in Section 4.1.

Impact on study participation due to COVID-19, including visit completion, visit location changes, and study drug dosing changes, will be summarized overall on the patient level with both continuous and categorical descriptives, and overall and by visit on the event level with categorical descriptives, based on the following categories.

4.10.2. Impact on Efficacy

Per protocol amendment 3 (17 July 2020), efficacy assessments that may be missed due to COVID-19 may be delayed up to 6 months after the scheduled timepoint to minimize missed endpoint ascertainment. Such delayed efficacy assessments due to COVID-19 will be included in analyses as described in Section 3.7.

Additional analyses of the primary and key secondary endpoints will be conducted based on the Month 9 Efficacy PP population using an ANCOVA model at Month 9, and based on the Month 18 Efficacy PP population using an MMRM at Month 18. The Month 9 and Month 18 Efficacy PP populations are defined in Section 2. These analyses represent the initial visit windows for the efficacy assessments in place prior to the COVID-19 pandemic.

Due to the potential impact on aspects of quality of life in multiple ways (eg, infection, anxiety and stress from the pandemic, the potential for loss of employment, and the disruptions in physical activity and social interactions due to social distancing and the closure of public gathering places), additional information on specific impacts on quality of life associated with the COVID-19 pandemic will be collected. The derivation of Norfolk QoL-DN total score and Physical Functioning/Large Fiber domains will be modified for patients reporting any impacts on quality of life; these modifications are described in Section 7.1.2.

Summaries of missing efficacy data due to the COVID-19 pandemic will be included in missing efficacy data summaries as described in Section 3.6.2.

Given the measures specified in the protocol designed to ensure data integrity and the additional and modified efficacy analyses describe above, analyses excluding patients with COVID-19-related protocol deviations will not be prespecified, but may be considered post hoc if warranted.

4.10.3. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any SAE, any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths. AEs mapping to the COVID-19 custom query will be summarized by high level term and preferred term. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

An overall summary of AEs by pandemic phase will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any SAE, any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths. AEs and SAEs will be summarized by pandemic phase, SOC, and preferred term. The number and percentage of patients with AEs during the pandemic will also be summarized over time by SOC and preferred term.

Events will be considered during the pandemic if the event occurs on or after first confirmed case of COVID-19 based on the country where the study site is located, described in Section 7.3.

4.10.4. Other Impacts

Treatment duration will also be summarized by pandemic phase. Adverse event, study drug exposure, and efficacy listings will include identification of assessments occurring during the pandemic.

For patients reporting an AE mapped to the COVID-19 custom query, AEs and prior and concomitant medications will also be presented in separate data listings. Additionally, patient profiles will be provided.

5. CHANGES TO PLANNED ANALYSES

Modifications to planned analysis specifications from the protocol are documented below:

1. Section 2: The Safety population definition was modified to include all patients who received any amount of study drug, regardless of randomization status. The updated definition is consistent with the APOLLO study.

6. REFERENCES

Hodges JL,Lehmann EL. Rank Methods for Combination of Indepdendent Experiments in Analysis of Variance. Annals of Mathematical Statistics. 1962;33(2):482-97.

Rubin D. Multiple Imputation after 18+ Years. Journal of the American Statistical Association. 1996;91(434):473-89.

7. APPENDICES

7.1. Questionnaire/Scoring

In questionnaires, if multiple responses are provided to a single-response question, the question is deemed as missing.

7.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS)

Note: the mNIS+7 and NIS measurements are conducted in duplicate per time point. The average of 2 complete duplicate values will be reported, except in cases of missing or partially missing data as described in the table below.

Assessment Tool	Total Points	Components (maximum points)
Modified NIS+7	304	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • Quantitative sensory testing by body surface area including touch pressure (TP) and heat as pain (HP): QST-BSA$_{TP+HP5}$ (80) • ∑5 nerve conduction studies (10) – Ulnar compound muscle action potential (ulnar CMAP) – Ulnar sensory nerve action potential (ulnar SNAP) – Sural sensory nerve action potential (sural SNAP) – Tibial compound muscle action potential (tibial CMAP) – Peroneal compound muscle action potential (peroneal CMAP) • Postural blood pressure (BP) (2)
NIS	244	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • NIS-S: Sensation (32)

7.1.1.1. Modified Neuropathy Impairment Score (mNIS+7)

There are 5 components within mNIS+7 total score including NIS-W, NIS-R, QST, ∑5 NC, and postural BP, as described in detail below.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted].

7.1.1.2. Neuropathy Impairment Score (NIS)

The components of NIS include the following:

1. NIS-W as described in previous section.
2. NIS-R as described in previous section.
3. NIS-S is the sum of the finger and toe sensation components (touch pressure, pin-prick, vibration, joint position). Assessments are performed separately for the right- and left-hand side of the body. Scoring for the sensory assessment is 0 (normal), 1 (decreased) and 2 (absent). The maximum total score for NIS-S is 32.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.1.1.3. Algorithms for Setting Normal Deviates and Points

[redacted]

[redacted]

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

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

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

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

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

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

[redacted] [redacted]

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

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

Norfolk QoL-DN is a tool for assessing patients' perception of the effects of diabetes and diabetic neuropathy. There are 35 questions divided into 5 domains. The range of possible total scores is -4 to 136.

Part I: Symptoms

Items 1-7 (Part I) are a simple inventory of symptoms of neuropathy. The presence of the symptom is checked in whichever box applies, and an absence of a symptom is checked under "none." Positive responses are scored as 1; and negative responses, as 0.

Part II: Activities of Daily Life

Items 8-35 (Part II) pertain to Activities of Daily Life, and most of these are scaled on a 5-point Likert scale ranging from 0 ("Not a problem") to 4 ("Severe problem"). However, Questions 31 and 32 are scored differently. In Question 31, "Good", the middle item, is scored as 0. "Very Good" is scored as –1, "Excellent" is scored as –2. "Fair" is scored as 1, and "Poor" is scored as 2. In Question 32, "About the Same," the middle item, is scored as 0. "Somewhat better" is scored as –1, "Much better" is scored as -2. "Somewhat worse" is scored as 1, and "Much worse" is scored as 2.

Subscales and Scoring Algorithm

The Total QOL and 5 domains should be summed as follows:

- Total QOL (35 items) [redacted]
- Physical Functioning/Large Fiber (15 items) [redacted]
- Activities of Daily Living (ADLs) (5 items) [redacted]
- Symptoms (8 items) [redacted]
- Small Fiber (4 items) [redacted]
- Autonomic (3 items) [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

7.1.3. EuroQol-5-Dimension 5-Level (EQ-5D-5L)

Each of the 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) is scored on a 5-point Likert scale from 1 (“I have no problems/pain/anxiety”) to 5 (“I am unable to…,” “I have extreme anxiety/depression”).

The 5 scores are concatenated together (in the order of Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) to create an EQ-5D-5L profile (e.g., 11111, 55555). The profile is then used to obtain an index value using the United States value set. The index values range from –0.109, associated with a profile of 55555, to 1.0, associated with a profile of 11111. Smaller index values indicate greater impairment.

Missing values are handled as follows:

- Missing items are coded as “9” in creating patient profiles.
- The index value is deemed as missing when responses are missing for 1 or more of the 5 dimensions.
- If the entire instrument is missing, the EQ-5D-5L index value is considered as missing.

7.1.4. 10-Meter Walk Test (10-MWT)

Two replicate assessments are expected to be performed approximately 24 hours apart and no more than 7 days apart per protocol. At baseline and for each postbaseline visit, the walk speed (m/s) analysis value is derived as follows:

Table 9: 10-MWT Derivation Scenarios

Scenario	Derivation
Both replicate assessments nonmissing	
Patient able to walk for both assessments	10/mean(time 1, time 2)
Patient unable to walk for 1 of the 2 assessments	mean(0, 10/assessable time)
Patient unable to walk for both assessments	0
One replicate assessment nonmissing	
Patient able to walk	10/assessable time
Patient unable to walk	0

7.1.5. Modified Body Mass Index (mBMI)

In the APOLLO study, mBMI was not assessed at Months 9 or 18. For the placebo (APOLLO) group, these assessments are derived as follows:

- Month 9 = mean of Day 189 (Week 27) and Day 357 (Week 51) assessments
- Month 18 = Day 546 (Week 78) assessment

7.1.6. Rasch-Built Overall Disability Scale (R-ODS)

The R-ODS consists of 24 items scored on a scale of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty). A total score will be calculated as the average of all nonmissing items multiplied by 24 if at least 90% of the items are nonmissing. The total score will be deemed as missing if more than 10% of the items (3 or more items) are missing.

7.2. Pattern-Mixture Model Details

Similar to the primary analysis methods, for the Month 9 analyses, assessments after initiation of local standard treatment will be treated as missing and thus imputed following the PMM procedure.

As an initial step, separate intermediate datasets for mNIS+7 and Norfolk QoL-DN total score will be prepared, which will include the key variables listed in Table 10.

[redacted] [redacted]

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

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

The following steps will be followed separately for the PMM analysis of change from baseline in mNIS+7 and Norfolk QoL-DN total score at Month 9.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3. Pandemic Phase Start Dates by Country

Table 7: Pandemic Phase Start Dates by Country

Country	**Date of 1st Confirmed Case**
Argentina	2020-03-03
Australia	2020-01-25

Country	**Date of 1st Confirmed Case**
Belgium	2020-02-04
Brazil	2020-02-26
Bulgaria	2020-03-08
Canada	2020-01-26
Cyprus	2020-03-09
France	2020-01-24
Germany	2020-01-28
Greece	2020-02-26
Italy	2020-01-29
Japan	2020-01-14
Korea	2020-01-19
Malaysia	2020-01-25
Mexico	2020-02-28
Netherlands	2020-02-27
Portugal	2020-03-02
Spain	2020-01-31
Sweden	2020-01-31
Taiwan	2020-01-22
United Kingdom	2020-01-31
United States	2020-01-20

As reported by the World Health Organization and the Taiwan Centers for Disease Control.

8. AMENDMENT HISTORY

Amendment 1: 17 July 2020

The Sponsor developed this SAP amendment without knowledge of postbaseline efficacy data in accordance with the Data Integrity Plan. Key changes include:

- Updates reflecting cumulative changes made after the original ALN-TTRSC02-002 protocol (11 October 2018) [amendment 1 (10 October 2019), amendment 2 (06 May 2020), and amendment 3 (17 July 2020)], including:
  - Changes to primary and secondary endpoints and associated MCP
  - Changes and/or additions to derivations, summaries, and analyses to account for and/or characterize the impact of the COVID-19 pandemic
- Updates reflecting feedback received from the FDA on the original statistical analysis plan and data submission plan
- Addition of summaries to characterize the long-term efficacy and safety of vutrisiran
- Addition of prefilled syringe vs vial summaries

Section	**Description**	**Rationale**
Throughout document	Updated co-primary endpoint language to primary and key secondary	To align with protocol amendment 3 revised endpoints
Section 1	Updated study design and objectives	To align with protocol amendment 3 updated language
Section 1.3.1 Section 1.3.2	Updated MCP and add MCP for EU/other regions	To align with updated primary/secondary endpoints; to specify a separate MCP reflecting EMA/SAWP's preference to evaluate efficacy through Month 18, which will be used for potential future submissions in other regions
Section 2 Section 4.4.3.3	Updated TTR percent reduction definition and associated TTR PP population and analyses	To reflect protocol amendment 2 change to analyze TTR percent reduction at Month 18 instead of Month 9 per protocol amendment 3; name revised to make distinct from added efficacy PP population
Section 2	Added efficacy PP population	To support analyses related to COVID-19 pandemic impact on efficacy to estimate treatment effects in an 'unimpacted' population
Section 2	Added all vutrisiran-treated population	To support long-term safety analyses during vutrisiran treatment
Section 3.2	Updated presented treatment groups	To clarify planned presentations with respect to data submission plan
Section 3.6.2	Updated missing efficacy data summary	To account for missingness associated with COVID-19 pandemic
Section 3.7	Added extended efficacy analysis windows	To allow inclusion of efficacy visit data delayed due to COVID-19 pandemic

Section	Description	Rationale
Section 4.1	Updated patient disposition summaries	To clarify time windows to align with efficacy analysis timepoints; to account for discontinuations associated with COVID-19 pandemic
Section 4.2	Added summary of COVID-19-related protocol deviations	To align with regulatory guidance recommendations
Section 4.4	Added details on Month 9 and 18 analyses	To clarify data intended to be cleaned and included in planned analysis submissions
Section 4.4.1.1	Added details on handling of patients with missing model covariates and factors Specify KPS to be included as continuous covariate	To clarify and align with approach used in APOLLO (ALN-TTR02-004) study
Section 4.4.1.3 Section 4.4.2.1 Section 4.4.2.2 Section 4.4.5	Added ANCOVA model for use in select sensitivity and subgroup analyses	To simplify models used for non-primary analyses
Section 4.4.2.2	Updated propensity score model covariates and factors	To incorporate FDA feedback on initial SAP to include additional potential sources of differences in treatment assignment propensity to achieve the best predictive model
Section 4.4.2.3	Added pattern-mixture model sensitivity analysis	To incorporate FDA feedback on original SAP to assess the robustness of results under MNAR assumptions
Section 4.4.3.1 Section 7.1.2	Added key secondary endpoint section Updated primary Norfolk derivation and added sensitivity analysis using original derivation	To align with protocol amendment 3 revised endpoints (Norfolk changed from co-primary to key secondary) To mitigate for potential COVID-19 pandemic impact on quality of life on select Norfolk items in the primary analysis
Section 4.4.4	Changed all-cause deaths and/or all-cause hospitalization analyses to exploratory	To align with protocol amendment 3 revised endpoints
Section 4.4.5 Section 4.4.6	Added Month 18 subgroup and component analyses	To support characterization of efficacy profile at Month 18 for consistency with the APOLLO study
Section 4.7.1	Added definitions of complete vs partial dose administrations	To clarify definitions aligning with CRF data collection instructions
Section 4.7.1 Section 4.7.2	Added prefilled syringe vs vial summaries	To support regulatory assessment of vutrisiran administration via prefilled syringe
Section 4.7.2	Added inclusion of external placebo comparison group	To incorporate FDA feedback on data submission plan to facilitate AE safety comparisons to the APOLLO study
Section 4.9	Added analyses of data in the Treatment Extension Period	To support long-term efficacy and safety objectives

Section	Description	Rationale
Section 4.10 Section 4.4.2.5	Added summaries of COVID-19 pandemic general impact and related impacts on efficacy and safety	To assess the impact of COVID-19 in acknowledgement of regulatory guidances
Section 6	Updated references and added in-text citations where appropriate	To document sources
Throughout document	Added minor definition details, summaries, and protocol-amendment updates Removed selected analyses Aligned tables with related in-text revisions Corrected general typographic and formatting errors Updated abbreviations	To streamline and clarify planned analyses needed to support overall objectives and address minor errors

Approval	[redacted]+0000

Approval	[redacted]1:22 GMT+0000

Approval	[redacted]+0000

STATISTICAL ANALYSIS PLAN
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:	Vutrisiran (ALN-TTRSC02)
EudraCT Number:	2018-002098-23
IND Number:	139086
Protocol Version and Date:	Original: 11 October 2018 Amendment 3: 17 July 2020
Analysis Plan Version and Date:	Original: 30 January 2019 Amendment 1: 20 July 2020 Amendment 2: 15 October 2020
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted] [redacted]

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without expressed written authorization of Alnylam Pharmaceuticals, Inc.

APPROVAL SIGNATURE PAGE

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)

Protocol: ALN-TTRSC02-002

Analysis Plan Version and Date: Amendment 2: 15 October 2020

This document has been authored by the following:

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

This document has been approved and signed electronically on the final page by the following:

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

[redacted]

[redacted]

Alnylam Pharmaceuticals, Inc.

TABLE OF CONTENTS

APPROVAL SIGNATURE PAGE 2
TABLE OF CONTENTS 3
LIST OF TABLES 6
LIST OF FIGURES 6
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 7
1. INTRODUCTION 10
1.1. Study Design 10
1.2. Study Objectives and Endpoints 13
1.3. Study Hypotheses 14
1.3.1. Multiple Comparisons Procedure (US/Japan/Brazil) 14
1.3.2. Multiple Comparisons Procedure (EU/Other Regions) 15
1.4. Sample Size Determination 16
2. PATIENT POPULATIONS 17
3. GENERAL CONSIDERATIONS 19
3.1. Computing Environment 19
3.2. General Methods 19
3.3. Baseline Definitions 19
3.4. Randomization Stratification Factors 20
3.5. Efficacy Censoring Rules 20
3.5.1. Initiation of Local Standard Treatment for hATTR Amyloidosis 20
3.5.2. Onset of Serious COVID-19 Adverse Events 21
3.6. Missing Data with Efficacy Endpoints 21
3.6.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints 21
3.6.2. Summary of Missing Data 21
3.7. Visit Windows 21
3.8. Interim Analyses 22
3.9. Planned Analyses 22
4. STUDY ANALYSES 23
4.1. Patient Disposition 23
4.2. Protocol Deviations 24
4.3. Demographics and Baseline Characteristics 24

4.4. Efficacy Evaluation 25
4.4.1. General Efficacy Methods 25
4.4.1.1. ANCOVA/MI 25
4.4.1.2. MMRM 26
4.4.1.3. ANCOVA 26
4.4.2. Primary Efficacy Evaluations 27
4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis or Post Serious COVID-19 AE 27
4.4.2.2. Sensitivity Analysis: Propensity Score 27
4.4.2.3. Sensitivity Analysis: Pattern-Mixture Model 28
4.4.2.4. Other Analysis: Binary Endpoint 29
4.4.2.5. Other Analysis: Efficacy PP Population 29
4.4.2.6. Overview of Primary Endpoint Analyses 29
4.4.3. Secondary Efficacy Evaluations 29
4.4.3.1. Key secondary endpoint: Norfolk QoL-DN Total Score 29
4.4.3.2. 10-meter Walk Test Speed, mBMI, and R-ODS 30
4.4.3.3. TTR Percent Reduction 30
4.4.3.4. Overview of Secondary Endpoint Analyses 30
4.4.4. Exploratory Efficacy Evaluations 31
4.4.5. Subgroup Analyses 32
4.4.6. Component/Domain Analyses 32
4.5. Pharmacodynamic Analyses 33
4.6. Pharmacokinetic Analyses 33
4.6.1. Study Variables 33
4.6.1.1. Concentration Data 33
4.6.1.2. Plasma Pharmacokinetic Parameters 34
4.6.2. Statistical Methods 34
4.7. Safety Analyses 35
4.7.1. Study Drug Exposure 35
4.7.2. Adverse Events 36
4.7.3. Laboratory Data 37
4.7.4. Vital Signs and Physical Examination 38
4.7.5. Electrocardiogram 38

4.7.6. Premedication 39
4.7.7. Prior and Concomitant Medications 39
4.7.8. Suicidality Questionnaire....40
4.8. Anti-Drug Antibody....40
4.9. Summaries of Treatment Extension Period Data....41
4.9.1. Summaries over the Duration of the Entire Study....41
4.9.2. Summaries During Vutrisiran Treatment 41
4.10. COVID-19 Pandemic Impact Analyses....41
4.10.1. General Impact....42
4.10.2. Impact on Efficacy....42
4.10.3. Impact on Adverse Events 43
4.10.4. Other Impacts....43
5. CHANGES TO PLANNED ANALYSES....44
6. REFERENCES 45
7. APPENDICES 46
7.1. Questionnaire/Scoring 46
7.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS) 46
7.1.1.1. Modified Neuropathy Impairment Score (mNIS+7) 46
7.1.1.2. Neuropathy Impairment Score (NIS)....48
7.1.2. Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN)....48
7.1.3. EuroQol-5-Dimension 5-Level (EQ-5D-5L)....50
7.1.4. 10-Meter Walk Test (10-MWT) 50
7.1.5. Modified Body Mass Index (mBMI)....50
7.1.6. Rasch-Built Overall Disability Scale (R-ODS) 51
7.2. Pattern-Mixture Model Details 51
7.3. Pandemic Phase Start Dates by Country 53
8. AMENDMENT HISTORY 55
8.1. Amendment 1: 17 July 2020....55
8.2. Amendment 2: 15 October 2020....57

LIST OF TABLES

Table 1: Multiple Comparisons Procedure (US/Japan/Brazil) 14

Table 2: Multiple Comparisons Procedure (EU/Other Regions) 15

Table 3: Postbaseline TTR Assessment Requirements by Treatment Group 18

Table 4: Analysis of Primary Endpoint mNIS+7 29

Table 5: Analysis of Secondary Endpoints 30

Table 6: QTc Derivation 39

Table 7: 10-MWT Derivation Scenarios 50

Table 8: Pattern-Mixture Model Intermediate Dataset 51

Table 9: Pandemic Phase Start Dates by Country 53

LIST OF FIGURES

Figure 1: Study Design 12

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
10-MWT	10-meter walk test
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATTR	Amyloid transthyretin
BMI	Body mass index
CI	Confidence Interval
CMAP	Compound muscle action potential
C_{max}	Observed peak concentration
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EQ-VAS	EuroQol visual analogue scale
FAP	Familial amyloidotic polyneuropathy, also known as hATTR amyloidosis with polyneuropathy
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
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
LLN	Lower limit of normal

Abbreviation	**Definition**
LS	Least-squares
LV	Left ventricle
mBMI	Modified body mass index
MCP	Multiple comparisons procedure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MNAR	Missing not at random
mNIS+7	Modified Neuropathy Impairment Score +7
NCS	Nerve conduction studies
NCS Σ5	NCS sum of 5 attributes
NIS	Neuropathy 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
PD	Pharmacodynamics
PK	Pharmacokinetics
PMM	Pattern-mixture model
PND	Polyneuropathy Disability
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
RBC	Red blood cell
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event

Abbreviation	**Definition**
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
siRNA	Small interfering ribonucleic acid
SMQ	Standardized MedDRA query
SNAP	Sensory nerve action potential
SOC	System organ class
t_{max}	Time of observed maximum concentration
TTR	Transthyretin
ULN	Upper limit of normal
V30M	Valine to methionine mutation at position 30
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan details comprehensive, technical specifications of the statistical analyses of the efficacy/safety data outlined and/or specified in the final protocol of Study ALN-TTRSC02-002. Specifications of tables, figures, and data listings are documented separately.

1.1. Study Design

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

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 to vutrisiran 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 vutrisiran administered as a subcutaneous (SC) injection once every 3 months (q3M) or patisiran 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.

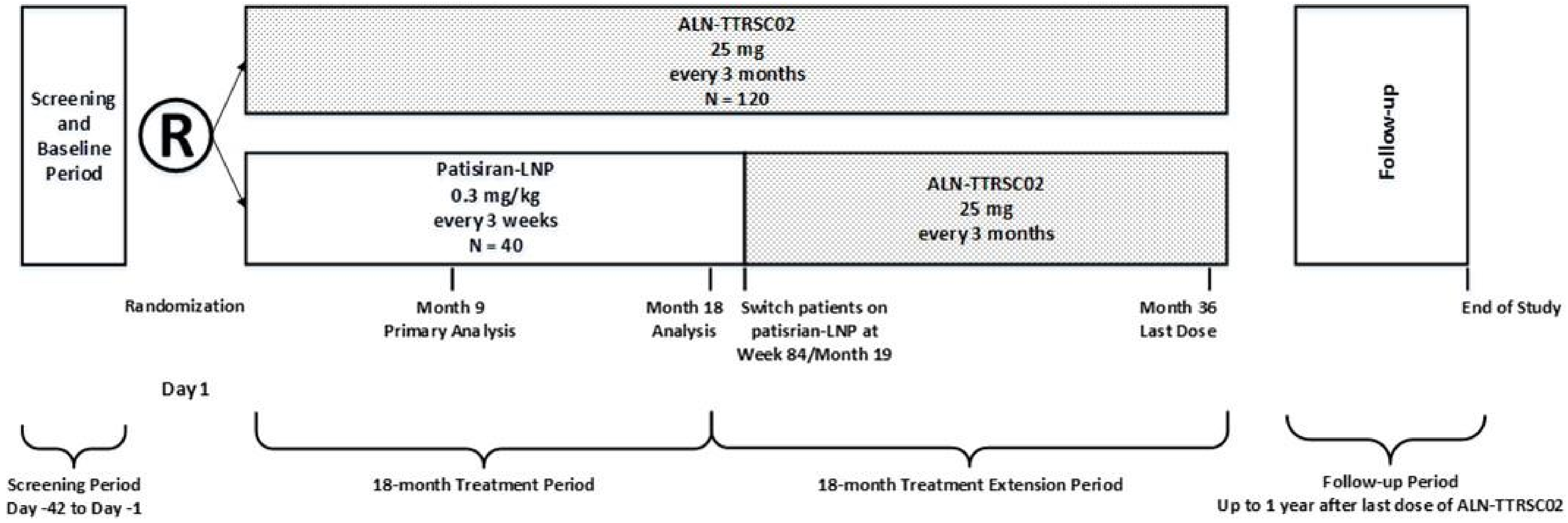
All efficacy visits must be conducted at the clinic (Month 9, Month 18, Month 27, Month 36, and modified efficacy visits). In situations in which a Month 9 or Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness 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 Study Month 15 or Month 24, respectively).

During the Treatment Extension Period, starting at Week 84/Month 19, all patients on the patisiran group will switch to treatment with vutrisiran (first dose) and remain on vutrisiran 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 vutrisiran 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 will undergo a follow-up visit 30 days after the last dose of study drug.

The placebo group of the APOLLO (ALN-TTR02-004) 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, and percent TTR reduction. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

Figure 1: Study Design


Screening and Baseline Period
R
ALN-TTRSC02
25 mg
every 3 months
N = 120
Patisiran-LNP
0.3 mg/kg
every 3 weeks
N = 40
ALN-TTRSC02
25 mg
every 3 months
Follow-up
Randomization
Month 9
Primary Analysis
Month 18
Analysis
Switch patients on
patisrian-LNP at
Week 84/Month 19
Month 36
Last Dose
End of Study
Day 1
Screening Period
Day -42 to Day -1
18-month Treatment Period
18-month Treatment Extension Period
Follow-up Period
Up to 1 year after last dose of ALN-TTRSC02

1.2. Study Objectives and Endpoints

The primary and most secondary and exploratory efficacy endpoints are in comparison to the placebo group of the Phase 3 pivotal patisiran-LNP study (APOLLO study) as specified in the statistical analysis section of the ALN-TTRSC02-002 (HELIOS-A) protocol.

Objectives	Endpoints
Primary	
• To determine the efficacy of vutrisiran in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment	• Change from baseline in the Modified Neuropathy Impairment Score +7 (mNIS+7) compared to the placebo group of the APOLLO study at Month 9
Secondary	
• To determine the efficacy of vutrisiran on quality of life, gait speed, neurologic impairment, nutritional status, and disability • To demonstrate the noninferiority of vutrisiran compared to patisiran with respect to serum TTR levels	• Change from baseline in the following parameters compared to the placebo group 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 vutrisiran group compared to the within-study patisiran group through Month 18
Exploratory	
• To determine the effect of vutrisiran 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 vutrisiran and patisiran on serum TTR and vitamin A levels • To characterize plasma pharmacokinetics (PK) of vutrisiran and patisiran • To assess presence of antidrug antibodies (ADA) to vutrisiran and patisiran	• Change from baseline in the following parameters compared to the placebo group of the APOLLO study at Month 9: – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R ODS) • 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 – Neuropathy Impairment Score (NIS) – EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the EuroQol-Visual Analog Scale (EQ-VAS)

Objectives	Endpoints
	– 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 vutrisiran and patisiran • Incidence and titers of ADA to vutrisiran and patisiran
Safety	
• To determine the safety and tolerability of vutrisiran in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

1.3. Study Hypotheses

For most inferentially-evaluated efficacy endpoints, the null hypothesis for the superiority comparison of vutrisiran vs placebo is defined as follows:

H_0: No difference between vutrisiran and placebo (APOLLO): difference (vutrisiran – placebo) = 0

For the TTR percent reduction endpoint, the null hypothesis for the noninferiority comparison of vutrisiran vs patisiran is defined as follows:

H_0: Vutrisiran is inferior to patisiran: difference in median TTR reduction (vutrisiran – patisiran) ≤ -10%

1.3.1. Multiple Comparisons Procedure (US/Japan/Brazil)

In the US, Japan, and Brazil, the overall familywise error rate will be controlled at α=0.05 for the primary and secondary endpoint hypothesis tests as follows:

Table 1: Multiple Comparisons Procedure (US/Japan/Brazil)

MCP Step[a]	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
Evaluated at the Month 9 analysis timepoint			
1	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
3	10-MWT gait speed change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
Evaluated at the Month 18 analysis timepoint			

MCP Step[a]	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
4	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
5	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
6	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
7	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
8	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
9	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%

[a] Per serial gatekeeping MCP, if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.

LCB=lower confidence bound; MCP=multiple comparisons procedure.

For the US filing, results for both the primary endpoint, mNIS+7 change from baseline at Month 9, and key secondary endpoint, Norfolk QoL-DN total score change from baseline at Month 9, must be statistically significant to declare a positive trial. For filings in Japan and Brazil, a positive trial will be declared if the result for the primary endpoint is statistically significant.

1.3.2. Multiple Comparisons Procedure (EU/Other Regions)

In the EU, during its scientific advice procedure, the EMA/CHMP/SAWP indicated a preference for a marketing authorization application based upon 18 months data. Therefore, the Month 9 endpoints included in the US/Japan/Brazil multiple comparisons procedure (MCP) will not be included in the MCP for the EU and other regions, where instead mNIS+7 change from baseline at Month 18 will be considered the primary endpoint. The overall familywise error rate in the EU and other regions will be controlled at α=0.05 for the primary and secondary endpoint hypothesis tests as follows:

Table 2: Multiple Comparisons Procedure (EU/Other Regions)

MCP Step[a]	Endpoint	Comparison group vs Vutrisiran	MCP Criteria
Evaluated at the Month 18 analysis timepoint			
1	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
3	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α

MCP Step[a]	**Endpoint**	**Comparison group vs Vutrisiran**	**MCP Criteria**
4	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
5	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
6	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%

[a] Per serial gatekeeping MCP, if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.
LCB=lower confidence bound; MCP=multiple comparisons procedure.

For filings in the EU and other regions, results for the primary endpoint, mNIS+7 change from baseline at Month 18, must be statistically significant to declare a positive trial.

References to the primary and secondary endpoints in the remainder of this document refer to those endpoints defined in the study objectives and endpoints (Section 1.2), corresponding to the US/Japan/Brazil MCP (Section 1.3.1).

1.4. Sample Size Determination

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

The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of vutrisiran in this patient population. For the primary efficacy endpoint of mNIS+7 and the secondary endpoint of Norfolk QoL-DN total score, the vutrisiran group in the Phase 3 study will be compared to the placebo group 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 group from the APOLLO study. Assuming a mean change of 0 points for the vutrisiran group, 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 group from the APOLLO study. Assuming a mean change of -4 points for the vutrisiran group, 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 vutrisiran 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 baseline NT-proBNP values greater than 3000 ng/L.

2. PATIENT POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data in this study, and for applicable analyses, relevant data from the APOLLO study.

- Modified Intent-to-Treat (mITT) population: All randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment to which they were randomized.
- TTR Per-protocol (PP) Population: All mITT population patients with a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment between Months 6 (Week 24) and Month 18 [Week 72]) that meets the requirements described in Table 3. Patients will be analyzed according to the treatment to which they were randomized.
- Month 9 Efficacy PP Population: All mITT population patients treated with vutrisiran or placebo meeting the following criteria:
    - Month 9 efficacy visit date within 3 calendar months of protocol-planned Month 9 efficacy visit window
    - No serious or severe COVID-19 custom query AE terms or reported on or before Month 9 efficacy visit date
    - For vutrisiran-treated patients, received all planned vutrisiran doses up to and including Week 36 with ≤ 28 day delay

  Patients will be analyzed according to the treatment to which they were randomized.
- Month 18 Efficacy PP Population: All mITT population patients treated with vutrisiran or placebo meeting the following criteria:
    - Month 18 efficacy visit date within 3 calendar months of protocol-planned Month 18 efficacy visit window
    - No serious or severe COVID-19 custom query AE terms reported on or before Month 18 efficacy visit date
    - For vutrisiran-treated patients, received all planned vutrisiran doses up to and including Week 72 with ≤ 28 day delay

  Patients will be analyzed according to the treatment to which they were randomized.
- Cardiac Subpopulation: All mITT population patients who had preexisting evidence of cardiac amyloid involvement, defined as patients with baseline left ventricular (LV) wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history. Patients will be analyzed according to the treatment to which they were randomized.
- Safety population: All patients who received any amount of study drug. Patients will be analyzed according to the treatment received.
- Pharmacokinetic (PK) population: All randomized patients who received at least one full dose of study drug and have at least 1 postdose blood sample for PK parameters

and have evaluable PK data. Patients will be analyzed according to the treatment received.

- All vutrisiran-treated population: All randomized patients who received any amount of vutrisiran treatment, including patients who took vutrisiran during the 18-month treatment period and patients who first receive vutrisiran during the 18-month treatment extension period.

Efficacy analyses (except TTR) and PD summaries will be conducted in the mITT population unless otherwise specified. The noninferiority of TTR will be assessed using the TTR PP population. Safety analyses will be conducted in the Safety population. PK analyses will be conducted in the PK population. The All vutrisiran-treated population will be used to summarize long-term efficacy and safety data during vutrisiran treatment.

Table 3: Postbaseline TTR Assessment Requirements by Treatment Group

Treatment Group	Postbaseline TTR Assessment Requirements
Vutrisiran or Patisiran	• Assessment must be before administration of study drug at the current visit • Assessment after initiation of local standard treatment for hATTR amyloidosis excluded (Section 3.5)
Vutrisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 12 weeks before the TTR assessment • Patient must receive planned, complete administration of study drug at 2 consecutive planned treatment visits at any time before the TTR assessment visit to ensure steady state
Patisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 3 weeks before the TTR assessment

3. GENERAL CONSIDERATIONS

3.1. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software version 9.4 (or later), unless otherwise noted. Figures may be generated using R version 3.6 (or later).

3.2. General Methods

All data listings that contain an evaluation date will contain a study day relative to the day of the first dose of study drug, which is designated as Day 1. On-treatment study days will be calculated as evaluation date – first dose date +1 and pretreatment days will be calculated as evaluation date – first dose date. There is no Day 0.

Categorical descriptives will include the count and percentage of patients (or events, if applicable) within each category (with a category for missing data) of the parameter. Continuous descriptives will include the number of patients, mean, median, standard deviation (SD), standard error (SE), minimum, and maximum values.

Laboratory data (including vitamin A) collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

For assessments that are repeated multiple times for the study visit, the average will be calculated unless otherwise noted.

All summaries will be presented by treatment group. Unless otherwise specified, treatment groups in the treatment period will be presented using the following labels:

- Placebo (APOLLO)
  - Presented primarily for efficacy (except TTR) analyses and most AE and baseline summaries
- Vutrisiran (HELIOS-A)
- Patisiran (HELIOS-A)
- Total (HELIOS-A)
  - Presented primarily for patient disposition, protocol deviations, and baseline summaries

In addition, for TTR sensitivity analyses, the following treatment groups will be presented:

- Patisiran (HELIOS-A + APOLLO)
- Patisiran (APOLLO)

3.3. Baseline Definitions

For the mNIS+7/NIS individual components, total scores and related endpoints, the 2 baseline assessments are performed on separate days. Baseline will be calculated as the mean of the nonmissing replicate measures.

For 10-MWT, 2 baseline assessments are performed on separate days. Baseline will be calculated as described in Section 7.1.4.

For PD parameters (TTR, Vitamin A), baseline will be defined as the average of all records, including those from any unscheduled visits, before the date and time of first dose.

For all other parameters, unless noted otherwise, baseline will be defined as the last nonmissing measurement on or before the first dose date.

3.4. Randomization Stratification Factors

Stratification factors for randomization include TTR genotype (V30M vs. non-V30M) and baseline NIS score (< 50 vs. ≥ 50).

Stratification factors are recorded in both the Interactive Response System (IRS) and the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database. In the presence of stratification errors, the stratification used in analysis may not match that in the IRS.

3.5. Efficacy Censoring Rules

3.5.1. Initiation of Local Standard Treatment for hATTR Amyloidosis

In the APOLLO study, there were placebo-treated patients who discontinued study drug, but remained on study and received local standard treatment. For the primary analysis of mNIS+7 and Norfolk QoL-DN, assessments were censored (excluded from analysis) after initiation of any of the following:

- Orthotopic liver transplant
- Use of TTR stabilizing agents (eg, tafamidis, diflunisal) for >14 days

For consistency of data handling, the placebo group from the APOLLO study will follow the same censoring rule as the APOLLO study.

For this study, APOLLO censoring rules will be applied. Additionally, assessments will be censored after initiation of any of the following recently approved treatments:

- Any use of TTR-targeting anti-sense oligonucleotides (eg, inotersen)
- Any use for patisiran (applicable for the vutrisiran treatment group only)

This data will be included and flagged in efficacy listings. These assessments from either study will be included in sensitivity analyses as specified.

For TTR percent reduction, TTR assessments collected after initiation of local standard treatment for hATTR amyloidosis will be excluded from the analysis. For all other efficacy endpoints, data from either study collected after initiation of local standard treatment for hATTR amyloidosis will be included in analyses.

A separate listing will be provided for patients who initiate local standard treatment for hATTR amyloidosis while on study.

3.5.2. Onset of Serious COVID-19 Adverse Events

Patients who experience a serious COVID-19 AE may have worsening in general health and wellbeing unassociated with the natural course of hATTR amyloidosis or with study drug. Assessments will be censored on or after the onset of a serious COVID-19 AE for all analyses of mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS, and any associated component/domain scores. This will reflect a hypothetical estimand of interest where the COVID-19 pandemic did not occur, as was the case for placebo group from the APOLLO study.

3.6. Missing Data with Efficacy Endpoints

All efficacy data collected during study, regardless of whether before or after treatment discontinuation, will be included for analyses, with the exception of mNIS+7 and Norfolk QoL-DN collected post local standard treatment for hATTR amyloidosis (discussed in Section 3.5), and mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS on or after the onset of a serious COVID-19 AE (Section 3.5.2).

3.6.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints

For each patient, missing subcomponents within the primary mNIS+7 endpoint and secondary efficacy endpoints will be imputed whenever possible according to the algorithms specified in Section 7.1. When this "partial imputation" is successful (ie, complete mNIS+7 values are produced), these values will be used in all statistical analyses. When partial imputation is unsuccessful, the efficacy endpoint will be treated as completely missing.

3.6.2. Summary of Missing Data

For each of the primary and secondary efficacy endpoints, the number and percentage of missing data (completely missing), including due to COVID-19, at each visit (Baseline, Month 9, and Month 18) will be summarized by study group.

3.7. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window.

For efficacy assessments, if the scheduled visit (eg, Month 9) is not performed, the unscheduled and/or discontinuation visits performed within a ± 3-month window will be grouped with the scheduled visit. 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, Month 9 and Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15 or Month 24, respectively). For patients impacted by the COVID-19 pandemic, efficacy visits delayed up to 6 months after the end of the protocol-defined efficacy visit window will be included in the analysis. The derived visits will be used for all analyses.

Unless otherwise specified above, data collected at unscheduled visits will be included in by-patient data listings and figures, but no assignment to a study visit will be made for the purpose of by-visit summary tabulations. However, unscheduled visits may be used in the calculation of baseline values (as discussed in Section 3.3) and for inclusion in any categorical shift summaries (e.g., shift from baseline to "worst" postbaseline value).

3.8. Interim Analyses

No interim analysis is planned for this study.

3.9. Planned Analyses

As this study will be ongoing at the time of the primary analysis at Month 9 and the additional analysis at Month 18, the study database will undergo an interim database lock at the Month 9 and Month 18 data cutoff dates (ie, data in EDC will be cleaned, frozen and electronically signed by investigators; external laboratory data will be cleaned and will undergo quality assurance). Additional details regarding the interim database locks will be documented in the study Data Management Plan.

The Month 9 and Month 18 analyses and associated clinical study reports (CSRs) will include all data on or before the respective data cutoff date. For assessments with start and end dates (eg, AEs, medications, medical history), data records with start dates after the specified data cutoff date will be excluded.

After the study is completed (ie, all patients complete the Treatment Extension Period and/or required follow-up visits), the database will undergo a final database lock, and the data will be summarized in a final CSR.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated for all randomized patients and will include categorical descriptives for the following parameters:

- Patients in each analysis population
- Patients randomized
- Patients treated
- Patients who complete or discontinue treatment
    - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete treatment through Month 9
- Patients who discontinue treatment before Month 9
    - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete treatment through Month 18
- Patients who discontinue treatment between Month 9 and Month 18 or through Month 18
    - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete treatment through Month 36
- Patients who discontinue treatment between Month 18 and Month 36
    - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete study participation
- Patients who stop study participation
    - Primary reasons for stopping study participation and stopping study participation due to COVID-19

Patient disposition by country and site will be summarized by randomized treatment group and overall. The number and percent of patients in each randomization stratification factor recorded in IRS, and a comparison of the number and percent of patients in each randomization stratification factor in IRS versus the clinical database will be summarized by randomized treatment group and in total.

Data listings of treatment/study completion information including the reason for treatment discontinuation and/or stopping participation in the study will be presented.

4.2. Protocol Deviations

Protocol deviations, including those related to COVID-19, will be defined in a separate document, including the process for major/minor classification.

All protocol deviations, COVID-19-related protocol deviations, and major protocol deviations will be summarized.

4.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics, baseline disease characteristics, baseline efficacy parameters, and medical history information will be summarized by treatment group and overall.

Age [years; at informed consent], height [cm], weight [kg], and body mass index (BMI) [kg/m^2] will be summarized using continuous descriptives. Age group (years) [<65; ≥65 to <75, ≥ 75], sex, race, ethnicity, and region [North America; Western Europe; Rest of World (Asia; Central and South America; Eastern Europe; Australia)] will be summarized using categorical descriptives.

The following baseline disease characteristics will be summarized by presenting categorical descriptives:

- Age at hATTR Symptom onset [< 50; ≥ 50]
- Neuropathy Impairment Score (NIS) [< 50; ≥ 50 & < 100; ≥ 100]
- Genotype [V30M; non-V30M]
- Early onset V30M [< 50 years of age at onset] vs. all other mutations [including late onset V30M]
- Previous tetramer stabilizer use [tafamidis or diflunisal] vs. no previous tetramer stabilizer use
- Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
- New York Heart Association (NYHA) Classification [No heart failure; I; II; III; IV]
- NT-proBNP [≤ 3000 ng/L; > 3000 ng/L]
- Cardiac Subpopulation [Yes; No]

Time (years) since diagnosis with hATTR will be summarized using descriptive statistics. For those who previously used tetramer stabilizers (tafamidis or diflunisal), the time from discontinuation of these previous therapies to the start of study drug will be summarized using descriptive statistics. Genotype by country will be summarized using categorical descriptives.

Continuous baseline efficacy parameters will be summarized using continuous descriptives. Categorical descriptives for baseline PND score (I, II, IIIA, IIIB, IV) and FAP stage (I, II, III) will also be summarized.

Medical history will be coded using the MedDRA coding system (version 23.0 or later) and will be summarized by system organ class (SOC), high level term (HLT), and preferred term. A patient contributes only once to the count for a given condition (overall, by SOC, by HLT, by preferred term).

All demographic and baseline data for each patient will be provided in data listings. Medical history data, including baseline cardiac and ophthalmology history, prior surgeries/procedures, and pregnancy test results, will be presented in a data listing. Screening test results will also be presented in data listings.

4.4. Efficacy Evaluation

This Phase 3 study will use 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.

Except for TTR endpoints, analysis models will include only the 2 treatment groups compared, vutrisiran and placebo (APOLLO), and only simple descriptives will be presented for patisiran (HELIOS-A). For TTR endpoints, vutrisiran and patisiran (HELIOS-A) will be compared unless otherwise specified.

For efficacy endpoints, 2-sided 95% confidence intervals and 2-sided nominal P values will be presented if applicable unless otherwise specified. Formal multiplicity-controlled hypothesis testing will be conducted as described in Section 1.3.1; all other P values presented will be considered descriptive.

4.4.1. General Efficacy Methods

Most continuous efficacy endpoints will be evaluated using an analysis of covariance (ANCOVA) model incorporating multiple imputation (MI) or a mixed-effects model for repeated measures (MMRM).

4.4.1.1. ANCOVA/MI

ANCOVA incorporating MI will be the default analysis for most continuous efficacy endpoints at Month 9.

MI is a broadly applicable technique for handling missing data. Missing data are imputed multiple times using a regression method. Each imputed data set is analyzed using the same analysis model, and the point estimates and standard errors are combined to provide inferences that reflect the uncertainty about the missing values. MI assumes the data are missing at random (MAR).

For a given endpoint, missing endpoint values will be multiply imputed separately for each treatment group using a regression procedure, with baseline information including baseline score and KPS as covariates and genotype, age at hATTR symptom onset, prior tetramer stabilizer use, region, FAP stage (I vs. II/III), Cardiac subpopulation, sex, and baseline NIS (<50 vs. ≥50) as factors. For NIS-related endpoints, the categorical baseline NIS score will not be included in the regression procedure.

One hundred imputed datasets (per treatment group) will be generated from the MI regression procedure using SAS PROC MI. Each of the imputed datasets will then be analyzed using an ANCOVA model, including a covariate (baseline value) and factors (treatment group; genotype; age of disease onset, baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

The resulting estimates (LS mean differences and standard errors) from the 100 imputed datasets will be combined using SAS PROC MIANALYZE to produce inferential results (difference in LS means, 95% CI for the difference, and the P value from the test that the difference is zero).[Rubin 1996] Combined LS mean estimates will be calculated as the average of the 100 complete-data estimates. A total variance estimate will be calculated as a weighted sum of within-imputation variance, which is the average of the complete-data variance estimates, and a between-imputation variance term. Complete details may be found in the SAS documentation for the MIANALYZE procedure (see Combining Inferences from Imputed Data Sets under Details: http://support.sas.com/documentation/onlinedoc/stat/131/mianalyze.pdf).

4.4.1.2. MMRM

MMRM will be the default analysis for most continuous efficacy endpoints at Month 18. MMRM makes use of fully and partially observed data sequences from individual patients by estimating the covariance between data from different time points. The MMRM will be implemented using an unstructured approach to modeling both the treatment-by-time means and the (co)variances, leading to what is essentially a multivariate normal model wherein treatment group means at the primary time point are adjusted to reflect both the actually observed data and the projected outcomes from the patients with missing data. MMRM also assumes data are missing at random (MAR).

For most endpoints, the MMRM will include a covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), and an interaction term (treatment group by visit), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

LS mean and mean difference estimates, SEs, 95% CIs, and p-values at Month 9 and Month 18 will be presented.

An unstructured covariance structure will be used to model the within-patient errors. If the model fails to converge, the following covariance structures will be specified in sequence and the first to converge will be used:

1. Toeplitz
2. First order autoregressive
3. Compound symmetry

The Satterthwaite approximation will be used to estimate the degrees of freedom.

4.4.1.3. ANCOVA

ANCOVA, without incorporating MI, will be the default Month 9 sensitivity and subgroup analyses unless otherwise specified. Patients who complete both baseline and Month 9 will be included in the analysis. For most endpoints, the ANCOVA will include a covariate (baseline value), and factors (treatment group; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

4.4.2. Primary Efficacy Evaluations

The primary endpoint is change from baseline at Month 9 for mNIS+7 (Section 7.1.1). The primary comparison will be conducted at Month 9. The primary endpoint will be analyzed using the general ANCOVA/MI methods.

Additionally, change from baseline at Month 18 for mNIS+7 will be analyzed as a secondary endpoint using the general MMRM methods, and Month 9 and 18 LS mean estimates from this MMRM will be presented graphically as well.

4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis or Post Serious COVID-19 AE

The primary analysis will not include assessments performed after the initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE (Section 3.5). Sensitivity analysis of mNIS+7 change from baseline including data post local standard treatment for hATTR amyloidosis or post serious COVID-19 AE from either study will be conducted using the ANCOVA method at Month 9 and MMRM method at Month 18.

4.4.2.2. Sensitivity Analysis: Propensity Score

To allow some control of more factors and covariates without saturating the model, a propensity score approach will be used to reduce the predictors to a single propensity score. The propensity score is defined as the probability of being treated with vutrisiran as obtained from a logistic regression model of treatment group [vutrisiran; placebo (APOLLO)]. The logistic regression model will include the following baseline variables:

- Continuous variables
  - NT-proBNP (log-transformed)
  - mNIS+7
  - Norfolk QoL-DN total score
- Categorical variables
  - Previous tetramer stabilizer use (tafamidis/diflunisal) [Yes; No]
  - Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
  - Cardiac Subpopulation [Yes; No]
  - PND score [I; II; IIIA; IIIB/IV]
  - Age at hATTR Symptom onset [< 50; ≥ 50]
  - Neuropathy Impairment Score (NIS) [< 50; ≥ 50]
  - Genotype [V30M; non-V30M]
  - FAP stage [I; II/III]

The primary endpoint will be analyzed in this sensitivity analysis using the ANCOVA method at Month 9 and MMRM method at Month 18, including the propensity score covariate in addition to the default model factors and covariates.

4.4.2.3. Sensitivity Analysis: Pattern-Mixture Model

The primary analysis ANCOVA/MI method addresses data under missing at random (MAR) assumptions. To assess the robustness of the primary analysis results under missing not at random (MNAR) assumptions, a sensitivity analysis using a pattern-mixture model (PMM) will be conducted at Month 9 using a modified ANCOVA/MI method.

The model will be based on the following assumptions:

1. Patients who have missing data due to COVID-19, including patients who have missing assessments, who have data censored because a serious COVID-19 AE was reported before Month 9, or who die due to COVID-19:
    a. Under the hypothetical estimand of interest where the COVID-19 pandemic did not occur, these assessments should have been obtained with no COVID-19 impact. Therefore, for patients meeting either of these criteria, assessments will be considered MAR, and will be imputed using MI estimated from all nonmissing data collected on treatment from the vutrisiran group.
2. Patients who have missing data unrelated to COVID-19 and are alive before Month 9:
    a. Placebo-treated patients who have missing data: The missing data are considered MAR and will be imputed using MI estimated from placebo-treated patients. The imputation is done regardless of whether a patient was on-treatment or discontinued treatment before the scheduled Month 9 efficacy assessment.
    b. Vutrisiran-treated patients who have missing data while on treatment: Patients are expected to continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, missing data during the on-treatment period (within 126 days of the patient's last dose before the scheduled Month 9 efficacy assessment) are considered MAR and will be imputed using MI estimated from all nonmissing data collected on treatment from the vutrisiran group. The 126-day window was selected given the long PD effect of vutrisiran.
    c. Vutrisiran-treated patients who have missing data after stopping their study treatment: Patients will no longer benefit from treatment in the future and will have trajectory similar to placebo-treated patients. Therefore, missing data after treatment discontinuation (more than 126 days after the patient's last dose of study drug before the scheduled Month 9 efficacy assessment) will be imputed using the data from placebo-treated patients.
3. Patients who have missing data and who die before Month 9 unrelated to COVID-19:
    a. Assuming deaths observed in the study will likely be related to worsening of disease, the missing data will be imputed by taking random samples from the worst 10% mNIS+7 change from baseline scores among vutrisiran- and placebo-treated patients at Month 9. The imputation will be done for patients from both vutrisiran and placebo groups.

Following the procedure describe above, 100 imputed datasets will be generated, and each imputed dataset will be analyzed and estimates combined following the same ANCOVA/MI model as the primary analysis.

More details on the implementation of PMM are discussed in Section 7.2.

4.4.2.4. Other Analysis: Binary Endpoint

The number and percentage of patients with a decrease (change from baseline < 0) in total score of mNIS+7 from baseline to Month 9 and to Month 18 will be summarized. The endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) test with Mantel-Haenszel odds ratios and associated CIs presented, stratified by genotype (V30M vs. non-V30M). Patients with missing change from baseline values due to COVID-19 will be excluded; all other patients with missing change from baseline values will be considered non-responders.

4.4.2.5. Other Analysis: Efficacy PP Population

To mitigate for the impact of the COVID-19 pandemic, mNIS+7 will also be analyzed using the Efficacy PP population; full details are provided in Section 4.10.2.

4.4.2.6. Overview of Primary Endpoint Analyses

The planned analyses of the primary endpoint mNIS+7 are summarized in Table 4.

Table 4: Analysis of Primary Endpoint mNIS+7

Statistical Method
Month 9: ANCOVA/MI
Month 18: MMRM
Sensitivity analysis: Including data post local standard treatment for hATTR amyloidosis or post serious COVID-19 AE (Month 9: ANCOVA; Month 18: MMRM)
Sensitivity analysis: Propensity score (Month 9: propensity-adjusted ANCOVA; Month 18: propensity-adjusted MMRM)
Sensitivity analysis: Pattern-mixture model with ANCOVA/MI at Month 9
Other analysis: Binary endpoint analysis using stratified CMH
Other analysis: Efficacy PP Population (Month 9: ANCOVA; Month 18: MMRM)

4.4.3. Secondary Efficacy Evaluations

4.4.3.1. Key secondary endpoint: Norfolk QoL-DN Total Score

Change from baseline in Norfolk QoL-DN total score (primary analysis incorporating COVID-19 pandemic impact questions, described in Section 7.1.2) will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. Sensitivity, binary, and Efficacy PP Population analyses for Norfolk QoL-DN total score will also be conducted as described for mNIS+7 in Section 4.4.2.

An additional sensitivity analysis of change from baseline in Norfolk QoL-DN total score (without incorporating COVID-19 impact questions, described in Section 7.1.2) will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18.

4.4.3.2. 10-meter Walk Test Speed, mBMI, and R-ODS

For 10-meter walk test speed (Section 7.1.4), mBMI (Section 7.1.5), and R-ODS (Section 7.1.6), change from baseline will be analyzed using an ANCOVA/MI model at Month 9 (with mBMI and R-ODS analyzed at Month 9 as exploratory endpoints), and using an MMRM at Month 18. Binary analyses for 10-meter walk test speed will also be conducted as described for mNIS+7 in Section 4.4.2.4.

4.4.3.3. TTR Percent Reduction

TTR percent reduction through Month 18 is defined as the average trough (ie, predose) TTR percent reduction from Month 6 to 18, which is the steady state period for both vutrisiran and patisiran. Only trough TTR assessments meeting requirements described in the TTR PP population definition (Section 2; Table 3) will be included. The Hodges-Lehmann method [Hodges and Lehmann 1962], stratified by previous TTR stabilizer use (yes vs no), where values within each stratum are first aligned by the within-stratum 1-sample Hodges-Lehmann median, will be used to estimate the 95% CI for the median difference between the vutrisiran and patisiran groups in this study. Non-inferiority of vutrisiran (versus patisiran) will be declared if the lower limit of the 95% CI for the median treatment difference in TTR percent reduction (vutrisiran - patisiran) in this study is greater than –10%.

Sensitivity analyses using the same analysis method will be conducted to compare the TTR percent reduction through Month 18 between the vutrisiran group from this study and the pooled patisiran group from this study and the APOLLO study.

4.4.3.4. Overview of Secondary Endpoint Analyses

The planned analyses of the secondary endpoints are summarized in Table 5 .

Table 5: Analysis of Secondary Endpoints

Endpoint	Statistical Method	Analysis Population	Special Notes
Norfolk QoL-DN total score	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.2 Sensitivity and binary analyses described in Section 4.4.2
10-meter walk test speed	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.4 Binary analyses described in Section 4.4.2.3
mBMI	Month 9 (exploratory endpoint): ANCOVA/MI Month 18: MMRM	mITT	In APOLLO study, mBMI was not assessed at Months 9 or 18. The average values of Day 189 and Day 357 will be derived as Month 9. Day 546 will be used as Month 18.
R-ODS	Month 9 (exploratory endpoint): ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 7.1.6

Endpoint	**Statistical Method**	**Analysis Population**	**Special Notes**
TTR percent reduction through Month 18	Stratified Hodges-Lehmann	TTR PP	Sensitivity analysis comparing against patisiran (HELIOS-A + APOLLO)

4.4.4. Exploratory Efficacy Evaluations

The exploratory continuous endpoints, including change from baseline in NIS (Section 7.1.1.2), EQ-5D-5L index (Section 7.1.3), and EQ VAS, will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. For EQ-5D-5L, categorical descriptives for ordinal response within each EQ-5D domain will be presented at each visit.

The exploratory categorical endpoints, PND score, FAP stage, NYHA class, and KPS, will be descriptively summarized by presenting categorical descriptives for each visit. Categorical descriptives for patients with improving, no change, and worsening in PND/FAP at each postbaseline visit will also be summarized.

Cardiac structure and function will be assessed for all patients through echocardiograms. Cardiac stress and injury will be measured using serum levels of the cardiac biomarkers NT-proBNP, troponin I, and troponin T. Quantification of these biomarkers will be performed at a central laboratory. Descriptive statistics will be provided for actual values, changes, and percentage changes from baseline in echocardiogram parameters and serum levels of troponin I, troponin T, and NT-proBNP by treatment group at each visit.

For the mITT Population, select echocardiographic parameters will be analyzed using an MMRM at Month 18, including:

- Mean left ventricular (LV) wall thickness
- LV mass
- Global longitudinal strain
- LV end-diastolic volume
- Cardiac output

Additionally, these select echocardiographic parameters will be analyzed at Month 18 for the Cardiac Subpopulation using an MMRM with covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]), and an interaction term (treatment group by visit).

Cardiac biomarker NT-proBNP will be analyzed for the mITT population using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. Additionally, NT-proBNP will be analyzed at Month 18 for the Cardiac Subpopulation using an MMRM with covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]), and an interaction term (treatment group by visit). A logarithmic transformation will be applied to both baseline and change from baselines values to normalize the data before fitting the MMRM. The adjusted geometric mean fold-change and the ratio of the fold-change (vutrisiran/placebo) from baseline will be presented.

For the mITT Population and Cardiac Subpopulation, change from baseline in heart-contralateral lung ratio as assessed by technetium scintigraphy will be summarized at Month 18.

All echocardiogram, cardiac, and technetium scintigraphy data will be presented in data listings.

Given the advanced disease setting where patients may experience recurrent hospitalizations, an analysis of time to first hospitalization or death does not characterize disease burden sufficiently. As such, the composite endpoint of all-cause deaths and/or all-cause hospitalizations over 18 months will be analyzed using the Andersen-Gill model, a survival analysis method accounting for recurrent events with covariate (baseline KPS) and factors (treatment group; age group; genotype). The endpoint will be analyzed for the mITT population.

4.4.5. Subgroup Analyses

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Region [North America; Western Europe; Rest of World]
  - Region groups may be adjusted if <20 patients included in any category
- NIS [< 50; ≥ 50]
- Previous tetramer stabilizer use [Yes; No]
- Genotype [V30M; non-V30M]
- FAP stage [I; II & III]
- Cardiac Subpopulation [Yes; No]

Subgroup analyses will be performed for the primary endpoint, mNIS+7, and key secondary endpoint, Norfolk QoL-DN, at Month 9 using separate ANCOVA models with covariate (baseline value) and factors (treatment group; genotype [not applicable to genotype subgroup analyses]), and at Month 18 using an MMRM with covariate (baseline value), factors (treatment group; visit; genotype [not applicable to genotype subgroup analyses]), and an interaction term (treatment group by visit). A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

4.4.6. Component/Domain Analyses

Component analyses will be conducted to assess the consistency of treatment effect on the change from baseline at Month 9 for each component of mNIS+7 (Section 7.1.1) and Norfolk QoL-DN domains (Section 7.1.2). The analyses will be performed at Month 9 using the ANCOVA/MI model used for the corresponding endpoint, and at Month 18 using the MMRM used for the corresponding endpoint . A forest plot will be generated to illustrate the estimated treatment effect along with 95% CIs for each component/domain.

4.5. Pharmacodynamic Analyses

The PD parameters include serum TTR and vitamin A. All summary tables and figures will be based on assessments within 21 days after last dose of patisiran or within 84 days after last dose of vutrisiran. Assessments more than 21 days after last dose of patisiran or more than 84 days after last dose of vutrisiran will be presented in listings and individual patient plots only.

Summary tables will be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group for TTR and vitamin A.

In addition to TTR percent reduction analyses specified in Section 4.4.3.3, the following parameters, derived using all available TTR samples within the specified windows (including nontrough and unscheduled), will be summarized using descriptive statistics:

- Maximum percentage reduction in serum TTR and vitamin A over 9 and 18 months
- Mean percentage reduction in serum TTR and vitamin A over 9 and 18 months
- Mean percentage reduction in serum TTR at steady-state from Month 6 to 9 and from Month 6 to 18

Subgroup analysis for maximum and mean percentage reduction in serum TTR described above will be provided for the following subgroups:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Previous tetramer stabilizer use [Yes; No]
- Genotype [V30M; non-V30M]
- Weight (kg) [(<65; ≥65]

Summary of TTR levels over time for patients in the patisiran group before and after the switch to vutrisiran will be presented to evaluate maintenance of serum TTR levels following switch from patisiran to vutrisiran.

All PD data will be displayed in data listings.

4.6. Pharmacokinetic Analyses

4.6.1. Study Variables

4.6.1.1. Concentration Data

For vutrisiran, plasma concentrations of ALN-TTRSC02(siRNA) will be obtained. For patisiran, plasma concentrations of ALN-18328(siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG will be obtained. Concentration values that are below the limit of quantification (LLOQ or BLQ) will be set to zero for analysis.

4.6.1.2. Plasma Pharmacokinetic Parameters

Model independent PK parameters to be calculated and summarized descriptively include:

- Study days 1 and 253:
  - Predose levels for vutrisiran and patisiran
  - Observed concentration 3-hour, 6-hour, 24-hour postdose (Cp [3 hr, 6 hr, 24hr]) for vutrisiran and 30-min, 6 hour, 24-hour postdose (Cp [30 min, 6 hr, 24 hr]) for patisiran
  - AUC0-24 for vutrisiran
  - Observed trough concentration (Ctrough) for patisiran
  - Observed maximum concentration (Cmax)
  - Time of observed maximum concentration (Tmax)
- All other visits:
  - Predose levels for vutrisiran and patisiran
  - Observed concentration 3-hour postdose (Cp [3 hr]) for vutrisiran and patisiran

4.6.2. Statistical Methods

Descriptive statistics for plasma concentration will include the number of patients, mean, SD, coefficient of variation (CV), geometric mean, geometric mean CV, median, minimum, and maximum.

The plasma Cmax, AUC, Cp (predose, 3 hr, 6hr, 24 hr), and Tmax of vutrisiran will be summarized by nominal sampling day as well as the plasma Cmax, Cp (predose, 30 min, 6 hr, 24 hr), C_{trough} and Tmax of ALN-18328 (siRNA), DLin-MC3-DMA and PEG_{2000}-C-DMG for patisiran. In addition, ratios of Day 253 vs Day 1 AUC (for vutrisiran only) and Cmax will be summarized. Mean concentrations (+SD) as well as individual concentrations will be plotted versus nominal sampling time.

Subgroup analysis of vutrisiran plasma Cmax, AUC, Tmax, and ratios of Day 253 vs Day 1 AUC and Cmax will be provided for the following subgroups:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Previous tetramer stabilizer use [Yes; No]
- Genotype [V30M; non-V30M]
- Weight (kg) [(<65; ≥65]

Plasma concentration data will be presented in by-patient listings.

The PK-PD relationship between the plasma concentration and the percent change from baseline in TTR protein and vitamin A will be explored graphically for vutrisiran and ALN-18328 (siRNA) of patisiran separately

The PK exposure-response relationships for primary endpoint (mNIS+7) and incidence of relevant AEs may also be explored. These may be summarized by exposure quartiles at 9-months for vutrisiran.

Population PK and exposure-response modeling will be reported separately.

4.7. Safety Analyses

Safety analyses will be conducted using the Safety population. All safety summaries will be descriptive and will be presented by treatment group.

4.7.1. Study Drug Exposure

Last exposure date is defined as the earliest of the following dates:

- Last dose date during the specified treatment period + treatment-specific window (83 days for vutrisiran; 27 days for patisiran)
- Analysis cutoff date
- End of study date

Duration of drug exposure will be defined as last exposure date – first dose date + 1. Duration of drug exposure, the total number of doses received, and total amount of study drug received will be summarized by descriptive statistics. Summaries of the numbers and percentages of patients with no missing dose, and the number of missing doses per patient will also be provided. The total volume infused or injected will be summarized as well.

Study drug exposure data collected in the CRFs of study drug administration will also be summarized for each dose or infusion. The numbers and percentages of patients with complete, partial, and missing dose administrations will be summarized. Complete and partial administration is defined as follows:

- Patisiran:
  - Complete: ≥80% (≥160 mL) of the planned infusion volume (200 mL)
  - Partial: >0% to <80% (>0 to <160 mL) of the planned infusion volume (200 mL)
- Vutrisiran:
  - Complete: 100% administered
  - Partial: >0% to <100% administered

For the patisiran group, the number of patients who experienced interruptions of infusions for any reason will be tabulated, as well as the number of patients with infusion interruptions due to an infusion-related reaction (IRR).

For the vutrisiran group, the above drug exposure summaries applicable to vutrisiran will also be provided by vial vs prefilled syringe dose presentations. Vutrisiran doses with missing dose presentation information before the date of first prefilled syringe administration to any patient will be treated as vial dose presentations.

Dosing information for each patient will be presented in a data listing.

4.7.2. Adverse Events

This Phase 3 study will use the APOLLO study as an external control. Patient-level data from this study will be compared with patient-level data from APOLLO for relevant AE summaries only.

AEs will be coded using the MedDRA coding system (version 23.0 or later) and displayed in tables and data listings using SOC and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, defined as any AE with onset during or after the administration of study drug through 28 days following the last dose of patisiran or 84 days following the last dose of vutrisiran. In addition, any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study will be considered treatment-emergent. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first administration of study drug.

Adverse events will be summarized by the numbers and percentages of patients reporting a given AE. A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Overall event counts and event rates may also be summarized.

An overall summary of AEs will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any serious AE (SAE), any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths.

Tabulations by SOC and preferred term will be produced for the following: all AEs; AEs related to treatment; severe AEs; AEs leading to infusion interruption (patisiran only); AEs leading to drug interruption; AEs leading to treatment discontinuation; AEs leading to stopping study participation; and SAEs. Adverse events and AEs related to treatment will also be tabulated by preferred term. Adverse events and SAEs will also be summarized by SOC and preferred term for the cardiac subpopulation. Subgroup tabulations by SOC and preferred term for AEs and SAEs will be provided for the following subgroups:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Region [North America; Western Europe; Rest of World]
    - Region groups may be adjusted if <20 patients included in any category
- Genotype [V30M; non-V30M]

- FAP stage [I; II & III]
- Weight (kg) [<65; ≥65]

Separate tables will present the number and percentage of AEs by maximum relationship to study drug and by maximum severity. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

AEs mapping to the standardized MedDRA queries (SMQs) Depression and Suicide/Self-injury, Torsade de pointes/QT prolongation, and Cardiac failure will be summarized by preferred term. Adverse events mapping to the SMQ Drug Related Hepatic Disorder and SMQ Acute Renal Failure will be summarized by SOC and preferred term. Adverse events mapping to Cardiac Arrhythmias high level group term and the SMQ Malignant or Unspecified Tumors will be summarized by high level term and preferred term. Other SMQs or AE groupings may be evaluated.

Separate tables will be provided summarizing signs and symptoms of IRRs (overall and by premedication regimen) and AEs related to premedication by SOC and preferred term for the patisiran group. Injection site reactions will be summarized for the vutrisiran group by presentation (vial vs prefilled syringe) and in total. The number and percentage of patients with AEs, ISRs, and IRRs over time will also be summarized by SOC and preferred term.

All AEs will be presented in patient data listings. Separate listings will be provided for death, SAEs, AEs leading to treatment discontinuation, AEs leading to stopping study participation, and AEs mapping to the SMQ as described above. A listing of ISRs will be provided for the vutrisiran group. Listing of IRRs and AEs related to premedications will also be provided for patisiran group. A listing of patients who underwent liver transplant will also be provided.

4.7.3. Laboratory Data

Clinical laboratory values will be expressed in SI units. Central laboratory data will be summarized. Local laboratory data will not be included for descriptive summaries by visit. For liver function test parameters, local laboratory data will be included in the derivation of “worst” or potentially clinically significant values under the following rules:

- Central laboratory data at both scheduled and unscheduled visits will be used
- If central laboratory data at a visit is missing, local laboratory data will be used
- If a patient has both local and central laboratory data at the same visit, the central data will be used

Summary tables and figures using central laboratory data alone and central and local laboratory data combined will be presented as applicable.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and liver function tests). Descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit.

A listing will be produced for all patients with abnormal liver function tests defined as an ALT > 3×ULN, AST > 3×ULN, and total bilirubin > 2×ULN at any time point.

A table will be produced to summarize the number and percentage of patients in each of the below categories at any postbaseline time point.

- ALT ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- AST ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- Maximum ALT or AST ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- ALP > 1.5 ×ULN,
- Total Bilirubin ≤ 1, > 1 & ≤ 1.5, > 1.5 & ≤ 2, > 2 & ≤ 3, > 3 & ≤ 5 and > 5 ×ULN,
- Total Bilirubin > 2 ×ULN concurrent with ALT or AST > 3 ×ULN.

A shift table from baseline to worst postbaseline for ALT, AST, and total bilirubin will also be provided. In separate figures, the peak total bilirubin (at any time postbaseline) will be plotted against the peak AST, the peak ALT, and the peak AST or ALT levels at any time postbaseline.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities will be provided. The results may also be graded according to the NCI CTCAE Version 5.0 or above. A shift summary of baseline to maximum postbaseline CTCAE grade may be presented, as appropriate.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) will be categorized as below: ≥ 90; ≥ 60 - < 90; ≥ 30 - < 60; ≥ 15 - < 30; and < 15. A shift summary of baseline to worst postbaseline eGFR category will be presented.

All laboratory data will be provided in data listings. Out-of-range laboratory results will be identified in the listings.

4.7.4. Vital Signs and Physical Examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. Summary tables of potentially clinically significant vital signs will be provided.

Vital sign measurements will be presented for each patient in a data listing.

4.7.5. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, and QTc interval. Baseline values will be the average of measurements from the baseline triplicate ECGs for each patient recorded. Descriptive statistics will be provided for each measure over time. Change from predose to each postdose assessment will also be summarized. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each study visit will also be summarized.

Corrected QT interval (QTc) will be calculated using the Fridericia's (QTcF) correction formula, derived as follows:

Table 6: QTc Derivation

Parameter	**Derivation**	
	If RR available	**If RR unavailable**
QTcF	$\dfrac{\text{QT (msec)}}{\text{Cubic root of RR (sec)}}$[a]	$\dfrac{\text{QT (msec)}}{\text{Cubic root of 60/HR (bpm)}}$

[a] RR (sec)=RR(msec)/1000.

QTcF=QTc Fridericia; HR = heart (ventricular) rate.

Categorical analyses of the QTc data will be conducted and summarized as follows:

- The number and percentage of patients with maximum increase from baseline in QTc (< 30, 30 – 60, >30, > 60 ms)
- The number and percentage of patients with maximum postbaseline QTc (< 450, 450 – < 480, 480 – 500, >480, > 500 ms)

All ECG data for each patient will be provided in a data listing. A separate listing will be provided for patients with any QTc postbaseline value > 500ms or an increase from baseline > 60 ms.

4.7.6. Premedication

Patisiran 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 histamine 1 (H1) blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous histamine 1 (H2) blocker (ranitidine 50 mg, or equivalent)

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

Premedications will be coded using the WHO Drug Dictionary (March 2020 or later). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Premedication data will be listed.

4.7.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (March 2020 or later). Prior medications include medications taken ≥ 1 time before the first dose of study drug, regardless of medication end date. Concomitant medications include medications taken ≥ 1 time on or after the first dose of study drug, regardless of medication start date. Results will be tabulated by ATC and preferred term.

When there are partial or missing dates, imputed dates will be used to determine 1) if a medication is prior or concomitant, and 2) duration of exposure of local standard treatment for hATTR amyloidosis. Imputed dates will not be presented in the listings.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug; medications will be classified as prior, concomitant or both depending on the medication stop dates. For medications with a completely missing stop date, the end of study date will be imputed.

For patients who receive local standard treatment (including liver transplant) for hATTR amyloidosis during the study, the type of treatment will be summarized categorically.

Prior and concomitant medications will be presented in data listings.

4.7.8. Suicidality Questionnaire

The number and percentage of patients experiencing the suicidal ideation, suicidal behavior, or self-injurious behavior composite outcomes (and individual components) will be summarized by visit. A shift table will be employed to summarize the baseline C-SSRS category versus the worst postbaseline C-SSRS category; the categories are defined as 1) no suicidal ideation or behavior, 2) suicidal ideation, and 3) suicidal behavior. Patients experiencing both suicidal ideation and suicidal behavior are included in the suicidal behavior category.

Data from the C-SSRS questionnaire will be provided in a data listing.

4.8. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at baseline and at any time during the Treatment Period, as well as treatment-emergent ADA during the Treatment Period, will be summarized. Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, defined as the following:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer > 4 x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

The titer results for patients with confirmed positive ADA and treatment-emergent ADA results will also be summarized using descriptive statistics.

For patients with confirmed positive ADA results, spaghetti plots for the serum TTR (ELISA) over time and the plasma concentration of vutrisiran and ALN-18328, DLin-MC3-DMA, and PEG2000-C-DMG for patisiran over time will be presented. Effect of positive ADA on efficacy and safety may also be explored.

ADA data and patients with confirmed positive ADA results will be presented in data listings.

4.9. Summaries of Treatment Extension Period Data

The study design includes an 18-month Treatment Period, where patients will be randomized to either vutrisiran or patisiran treatment, followed by an 18-month Treatment Extension Period, where all patients will receive vutrisiran treatment. The primary objective is to evaluate the efficacy and safety of vutrisiran during the initial 18-month Treatment Period; most analyses described in this SAP focus on this objective. Additionally, the long-term visit-based efficacy and safety of vutrisiran will be characterized over the entire study including the Treatment Extension Period, and the long-term period-based safety of vutrisiran will be characterized for the All vutrisiran-treated population.

4.9.1. Summaries over the Duration of the Entire Study

Descriptive summaries for visit-based parameters throughout the study, including the Treatment Extension period, will be conducted to characterize effect of vutrisiran following patisiran treatment relative to sustained vutrisiran treatment. Efficacy endpoints will be summarized by visit on the mITT population and safety parameters (labs, ECGs, vital signs) will be summarized by visit on the Safety population. Baseline definitions will remain as previously defined.

4.9.2. Summaries During Vutrisiran Treatment

Data in the vutrisiran-treatment period will consist of all data on or after the first administration of vutrisiran treatment:

- For patients randomized to vutrisiran, all data in the Treatment and Treatment Extension periods will be included
- For patients randomized to patisiran, all data in the Treatment Extension period will be included; data in the Treatment Period while on patisiran treatment will be excluded

Adverse events, concomitant medications, overall study drug exposure, and ADA during the vutrisiran-treatment period will be summarized on the All vutrisiran-treated population. AE and ISR summaries described in Section 4.7.2 will also be provided for vutrisiran-emergent adverse events, defined as treatment-emergent adverse events occurring on or after the first dose of vutrisiran treatment.

4.10. COVID-19 Pandemic Impact Analyses

Additional data were collected to characterize the impact of the COVID-19 pandemic on general study conduct, disposition, and quality of life, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidances (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

4.10.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries as described in Section 4.1.

Impact on study participation due to COVID-19, including visit completion, visit location changes, and study drug dosing changes, will be summarized overall on the patient level with both continuous and categorical descriptives, and overall and by visit on the event level with categorical descriptives, based on the following categories.

4.10.2. Impact on Efficacy

Per protocol amendment 3 (17 July 2020), efficacy assessments that may be missed due to COVID-19 may be delayed up to 6 months after the scheduled timepoint to minimize missed endpoint ascertainment. Such delayed efficacy assessments due to COVID-19 will be included in analyses as described in Section 3.7.

Additional analyses of the primary and key secondary endpoints will be conducted based on the Month 9 Efficacy PP population using an ANCOVA model at Month 9, and based on the Month 18 Efficacy PP population using an MMRM at Month 18. The Month 9 and Month 18 Efficacy PP populations are defined in Section 2. These analyses represent the initial visit windows for the efficacy assessments in place prior to the COVID-19 pandemic.

Additional descriptive summaries for the primary and secondary endpoints by pandemic phase will be provided. Pandemic phase definitions may vary over time given the evolving nature of the COVID-19 pandemic; potential definitions may include the following:

- Before and during pandemic, where assessments will be considered during the pandemic if the event occurs on or after first confirmed case of COVID-19 based on the country where the study site is located, described in Section 7.3.
- Before March 2020, between March 2020 and June 2020, and after June 2020.

Due to the potential impact on aspects of quality of life in multiple ways (eg, infection, anxiety and stress from the pandemic, the potential for loss of employment, and the disruptions in physical activity and social interactions due to social distancing and the closure of public gathering places), additional information on specific impacts on quality of life associated with the COVID-19 pandemic will be collected. The derivation of Norfolk QoL-DN total score and Physical Functioning/Large Fiber domains will be modified for patients reporting any impacts on quality of life; these modifications are described in Section 7.1.2.

Summaries of missing efficacy data due to the COVID-19 pandemic will be included in missing efficacy data summaries as described in Section 3.6.2.

Given the measures specified in the protocol designed to ensure data integrity and the additional and modified efficacy analyses describe above, analyses excluding patients with COVID-19-related protocol deviations will not be prespecified, but may be considered post hoc if warranted.

4.10.3. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will include the number and percentage of patients, as well as events and event rates, with any AE, any severe AE, any SAE, any AE leading to treatment discontinuation, any AE leading to study discontinuation, and any deaths. AEs mapping to the COVID-19 custom query will be summarized by high level term and preferred term. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

An overall summary of AEs by pandemic phase will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any SAE, any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths. AEs and SAEs will be summarized by pandemic phase, SOC, and preferred term. The number and percentage of patients with AEs during the pandemic will also be summarized over time by SOC and preferred term.

4.10.4. Other Impacts

Treatment duration will also be summarized by pandemic phase. Adverse event, study drug exposure, and efficacy listings will include identification of assessments occurring during the pandemic.

For patients reporting an AE mapped to the COVID-19 custom query, AEs and prior and concomitant medications will also be presented in separate data listings. Additionally, patient profiles will be provided.

5. CHANGES TO PLANNED ANALYSES

Modifications to planned analysis specifications from the protocol are documented below:

1. Section 2: The Safety population definition was modified to include all patients who received any amount of study drug, regardless of randomization status. The updated definition is consistent with the APOLLO study.
2. Section 1.3.1 and Section 1.3.2: Language was added to specify US-specific positive trial criteria in accordance with FDA advice (received 14 September 2020), ie, both the primary and key secondary endpoints are deemed statistically significant. Additional language was added to clarify the implicit positive trial criteria for other regions.

6. REFERENCES

Hodges JL,Lehmann EL. Rank Methods for Combination of Indepdendent Experiments in Analysis of Variance. Annals of Mathematical Statistics. 1962;33(2):482-97.

Rubin D. Multiple Imputation after 18+ Years. Journal of the American Statistical Association. 1996;91(434):473-89.

7. APPENDICES

7.1. Questionnaire/Scoring

In questionnaires, if multiple responses are provided to a single-response question, the question is deemed as missing.

7.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS)

Note: the mNIS+7 and NIS measurements are conducted in duplicate per time point. The average of 2 complete duplicate values will be reported, except in cases of missing or partially missing data as described in the table below.

Assessment Tool	Total Points	Components (maximum points)
Modified NIS+7	304	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • Quantitative sensory testing by body surface area including touch pressure (TP) and heat as pain (HP): QST-BSA$_{TP+HP5}$ (80) • ∑5 nerve conduction studies (10) – Ulnar compound muscle action potential (ulnar CMAP) – Ulnar sensory nerve action potential (ulnar SNAP) – Sural sensory nerve action potential (sural SNAP) – Tibial compound muscle action potential (tibial CMAP) – Peroneal compound muscle action potential (peroneal CMAP) • Postural blood pressure (BP) (2)
NIS	244	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • NIS-S: Sensation (32)

7.1.1.1. Modified Neuropathy Impairment Score (mNIS+7)

There are 5 components within mNIS+7 total score including NIS-W, NIS-R, QST, ∑5 NC, and postural BP, as described in detail below.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

7.1.1.2. Neuropathy Impairment Score (NIS)

The components of NIS include the following:

1. NIS-W as described in previous section.
2. NIS-R as described in previous section.
3. NIS-S is the sum of the finger and toe sensation components (touch pressure, pin-prick, vibration, joint position). Assessments are performed separately for the right- and left-hand side of the body. Scoring for the sensory assessment is 0 (normal), 1 (decreased) and 2 (absent). The maximum total score for NIS-S is 32.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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

Norfolk QoL-DN is a tool for assessing patients' perception of the effects of diabetes and diabetic neuropathy. There are 35 questions divided into 5 domains. The range of possible total scores is -4 to 136.

Part I: Symptoms

Items 1-7 (Part I) are a simple inventory of symptoms of neuropathy. The presence of the symptom is checked in whichever box applies, and an absence of a symptom is checked under "none." Positive responses are scored as 1; and negative responses, as 0.

Part II: Activities of Daily Life

Items 8-35 (Part II) pertain to Activities of Daily Life, and most of these are scaled on a 5-point Likert scale ranging from 0 (“Not a problem”) to 4 (“Severe problem”). However, Questions 31 and 32 are scored differently. In Question 31, “Good”, the middle item, is scored as 0. “Very Good” is scored as –1, “Excellent” is scored as –2. “Fair” is scored as 1, and “Poor” is scored as 2. In Question 32, “About the Same,” the middle item, is scored as 0. “Somewhat better” is scored as –1, “Much better” is scored as -2. “Somewhat worse” is scored as 1, and “Much worse” is scored as 2.

Subscales and Scoring Algorithm

The Total QOL and 5 domains should be summed as follows:

- Total QOL (35 items) [redacted]
- Physical Functioning/Large Fiber (15 items) [redacted]
- Activities of Daily Living (ADLs) (5 items) [redacted]
- Symptoms (8 items) [redacted]
- Small Fiber (4 items) [redacted]
- Autonomic (3 items) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.3. EuroQol-5-Dimension 5-Level (EQ-5D-5L)

Each of the 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) is scored on a 5-point Likert scale from 1 ("I have no problems/pain/anxiety") to 5 ("I am unable to…," "I have extreme anxiety/depression").

The 5 scores are concatenated together (in the order of Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) to create an EQ-5D-5L profile (e.g., 11111, 55555). The profile is then used to obtain an index value using the United States value set. The index values range from –0.109, associated with a profile of 55555, to 1.0, associated with a profile of 11111. Smaller index values indicate greater impairment.

Missing values are handled as follows:

- Missing items are coded as "9" in creating patient profiles.
- The index value is deemed as missing when responses are missing for 1 or more of the 5 dimensions.
- If the entire instrument is missing, the EQ-5D-5L index value is considered as missing.

7.1.4. 10-Meter Walk Test (10-MWT)

Two replicate assessments are expected to be performed approximately 24 hours apart and no more than 7 days apart per protocol. At baseline and for each postbaseline visit, the walk speed (m/s) analysis value is derived as follows:

Table 7: 10-MWT Derivation Scenarios

Scenario	Derivation
Both replicate assessments nonmissing	
Patient able to walk for both assessments	10/mean(time 1, time 2)
Patient unable to walk for 1 of the 2 assessments	mean(0, 10/assessable time)
Patient unable to walk for both assessments	0
One replicate assessment nonmissing	
Patient able to walk	10/assessable time
Patient unable to walk	0

7.1.5. Modified Body Mass Index (mBMI)

In the APOLLO study, mBMI was not assessed at Months 9 or 18. For the placebo (APOLLO) group, these assessments are derived as follows:

- Month 9 = mean of Day 190 (Week 27) and Day 358 (Week 51) assessments
- Month 18 = Day 547 (Week 78) assessment

7.1.6. Rasch-Built Overall Disability Scale (R-ODS)

The R-ODS consists of 24 items scored on a scale of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty). A total score will be calculated as the average of all nonmissing items multiplied by 24 if at least 90% of the items are nonmissing. The total score will be deemed as missing if more than 10% of the items (3 or more items) are missing.

7.2. Pattern-Mixture Model Details

Similar to the primary analysis methods, for the Month 9 analyses, assessments after initiation of local standard treatment will be treated as missing and thus imputed following the PMM procedure.

As an initial step, separate intermediate datasets for mNIS+7 and Norfolk QoL-DN total score will be prepared, which will include the key variables listed in Table 8.

[redacted] [redacted]

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

The following steps will be followed separately for the PMM analysis of change from baseline in mNIS+7 and Norfolk QoL-DN total score at Month 9.

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3. Pandemic Phase Start Dates by Country

Table 9: Pandemic Phase Start Dates by Country

Country	Date of 1st Confirmed Case
Argentina	2020-03-03
Australia	2020-01-25
Belgium	2020-02-04
Brazil	2020-02-26
Bulgaria	2020-03-08
Canada	2020-01-26
Cyprus	2020-03-09
France	2020-01-24
Germany	2020-01-28
Greece	2020-02-26
Italy	2020-01-29
Japan	2020-01-14
Korea	2020-01-19
Malaysia	2020-01-25
Mexico	2020-02-28
Netherlands	2020-02-27
Portugal	2020-03-02

Country	**Date of 1st Confirmed Case**
Spain	2020-01-31
Sweden	2020-01-31
Taiwan	2020-01-22
United Kingdom	2020-01-31
United States	2020-01-20

As reported by the World Health Organization and the Taiwan Centers for Disease Control.

8. AMENDMENT HISTORY

8.1. Amendment 1: 17 July 2020

The Sponsor developed this SAP amendment without knowledge of postbaseline efficacy data in accordance with the Data Integrity Plan. Key changes include:

- Updates reflecting cumulative changes made after the original ALN-TTRSC02-002 protocol (11 October 2018) [amendment 1 (10 October 2019), amendment 2 (06 May 2020), and amendment 3 (17 July 2020)], including:
  - Changes to primary and secondary endpoints and associated MCP
  - Changes and/or additions to derivations, summaries, and analyses to account for and/or characterize the impact of the COVID-19 pandemic
- Updates reflecting feedback received from the FDA on the original statistical analysis plan and data submission plan
- Addition of summaries to characterize the long-term efficacy and safety of vutrisiran
- Addition of prefilled syringe vs vial summaries

Section	**Description**	**Rationale**
Throughout document	Updated co-primary endpoint language to primary and key secondary	To align with protocol amendment 3 revised endpoints
Section 1	Updated study design and objectives	To align with protocol amendment 3 updated language
Section 1.3.1 Section 1.3.2	Updated MCP and add MCP for EU/other regions	To align with updated primary/secondary endpoints; to specify a separate MCP reflecting EMA/SAWP's preference to evaluate efficacy through Month 18, which will be used for potential future submissions in other regions
Section 2 Section 4.4.3.3	Updated TTR percent reduction definition and associated TTR PP population and analyses	To reflect protocol amendment 2 change to analyze TTR percent reduction at Month 18 instead of Month 9 per protocol amendment 3; name revised to make distinct from added efficacy PP population
Section 2	Added efficacy PP population	To support analyses related to COVID-19 pandemic impact on efficacy to estimate treatment effects in an 'unimpacted' population
Section 2	Added all vutrisiran-treated population	To support long-term safety analyses during vutrisiran treatment
Section 3.2	Updated presented treatment groups	To clarify planned presentations with respect to data submission plan
Section 3.6.2	Updated missing efficacy data summary	To account for missingness associated with COVID-19 pandemic
Section 3.7	Added extended efficacy analysis windows	To allow inclusion of efficacy visit data delayed due to COVID-19 pandemic

Section	Description	Rationale
Section 4.1	Updated patient disposition summaries	To clarify time windows to align with efficacy analysis timepoints; to account for discontinuations associated with COVID-19 pandemic
Section 4.2	Added summary of COVID-19-related protocol deviations	To align with regulatory guidance recommendations
Section 4.4	Added details on Month 9 and 18 analyses	To clarify data intended to be cleaned and included in planned analysis submissions
Section 4.4.1.1	Added details on handling of patients with missing model covariates and factors Specify KPS to be included as continuous covariate	To clarify and align with approach used in APOLLO (ALN-TTR02-004) study
Section 4.4.1.3 Section 4.4.2.1 Section 4.4.2.2 Section 4.4.5	Added ANCOVA model for use in select sensitivity and subgroup analyses	To simplify models used for non-primary analyses
Section 4.4.2.2	Updated propensity score model covariates and factors	To incorporate FDA feedback on initial SAP to include additional potential sources of differences in treatment assignment propensity to achieve the best predictive model
Section 4.4.2.3	Added pattern-mixture model sensitivity analysis	To incorporate FDA feedback on original SAP to assess the robustness of results under MNAR assumptions
Section 4.4.3.1 Section 7.1.2	Added key secondary endpoint section Updated primary Norfolk derivation and added sensitivity analysis using original derivation	To align with protocol amendment 3 revised endpoints (Norfolk changed from co-primary to key secondary) To mitigate for potential COVID-19 pandemic impact on quality of life on select Norfolk items in the primary analysis
Section 4.4.4	Changed all-cause deaths and/or all-cause hospitalization analyses to exploratory	To align with protocol amendment 3 revised endpoints
Section 4.4.5 Section 4.4.6	Added Month 18 subgroup and component analyses	To support characterization of efficacy profile at Month 18 for consistency with the APOLLO study
Section 4.7.1	Added definitions of complete vs partial dose administrations	To clarify definitions aligning with CRF data collection instructions
Section 4.7.1 Section 4.7.2	Added prefilled syringe vs vial summaries	To support regulatory assessment of vutrisiran administration via prefilled syringe
Section 4.7.2	Added inclusion of external placebo comparison group	To incorporate FDA feedback on data submission plan to facilitate AE safety comparisons to the APOLLO study
Section 4.9	Added analyses of data in the Treatment Extension Period	To support long-term efficacy and safety objectives

Section	Description	Rationale
Section 4.10 Section 4.4.2.5	Added summaries of COVID-19 pandemic general impact and related impacts on efficacy and safety	To assess the impact of COVID-19 in acknowledgement of regulatory guidances
Section 6	Updated references and added in-text citations where appropriate	To document sources
Throughout document	Added minor definition details, summaries, and protocol-amendment updates Removed selected analyses Aligned tables with related in-text revisions Corrected general typographic and formatting errors Updated abbreviations	To streamline and clarify planned analyses needed to support overall objectives and address minor errors

8.2. Amendment 2: 15 October 2020

The Sponsor developed this SAP amendment primarily to address feedback received from the FDA regarding Norfolk QoL-DN total score in relation to criteria to declare a positive trial.

Section	Description	Rationale
Section 1.3.1 Section 1.3.2 Section 5	Define positive trial criteria within different regions	To address FDA feedback regarding the importance of Norfolk QoL-DN total score in declaring a positive trial To document this change from protocol language
Section 3.9	Moved database lock and cutoff date content from Section 4.4 into standalone subsection and removed content to be defined in the Data Management Plan	To improve organizational flow and streamline content
Section 4.5 Section 4.6	Updated PK/PD parameters Added PK/PD subgroup analyses	To support PK/PD data interpretation
Section 4.7.1	Updated duration of drug exposure definition	To account for treatment period and cutoff date definitions
Section 4.7.2	Added AE subgroup analyses	To support AE data interpretation
Section 4.7.3	Updated local laboratory data inclusion and summaries	To clarify rules for including local laboratory data
Section 4.8	Added treatment-emergent ADA definition	To align with ADA summaries from recent submissions
Section 4.10.2	Added efficacy summaries by pandemic phase	To incorporate FDA guidance on assessing impact of pandemic on efficacy
Former Section 7.1.1.3	Removed algorithms for transforming to normal deviates and points and moved to programming specifications	To prevent disclosure of information proprietary to [redacted]

Section	**Description**	**Rationale**
Section 7.1.5	Updated corresponding APOLLO assessment days	To align with HELIOS-A study design with first dose date = Day 1 rather than Day 0 in APOLLO
Throughout document	Corrected general typographic and formatting errors Updated minor details	To address minor errors and clarifications

Signature Page for VV-CLIN-005068 v1.0
ALN-TTRSC02-002 SAP Amend2

Approval	[redacted]T+0000

Approval	[redacted]24:27 GMT+0000

STATISTICAL ANALYSIS PLAN
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:	Vutrisiran (ALN-TTRSC02)
EudraCT Number:	2018-002098-23
IND Number:	139086
Protocol Version and Date:	Original: 11 October 2018 Amendment 1: 10 October 2019 Amendment 2: 06 May 2020 Amendment 3: 17 July 2020 Amendment 4: 19 February 2021
Analysis Plan Version and Date:	Original: 30 January 2019 Amendment 1: 20 July 2020 Amendment 2: 15 October 2020 Amendment 3: 24 August 2021
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: [redacted]
Sponsor Contact:	[redacted]

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without expressed written authorization of Alnylam Pharmaceuticals, Inc.

APPROVAL SIGNATURE PAGE

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)

Protocol: ALN-TTRSC02-002

Analysis Plan Version and Date: Amendment 3: 24 August 2021

This document has been authored by the following:

[redacted]

Alnylam Pharmaceuticals, Inc.

This document has been approved and signed electronically on the final page by the following:

[redacted]

Alnylam Pharmaceuticals, Inc.

[redacted]

Alnylam Pharmaceuticals, Inc.

TABLE OF CONTENTS

APPROVAL SIGNATURE PAGE 2
TABLE OF CONTENTS 3
LIST OF TABLES 6
LIST OF FIGURES 6
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 7
1. INTRODUCTION 10
1.1. Study Design 10
1.2. Study Objectives and Endpoints 14
1.3. Study Hypotheses 15
1.3.1. Multiple Comparisons Procedure (US/Japan/Brazil) 15
1.3.2. Multiple Comparisons Procedure (EU/Other Regions) 16
1.4. Sample Size Determination 17
2. PATIENT POPULATIONS 18
3. GENERAL CONSIDERATIONS 20
3.1. Computing Environment 20
3.2. General Methods 20
3.3. Baseline Definitions 21
3.3.1. 18-Month Treatment Period Analyses 21
3.3.2. All Vutrisiran-Treated Population Analyses 21
3.3.3. Re-randomized Population Analyses 21
3.4. Randomization Stratification Factors 22
3.5. Efficacy Censoring Rules 22
3.5.1. Initiation of Local Standard Treatment for hATTR Amyloidosis 22
3.5.2. Onset of Serious COVID-19 Adverse Events 23
3.6. Missing Data with Efficacy Endpoints 23
3.6.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints 23
3.6.2. Summary of Missing Data 23
3.7. Visit Windows 23
3.8. Interim Analyses 24
3.9. Planned Analyses 24
4. ANALYSIS OF THE 18-MONTH TREATMENT PERIOD 24

4.1. Patient Disposition 24
4.2. Protocol Deviations 25
4.3. Demographics and Baseline Characteristics 25
4.4. Efficacy Evaluation 26
4.4.1. General Efficacy Methods 27
4.4.1.1. ANCOVA/MI 27
4.4.1.2. MMRM 27
4.4.1.3. ANCOVA 28
4.4.2. Primary Efficacy Evaluations 28
4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis or Post Serious COVID-19 AE 28
4.4.2.2. Sensitivity Analysis: Propensity Score 28
4.4.2.3. Sensitivity Analysis: Pattern-Mixture Model 29
4.4.2.4. Other Analysis: Binary Endpoint 30
4.4.2.5. Other Analysis: Efficacy PP Population 30
4.4.2.6. Overview of Primary Endpoint Analyses 30
4.4.3. Secondary Efficacy Evaluations 31
4.4.3.1. Key secondary endpoint: Norfolk QoL-DN Total Score 31
4.4.3.2. 10-meter Walk Test Speed, mBMI, and R-ODS 31
4.4.3.3. Time-averaged Trough TTR Percent Reduction 31
4.4.3.4. Overview of Secondary Endpoint Analyses 32
4.4.4. Exploratory Efficacy Evaluations 32
4.4.5. Subgroup Analyses 33
4.4.6. Component/Domain Analyses 34
4.5. Pharmacodynamic Analyses 34
4.6. Pharmacokinetic Analyses 35
4.6.1. Study Variables 35
4.6.1.1. Concentration Data 35
4.6.1.2. Plasma Pharmacokinetic Parameters 35
4.6.2. Statistical Methods 35
4.7. Safety Analyses 36
4.7.1. Study Drug Exposure 36
4.7.2. Adverse Events 37

4.7.3. Laboratory Data 39
4.7.4. Vital Signs and Physical Examination 40
4.7.5. Electrocardiogram 40
4.7.6. Premedication 41
4.7.7. Prior and Concomitant Medications 41
4.7.8. Suicidality Questionnaire 41
4.8. Anti-Drug Antibody 42
4.9. COVID-19 Pandemic Impact Analyses 42
4.9.1. General Impact 42
4.9.2. Impact on Efficacy 43
4.9.3. Impact on Adverse Events 43
4.9.4. Other Impacts 44
5. ANALYSIS OF THE RANDOMIZED TREATMENT EXTENSION (RTE) PERIOD 45
5.1. Patient Disposition 45
5.2. Demographics and Baseline Characteristics 45
5.3. Efficacy Analyses 45
5.4. PD/PK Analyses 45
5.5. Safety Analyses 46
6. SUMMARY OF THE ENTIRE STUDY 47
6.1. During the Entire Study 47
6.2. During Vutrisiran Treatment 47
7. CHANGES TO PLANNED ANALYSES 48
8. REFERENCES 48
9. APPENDICES 49
9.1. Questionnaire/Scoring 49
9.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS) 49
9.1.1.1. Modified Neuropathy Impairment Score (mNIS+7) 49
9.1.1.2. Neuropathy Impairment Score (NIS) 51
9.1.2. Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) 51
9.1.3. EuroQol-5-Dimension 5-Level (EQ-5D-5L) 53
9.1.4. 10-Meter Walk Test (10-MWT) 53

9.1.5. Modified Body Mass Index (mBMI) 53
9.1.6. Rasch-Built Overall Disability Scale (R-ODS) 54
9.2. Pattern-Mixture Model Details 54
9.2.1. Month 9 Analysis 54
9.2.2. Month 18 Analysis 56
9.3. Pandemic Phase Start Dates by Country 59
10. AMENDMENT HISTORY 60
10.1. Amendment 1: 17 July 2020 60
10.2. Amendment 2: 15 October 2020 62
10.3. Amendment 3: 24 August 2021 63

LIST OF TABLES

Table 1: Multiple Comparisons Procedure (US/Japan/Brazil) 15
Table 2: Multiple Comparisons Procedure (EU/Other Regions) 16
Table 3: Postbaseline TTR Assessment Requirements by Treatment Group 19
Table 4: Analysis of Primary Endpoint mNIS+7 31
Table 5: Analysis of Secondary Endpoints 32
Table 6: QTc Derivation 40
Table 7: 10-MWT Derivation Scenarios 53
Table 8: Pattern-Mixture Model Intermediate Dataset for Month 9 54
Table 9: Pattern-Mixture Model Intermediate Dataset for Month 18 56
Table 10: Pandemic Phase Start Dates by Country 59

LIST OF FIGURES

Figure 1: Study Design 12
Figure 2: Study Design – Randomized Treatment Extension Period 13

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
10-MWT	10-meter walk test
ADA	Antidrug antibodies
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATTR	Amyloid transthyretin
BMI	Body mass index
CI	Confidence Interval
CMAP	Compound muscle action potential
C_{max}	Observed peak concentration
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
EQ-VAS	EuroQol visual analogue scale
FAP	Familial amyloidotic polyneuropathy, also known as hATTR amyloidosis with polyneuropathy
H1	Histamine 1 receptor
H2	Histamine 2 receptor
hATTR	Hereditary ATTR
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
LLN	Lower limit of normal

Abbreviation	Definition
LS	Least-squares
LV	Left ventricle
mBMI	Modified body mass index
MCP	Multiple comparisons procedure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MNAR	Missing not at random
mNIS+7	Modified Neuropathy Impairment Score +7
NCS	Nerve conduction studies
NCS Σ5	NCS sum of 5 attributes
NIS	Neuropathy 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
PD	Pharmacodynamics
PK	Pharmacokinetics
PMM	Pattern-mixture model
PND	Polyneuropathy Disability
q3M	Once every 3 months
q3w	Once every 3 weeks
QoL or QOL	Quality of life
QST	Quantitative sensory testing
$\text{QST-BSA}_{\text{HP}}$	QST heat pain by body surface area
$\text{QST-BSA}_{\text{TP}}$	QST touch pressure by body surface area
QTc	Corrected QT interval
QTcF	QT obtained using Fridericia's formula
RBC	Red blood cell
R-ODS	Rasch-built Overall Disability Scale
RTE	Randomized Treatment Extension

Abbreviation	Definition
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
siRNA	Small interfering ribonucleic acid
SMQ	Standardized MedDRA query
SNAP	Sensory nerve action potential
SOC	System organ class
t_{max}	Time of observed maximum concentration
TTR	Transthyretin
ULN	Upper limit of normal
V30M	Valine to methionine mutation at position 30
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan details comprehensive, technical specifications of the statistical analyses of the efficacy/safety data outlined and/or specified in the final protocol of Study ALN-TTRSC02-002. Specifications of tables, figures, and data listings are documented separately.

1.1. Study Design

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

The study will consist of a Screening Period of up to 42 days, an 18-month Treatment Period, an 18-month Randomized Treatment Extension (RTE) Period as of Amendment 4 (in lieu of the 18-month Treatment Extension Period, hereafter referred to as the Legacy Treatment Extension Period) which will include collection of safety, PD, and efficacy in all patients [redacted] 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 vutrisiran administered as a subcutaneous (SC) injection once every 3 months (q3M) or patisiran 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.

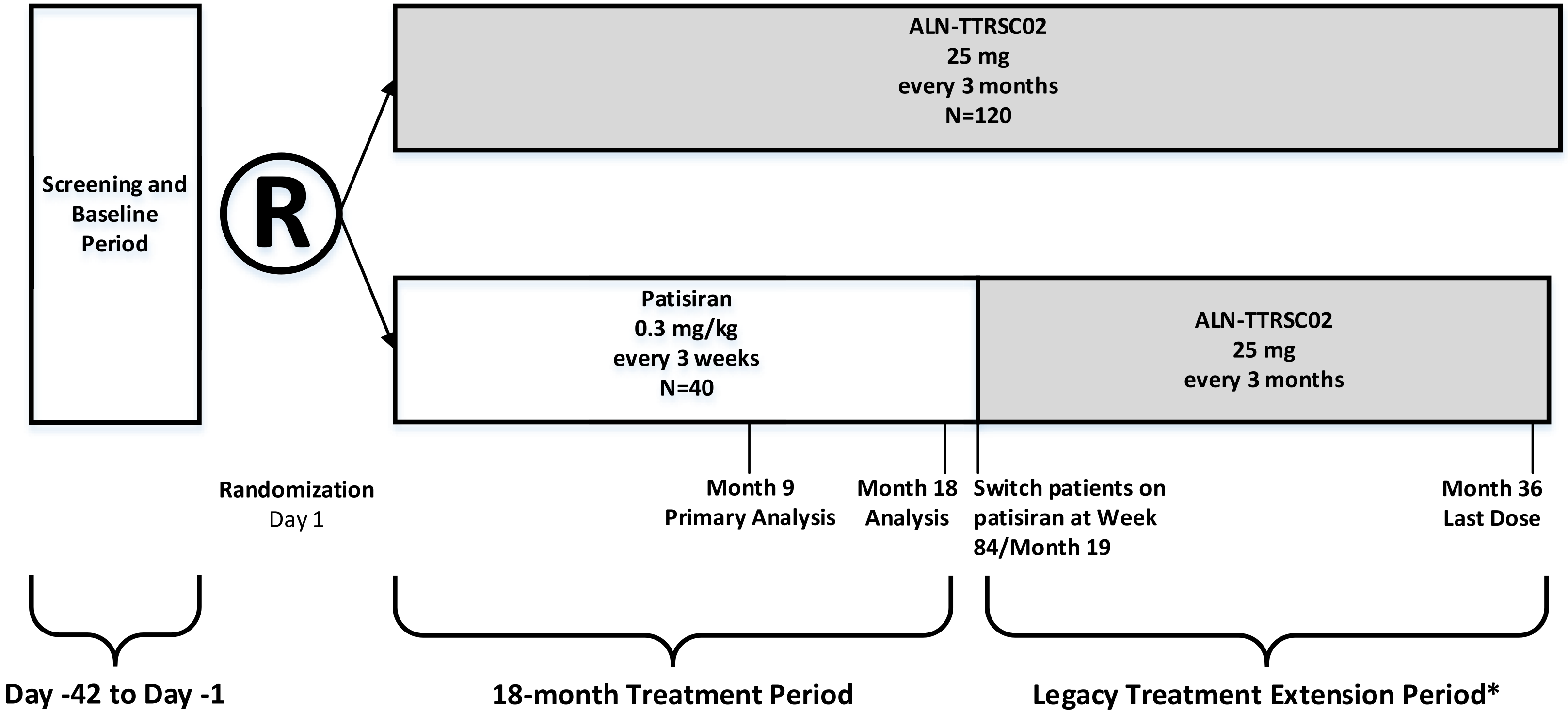
All efficacy visits must be conducted at the clinic (Month 9, Month 18, [redacted], and modified efficacy visits). In situations in which a Month 9 or Month 18 efficacy visit is unable to be completed due to the Coronavirus disease 2019 (COVID-19) pandemic limiting the patient's ability or willingness 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 Study Month 15 or Month 24, respectively).

The study has been amended (Amendment 4) to include an RTE Period (in lieu of the Legacy Treatment Extension Period) [redacted]

During the Follow-up Period, all patients on vutrisiran 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 will undergo a follow-up visit 30 days after the last dose of study drug.

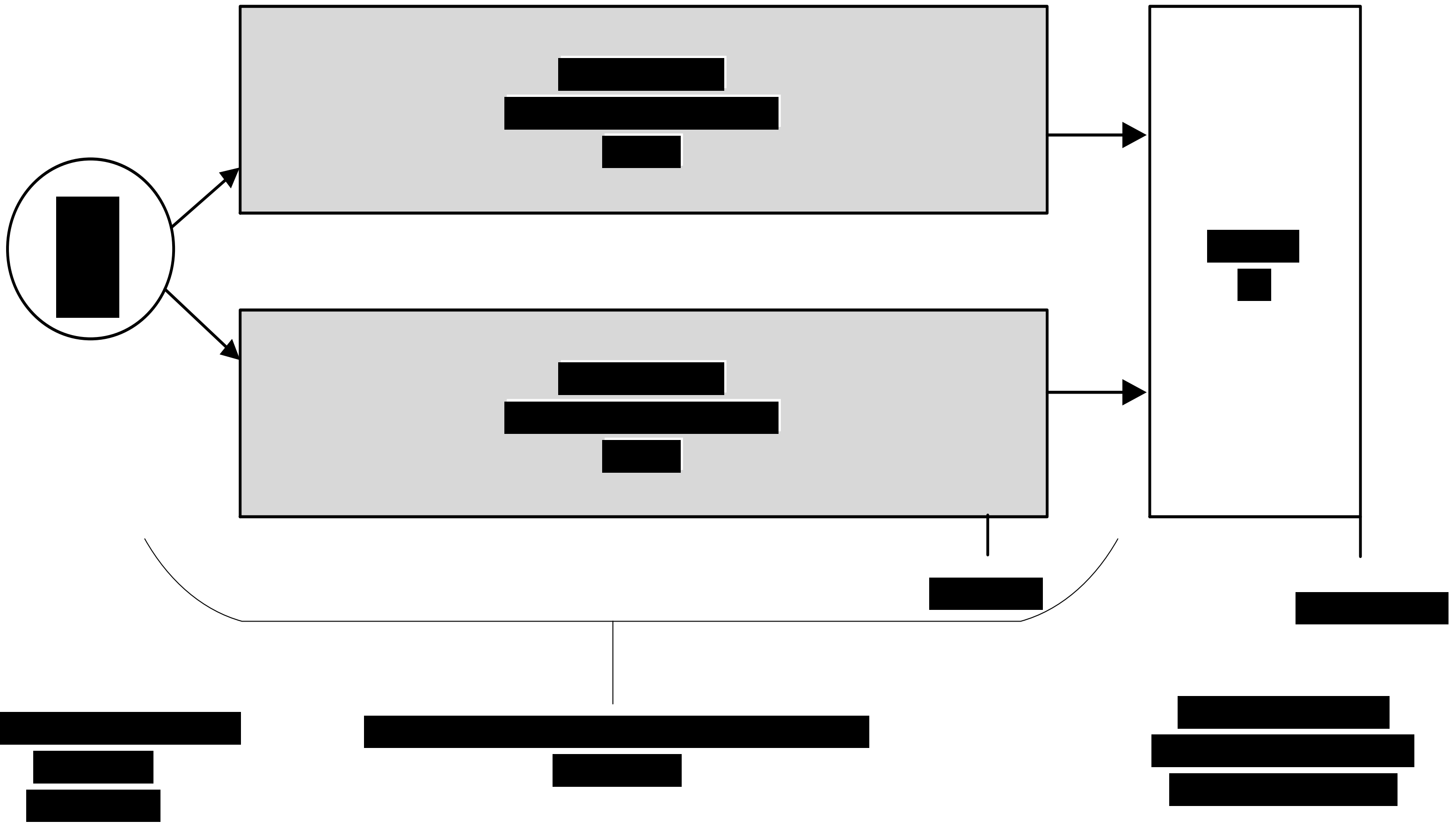
The placebo group of the APOLLO (ALN-TTR02-004) study will be used as an external control for the primary, most secondary, and most exploratory efficacy analyses. Primary and secondary efficacy evaluations will include mNIS+7, Norfolk QoL-DN questionnaire, 10-MWT, mBMI, R-ODS questionnaire, and percent TTR reduction. Study personnel performing the mNIS+7 component assessments will not reference the results of any previous assessments.

Figure 1: Study Design


Screening and Baseline Period
R
ALN-TTRSC02
25 mg
every 3 months
N=120
Patisiran
0.3 mg/kg
every 3 weeks
N=40
ALN-TTRSC02
25 mg
every 3 months
Randomization
Day 1
Month 9
Primary Analysis
Month 18
Analysis
Switch patients on patisiran at Week 84/Month 19
Month 36
Last Dose
Day -42 to Day -1
18-month Treatment Period
Legacy Treatment Extension Period*

[redacted]

[redacted] [redacted]


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

[redacted] [redacted] [redacted]

1.2. Study Objectives and Endpoints

The primary and most secondary and exploratory efficacy endpoints are in comparison to the placebo group of the Phase 3 pivotal patisiran-LNP study (APOLLO study) as specified in the statistical analysis section of the ALN-TTRSC02-002 (HELIOS-A) protocol.

Objectives	Endpoints
Primary	
• To determine the efficacy of vutrisiran in patients with hATTR amyloidosis by evaluating the effect on neurologic impairment	• Change from baseline in the Modified Neuropathy Impairment Score +7 (mNIS+7) compared to the placebo group of the APOLLO study at Month 9
Secondary	
• To determine the efficacy of vutrisiran on quality of life, gait speed, neurologic impairment, nutritional status, and disability • To demonstrate the noninferiority of vutrisiran compared to patisiran with respect to serum TTR levels	• Change from baseline in the following parameters compared to the placebo group 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 vutrisiran group compared to the within-study patisiran group through Month 18
Exploratory	
• To determine the effect of vutrisiran 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 vutrisiran and patisiran on serum TTR and vitamin A levels • To characterize plasma pharmacokinetics (PK) of vutrisiran and patisiran • To assess presence of antidrug antibodies (ADA) to vutrisiran and patisiran	• Change from baseline in the following parameters compared to the placebo group of the APOLLO study at Month 9: – Modified body mass index (mBMI) – Rasch-built Overall Disability Scale (R ODS) • 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 – Neuropathy Impairment Score (NIS) – EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire and the EuroQol-Visual Analog Scale (EQ-VAS)

Objectives	Endpoints
	– 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 vutrisiran and patisiran • Incidence and titers of ADA to vutrisiran and patisiran
Safety	
• To determine the safety and tolerability of vutrisiran in patients with hATTR amyloidosis	• Frequency of adverse events (AE)

1.3. Study Hypotheses

For most inferentially-evaluated efficacy endpoints, the null hypothesis for the superiority comparison of vutrisiran vs placebo is defined as follows:

H_0: No difference between vutrisiran and placebo (APOLLO): difference (vutrisiran – placebo) = 0

For the TTR percent reduction endpoint, the null hypothesis for the noninferiority comparison of vutrisiran vs patisiran is defined as follows:

H_0: Vutrisiran is inferior to patisiran: difference in median TTR reduction (vutrisiran – patisiran) ≤ -10%

1.3.1. Multiple Comparisons Procedure (US/Japan/Brazil)

In the US, Japan, and Brazil, the overall familywise error rate will be controlled at α=0.05 for the primary and secondary endpoint hypothesis tests as follows:

Table 1: Multiple Comparisons Procedure (US/Japan/Brazil)

MCP Step[a]	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
Evaluated at the Month 9 analysis timepoint			
1	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α
3	10-MWT gait speed change from baseline at Month 9	Placebo (APOLLO)	Nominal P value ≤ α

MCP Step[a]	Endpoint	Comparison Group vs Vutrisiran	MCP Criteria
Evaluated at the Month 18 analysis timepoint			
4	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
5	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
6	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
7	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
8	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
9	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%

[a] Per serial gatekeeping MCP, if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.

LCB=lower confidence bound; MCP=multiple comparisons procedure.

For the US filing, results for both the primary endpoint, mNIS+7 change from baseline at Month 9, and key secondary endpoint, Norfolk QoL-DN total score change from baseline at Month 9, must be statistically significant to declare a positive trial. For filings in Japan and Brazil, a positive trial will be declared if the result for the primary endpoint is statistically significant.

1.3.2. Multiple Comparisons Procedure (EU/Other Regions)

In the EU, during its scientific advice procedure, the EMA/CHMP/SAWP indicated a preference for a marketing authorization application based upon 18 months data. Therefore, the Month 9 endpoints included in the US/Japan/Brazil multiple comparisons procedure (MCP) will not be included in the MCP for the EU and other regions, where instead mNIS+7 change from baseline at Month 18 will be considered the primary endpoint. The overall familywise error rate in the EU and other regions will be controlled at α=0.05 for the primary and secondary endpoint hypothesis tests as follows:

Table 2: Multiple Comparisons Procedure (EU/Other Regions)

MCP Step[a]	Endpoint	Comparison group vs Vutrisiran	MCP Criteria
Evaluated at the Month 18 analysis timepoint			
1	Modified Neuropathy Impairment Score +7 (mNIS+7) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
2	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α

MCP Step[a]	Endpoint	Comparison group vs Vutrisiran	MCP Criteria
3	10-MWT gait speed change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
4	mBMI (BMI [kg/m2] multiplied by serum albumin level [g/L]) change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
5	R-ODS change from baseline at Month 18	Placebo (APOLLO)	Nominal P value ≤ α
6	TTR percent reduction through Month 18	Patisiran (HELIOS-A)	2-sided 95% LCB for treatment difference > -10%

[a] Per serial gatekeeping MCP, if the MCP criterion is satisfied in a given step, the hypothesis test is deemed statistically significant and the next step will be evaluated; otherwise all hypotheses in the given and subsequent steps are deemed not statistically significant.

LCB=lower confidence bound; MCP=multiple comparisons procedure.

For filings in the EU and other regions, results for the primary endpoint, mNIS+7 change from baseline at Month 18, must be statistically significant to declare a positive trial.

References to the primary and secondary endpoints in the remainder of this document refer to those endpoints defined in the study objectives and endpoints (Section 1.2), corresponding to the US/Japan/Brazil MCP (Section 1.3.1).

1.4. Sample Size Determination

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

The sample size was chosen to enable an adequate characterization of the long-term safety profile, as well as the efficacy of vutrisiran in this patient population. For the primary efficacy endpoint of mNIS+7 and the secondary endpoint of Norfolk QoL-DN total score, the vutrisiran group in the Phase 3 study will be compared to the placebo group 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 group from the APOLLO study. Assuming a mean change of 0 points for the vutrisiran group, 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 group from the APOLLO study. Assuming a mean change of -4 points for the vutrisiran group, 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 vutrisiran 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 baseline NT-proBNP values greater than 3000 ng/L.

2. PATIENT POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data in this study, and for applicable analyses, relevant data from the APOLLO study.

- Modified Intent-to-Treat (mITT) Population: All randomized patients who received any amount of study drug. Patients will be analyzed according to the treatment to which they were randomized.
- TTR Per-protocol (PP) Population: All mITT population patients with a nonmissing TTR assessment at baseline and ≥1 trough TTR assessment between Months 6 (Week 24) and Month 18 [Week 72]) that meets the requirements described in Table 3. Patients will be analyzed according to the treatment to which they were randomized.
- Month 9 Efficacy PP Population: All mITT population patients treated with vutrisiran or placebo meeting the following criteria:
  - Month 9 efficacy visit date within 3 calendar months of protocol-planned Month 9 efficacy visit window
  - No serious or severe COVID-19 custom query AE terms reported on or before Month 9 efficacy visit date
  - For vutrisiran-treated patients, received all planned vutrisiran doses up to and including Week 36 with ≤ 28 day delay

  Patients will be analyzed according to the treatment to which they were randomized.
- Month 18 Efficacy PP Population: All mITT population patients treated with vutrisiran or placebo meeting the following criteria:
  - Month 18 efficacy visit date within 3 calendar months of protocol-planned Month 18 efficacy visit window
  - No serious or severe COVID-19 custom query AE terms reported on or before Month 18 efficacy visit date
  - For vutrisiran-treated patients, received all planned vutrisiran doses up to and including Week 72 with ≤ 28 day delay

  Patients will be analyzed according to the treatment to which they were randomized.
- Cardiac Subpopulation: All mITT population patients who had preexisting evidence of cardiac amyloid involvement, defined as patients with baseline left ventricular (LV) wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history. Patients will be analyzed according to the treatment to which they were randomized.
- Safety Population: All patients who received any amount of study drug. Patients will be analyzed according to the treatment received.
- Pharmacokinetic (PK) Population: All randomized patients who received at least one full dose of study drug and have at least 1 postdose blood sample for PK parameters

and have evaluable PK data. Patients will be analyzed according to the treatment received.

- All Vutrisiran-Treated Population: All randomized patients who received any amount of vutrisiran treatment, including patients who took vutrisiran during the 18-month treatment period and patients who first receive vutrisiran during the treatment extension periods.
- [redacted]

For the 18-month Treatment Period, efficacy analyses (except TTR) and PD summaries will be conducted in the mITT Population unless otherwise specified. The noninferiority of TTR will be assessed using the TTR PP Population. Safety analyses will be conducted in the Safety Population. PK analyses will be conducted in the PK Population.

The All Vutrisiran-Treated Population will be used to summarize long-term safety data during vutrisiran treatment. [redacted]

Table 3: Postbaseline TTR Assessment Requirements by Treatment Group

Treatment Group	Postbaseline TTR Assessment Requirements
Vutrisiran or Patisiran	• Assessment must be before administration of study drug at the current visit • Assessment after initiation of local standard treatment for hATTR amyloidosis excluded (Section 3.5)
Vutrisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 12 weeks before the TTR assessment • Patient must receive planned, complete administration of study drug at 2 consecutive planned treatment visits at any time before the TTR assessment visit to ensure steady state
Patisiran	• Patient must receive planned, complete administration of study drug at the planned treatment visit approximately 3 weeks before the TTR assessment

3. GENERAL CONSIDERATIONS

3.1. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software version 9.4 (or later), unless otherwise noted. Figures may be generated using R version 3.6 (or later).

3.2. General Methods

All data listings that contain an evaluation date will contain a study day relative to the day of the first dose of study drug, which is designated as Day 1. On-treatment study days will be calculated as evaluation date – first dose date +1 and pretreatment days will be calculated as evaluation date – first dose date. There is no Day 0.

Categorical descriptives will include the count and percentage of patients (or events, if applicable) within each category (with a category for missing data) of the parameter. Continuous descriptives will include the number of patients, mean, median, standard deviation (SD), standard error (SE), minimum, and maximum values.

Laboratory data (including vitamin A) collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

For assessments that are repeated multiple times for the study visit, the average will be calculated unless otherwise noted.

All summaries will be presented by treatment group. Unless otherwise specified, treatment groups in the Treatment Period will be presented using the following labels:

- Placebo (APOLLO)
    - Presented primarily for efficacy (except TTR) analyses and most safety and baseline summaries
- Vutrisiran (HELIOS-A)
- Patisiran (HELIOS-A)
- Total (HELIOS-A)
    - Presented primarily for patient disposition, protocol deviations, and baseline summaries

In addition, for TTR sensitivity analyses, the following treatment groups will be presented:

- Patisiran (HELIOS-A + APOLLO)
- Patisiran (APOLLO)

For analyses on the All Vutrisiran-Treated Population, the following treatment arms will be presented:

- Vutrisiran/Vutrisiran
- Patisiran/Vutrisiran
- Total

These 3 treatment arms represent the respective Vutrisiran (HELIOS-A), Patisiran (HELIOS-A), and Total (HELIOS-A) treatment groups, reflecting the transition from the initial randomized treatment (either vutrisiran or patisiran) during the Treatment Period to vutrisiran in the subsequent Legacy Treatment Extension or RTE periods. The experience while receiving vutrisiran will be summarized.

For analyses on the Re-randomized Population, the following treatment groups will be presented:

- Vutrisiran 25 mg q3M
- [redacted]
- Total

3.3. Baseline Definitions

Baseline definitions will be defined separately for analyses in the 18-Month Treatment Period, during vutrisiran treatment (ie, All Vutrisiran-Treated Population), and the 18-Month Randomized Treatment Extension Period (ie, Re-randomized Population).

3.3.1. 18-Month Treatment Period Analyses

For the mNIS+7/NIS individual components, total scores and related endpoints, the 2 baseline assessments are performed on separate days. Baseline will be calculated as the mean of the nonmissing replicate measures.

For 10-MWT, 2 baseline assessments are performed on separate days. Baseline will be calculated as described in Section 9.1.4.

For PD parameters (TTR, Vitamin A), baseline will be defined as the average of all records, including those from any unscheduled visits, before the date and time of first dose.

For all other parameters, unless noted otherwise, baseline will be defined as the last nonmissing measurement on or before the first dose date.

3.3.2. All Vutrisiran-Treated Population Analyses

For patients in the Patisiran/Vutrisiran arm, baseline ADA status will be defined as the last nonmissing anti-TTRSC02 ADA assay measurement before the first vutrisiran dose in the extension periods. In most cases, this will correspond to either the Month 18 or Week 72 measurement.

For all other parameters, unless noted otherwise, baseline will be defined the same as for the 18-Month Treatment Period (Section 3.3.1).

3.3.3. Re-randomized Population Analyses

For the mNIS+7/NIS individual components, total scores, and related endpoints, and 10-MWT, baseline will be defined as the last nonmissing derived value before the first dose in the RTE Period. In most cases, this will correspond to the Month 18 derived values.

For all other efficacy and all safety parameters, unless noted otherwise, baseline will be defined as the last nonmissing measurement before the first dose in the RTE Period.

Baseline ADA status will be defined as the last nonmissing anti-TTRSC02 ADA assay measurement before the first dose in the RTE Period. In most cases, this will correspond to the RTE Day 1 measurement.

For PD parameters (TTR, Vitamin A), baseline will be defined the same as for the 18-Month Treatment Period (Section 3.3.1).

3.4. Randomization Stratification Factors

Stratification factors for randomization into the 18-Month Treatment Period include TTR genotype (V30M vs. non-V30M) and baseline NIS score (< 50 vs. ≥ 50).

Stratification factors are recorded in both the Interactive Response System (IRS) and the clinical database. In statistical analyses that use randomization stratification factors as covariates, the stratum assignment will reflect the values as recorded in the clinical database. In the presence of stratification errors, the stratification used in analysis may not match that in the IRS.

In addition to the initial randomization, [redacted] For patients initially randomized to vutrisiran, stratification factors for this 2nd randomization include TTR genotype (V30M vs. non-V30M) and the most recent FAP stage (0/1 vs 2/3) before the 2nd randomization. For patients initially randomized to patisiran, there is no stratification for this 2nd randomization.

3.5. Efficacy Censoring Rules

The censoring rules are applicable to analyses described in Section 4 for the 18-Month Treatment Period.

3.5.1. Initiation of Local Standard Treatment for hATTR Amyloidosis

In the APOLLO study, there were placebo-treated patients who discontinued study drug, but remained on study and received local standard treatment. For the primary analysis of mNIS+7 and Norfolk QoL-DN, assessments were censored (excluded from analysis) after initiation of any of the following:

- Orthotopic liver transplant
- Use of TTR stabilizing agents (eg, tafamidis, diflunisal) for >14 days

For consistency of data handling, the placebo group from the APOLLO study will follow the same censoring rule as the APOLLO study.

For this study, APOLLO censoring rules will be applied. Additionally, assessments will be censored after initiation of any of the following recently approved treatments:

- Any use of TTR-targeting anti-sense oligonucleotides (eg, inotersen)
- Any use of patisiran (applicable for the vutrisiran treatment group only)

This data will be included and flagged in efficacy listings. These assessments from either study will be included in sensitivity analyses as specified.

For TTR percent reduction, TTR assessments collected after initiation of local standard treatment for hATTR amyloidosis will be excluded from the analysis. For all other efficacy endpoints, data from either study collected after initiation of local standard treatment for hATTR amyloidosis will be included in analyses.

A separate listing will be provided for patients who initiate local standard treatment for hATTR amyloidosis while on study.

3.5.2. Onset of Serious COVID-19 Adverse Events

Patients who experience a serious COVID-19 AE may have worsening in general health and wellbeing unassociated with the natural course of hATTR amyloidosis or with study drug. Assessments will be censored on or after the onset of a serious COVID-19 AE for all analyses of mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS, and any associated component/domain scores. This will reflect a hypothetical estimand of interest where the COVID-19 pandemic did not occur, as was the case for placebo group from the APOLLO study.

3.6. Missing Data with Efficacy Endpoints

All efficacy data collected during study, regardless of whether before or after treatment discontinuation, will be included for analyses, with the exception of mNIS+7 and Norfolk QoL-DN collected post local standard treatment for hATTR amyloidosis (discussed in Section 3.5), and mNIS+7, Norfolk QoL-DN, 10-MWT, mBMI, and R-ODS on or after the onset of a serious COVID-19 AE (Section 3.5.2).

3.6.1. Missing Subcomponents within Primary and Secondary Efficacy Endpoints

For each patient, missing subcomponents within the primary mNIS+7 endpoint and secondary efficacy endpoints will be imputed whenever possible according to the algorithms specified in Section 9.1. When this “partial imputation” is successful (ie, complete mNIS+7 values are produced), these values will be used in all statistical analyses. When partial imputation is unsuccessful, the efficacy endpoint will be treated as completely missing.

3.6.2. Summary of Missing Data

For each of the primary and secondary efficacy endpoints, the number and percentage of missing data (completely missing), including due to COVID-19, at each visit (Baseline, Month 9, and Month 18) will be summarized by study group.

Summary of missing data for the primary and secondary efficacy endpoints during the RTE period may be provided, including due to the COVID-19.

3.7. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated and analyzed per the evaluation visit as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window.

For efficacy assessments, if the scheduled visit (eg, Month 9) is not performed, the unscheduled and/or discontinuation visits performed within a ± 3-month window will be grouped with the scheduled visit. 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, Month 9 and Month 18 efficacy assessments may be completed within 6 months after the intended time point (ie, up to Study Month 15 or Month 24, respectively). For patients impacted by the COVID-19 pandemic, efficacy visits delayed up to 6 months after the end of the protocol-defined efficacy visit window will be included in the analysis. The derived visits will be used for all analyses. [redacted]

Unless otherwise specified above, data collected at unscheduled visits will be included in by-patient data listings and figures, but no assignment to a study visit will be made for the purpose of by-visit summary tabulations. However, unscheduled visits may be used in the calculation of baseline values (as discussed in Section 3.3) and for inclusion in any categorical shift summaries (e.g., shift from baseline to "worst" postbaseline value).

3.8. Interim Analyses

No interim analysis is planned for this study.

3.9. Planned Analyses

As this study will be ongoing at the time of the primary analysis at Month 9 and the additional analysis at Month 18, the study database will undergo an interim database lock at the Month 9 and Month 18 data cutoff dates (ie, data in EDC will be cleaned, frozen and electronically signed by investigators; external laboratory data will be cleaned and will undergo quality assurance). Additional details regarding the interim database locks will be documented in the study Data Management Plan.

The Month 9 and Month 18 analyses and associated clinical study reports (CSRs) will include all data on or before the respective data cutoff date. For assessments with start and end dates (eg, AEs, medications, medical history), data records with start dates after the specified data cutoff date will be excluded.

[redacted]

After the study is completed (ie, all patients discontinue or complete the RTE Period and/or required follow-up visits), the database will undergo a final database lock, and the data will be summarized in a final CSR.

4. ANALYSIS OF THE 18-MONTH TREATMENT PERIOD

The primary objective of this study is to evaluate the efficacy and safety of vutrisiran during the initial 18-month Treatment Period; analyses described in this section focus on this objective.

4.1. Patient Disposition

Patient disposition will be tabulated for all randomized patients and will include categorical descriptives for the following parameters:

- Patients in each analysis population
- Patients randomized

- Patients treated
- Patients who complete or discontinue treatment
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who discontinue treatment before Month 18
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who discontinue treatment after Month 18
  - Primary reasons for treatment discontinuation and discontinuation due to COVID-19
- Patients who complete study participation
- Patients who stop study participation
  - Primary reasons for stopping study participation and stopping study participation due to COVID-19

Patient disposition by country and site will be summarized by randomized treatment group and overall. The number and percent of patients in each randomization stratification factor recorded in IRS, and a comparison of the number and percent of patients in each randomization stratification factor in IRS versus the clinical database will be summarized by randomized treatment group and in total.

Data listings of treatment/study completion information including the reason for treatment discontinuation and/or stopping participation in the study will be presented.

4.2. Protocol Deviations

Protocol deviations, including those related to COVID-19, will be defined in a separate document, including the process for major/minor classification.

All protocol deviations, COVID-19-related protocol deviations, and major protocol deviations will be summarized.

4.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics, baseline disease characteristics, baseline efficacy parameters, and medical history information will be summarized by treatment group and overall.

Age [years; at informed consent], height [cm], weight [de Souza Cavalcanti 2014], and body mass index (BMI) [kg/m^2] will be summarized using continuous descriptives. Age group (years) [<65; ≥65 to <75, ≥ 75], sex, race, ethnicity, and region [North America; Western Europe; Rest of World (Asia; Central and South America; Eastern Europe; Australia)] will be summarized using categorical descriptives.

The following baseline disease characteristics will be summarized by presenting categorical descriptives:

- Age at hATTR Symptom onset [< 50; ≥ 50]
- Neuropathy Impairment Score (NIS) [< 50; ≥ 50 & < 100; ≥ 100]
- Genotype [V30M; non-V30M]
- Early onset V30M [< 50 years of age at onset] vs. all other mutations [including late onset V30M]
- Previous tetramer stabilizer use [tafamidis or diflunisal] vs. no previous tetramer stabilizer use
- Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
- New York Heart Association (NYHA) Classification [No heart failure; I; II; III; IV]
- NT-proBNP [≤ 3000 ng/L; > 3000 ng/L]
- Cardiac Subpopulation [Yes; No]

Time (years) since diagnosis with hATTR will be summarized using descriptive statistics. For those who previously used tetramer stabilizers (tafamidis or diflunisal), the time from discontinuation of these previous therapies to the start of study drug will be summarized using descriptive statistics. Genotype by country will be summarized using categorical descriptives.

Continuous baseline efficacy parameters will be summarized using continuous descriptives. Categorical descriptives for baseline PND score (I, II, IIIA, IIIB, IV) and FAP stage (I, II, III) will also be summarized.

Medical history will be coded using the MedDRA coding system (version 23.0 or later) and will be summarized by system organ class (SOC), high level term (HLT), and preferred term. A patient contributes only once to the count for a given condition (overall, by SOC, by HLT, by preferred term).

All demographic and baseline data for each patient will be provided in data listings. Medical history data, including baseline cardiac and ophthalmology history, prior surgeries/procedures, and pregnancy test results, will be presented in a data listing. Screening test results will also be presented in data listings.

4.4. Efficacy Evaluation

This Phase 3 study will use 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.

Except for TTR endpoints, analysis models will include only the 2 treatment groups compared, vutrisiran and placebo (APOLLO), and only simple descriptives will be presented for patisiran (HELIOS-A). For TTR endpoints, vutrisiran and patisiran (HELIOS-A) will be compared unless otherwise specified.

For efficacy endpoints, 2-sided 95% confidence intervals and 2-sided nominal P values will be presented if applicable unless otherwise specified. Formal multiplicity-controlled hypothesis testing will be conducted as described in Section 1.3.1; all other P values presented will be considered descriptive.

4.4.1. General Efficacy Methods

Most continuous efficacy endpoints will be evaluated using an analysis of covariance (ANCOVA) model incorporating multiple imputation (MI) or a mixed-effects model for repeated measures (MMRM).

4.4.1.1. ANCOVA/MI

ANCOVA incorporating MI will be the default analysis for most continuous efficacy endpoints at Month 9.

MI is a broadly applicable technique for handling missing data. Missing data are imputed multiple times using a regression method. Each imputed data set is analyzed using the same analysis model, and the point estimates and standard errors are combined to provide inferences that reflect the uncertainty about the missing values. MI assumes the data are missing at random (MAR).

For a given endpoint, missing endpoint values will be multiply imputed separately for each treatment group using a regression procedure, with baseline information including baseline score and KPS as covariates and genotype, age at hATTR symptom onset, prior tetramer stabilizer use, region, FAP stage (I vs. II/III), Cardiac subpopulation, sex, and baseline NIS (<50 vs. ≥50) as factors. For NIS-related endpoints, the categorical baseline NIS score will not be included in the regression procedure.

One hundred imputed datasets (per treatment group) will be generated from the MI regression procedure using SAS PROC MI. Each of the imputed datasets will then be analyzed using an ANCOVA model, including a covariate (baseline value) and factors (treatment group; genotype; age of disease onset, baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

The resulting estimates (LS mean differences and standard errors) from the 100 imputed datasets will be combined using SAS PROC MIANALYZE to produce inferential results (difference in LS means, 95% CI for the difference, and the P value from the test that the difference is zero).[Rubin 1996] Combined LS mean estimates will be calculated as the average of the 100 complete-data estimates. A total variance estimate will be calculated as a weighted sum of within-imputation variance, which is the average of the complete-data variance estimates, and a between-imputation variance term. Complete details may be found in the SAS documentation for the MIANALYZE procedure (see Combining Inferences from Imputed Data Sets under Details: http://support.sas.com/documentation/onlinedoc/stat/131/mianalyze.pdf).

4.4.1.2. MMRM

MMRM will be the default analysis for most continuous efficacy endpoints at Month 18. MMRM makes use of fully and partially observed data sequences from individual patients by estimating the covariance between data from different time points. The MMRM will be implemented using an unstructured approach to modeling both the treatment-by-time means and the (co)variances, leading to what is essentially a multivariate normal model wherein treatment group means at the primary time point are adjusted to reflect both the actually observed data and the projected outcomes from the patients with missing data. MMRM also assumes data are missing at random (MAR).

For most endpoints, the MMRM will include a covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), and an interaction term (treatment group by visit), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

LS mean and mean difference estimates, SEs, 95% CIs, and p-values at Month 9 and Month 18 will be presented.

An unstructured covariance structure will be used to model the within-patient errors. If the model fails to converge, the following covariance structures will be specified in sequence and the first to converge will be used:

1. Toeplitz
2. First order autoregressive
3. Compound symmetry

The Satterthwaite approximation will be used to estimate the degrees of freedom.

4.4.1.3. ANCOVA

ANCOVA, without incorporating MI, will be the default Month 9 sensitivity and subgroup analyses unless otherwise specified. Patients who complete both baseline and Month 9 will be included in the analysis. For most endpoints, the ANCOVA will include a covariate (baseline value), and factors (treatment group; genotype; age of disease onset; baseline NIS score [<50 vs ≥50]), unless otherwise specified. For NIS-related endpoints, the categorical baseline NIS score will not be included in the model.

4.4.2. Primary Efficacy Evaluations

The primary endpoint is change from baseline at Month 9 for mNIS+7 (Section 9.1.1). The primary comparison will be conducted at Month 9. The primary endpoint will be analyzed using the general ANCOVA/MI methods.

Additionally, change from baseline at Month 18 for mNIS+7 will be analyzed as a secondary endpoint using the general MMRM methods.

4.4.2.1. Sensitivity Analysis: Including Data Post Local Standard Treatment for hATTR amyloidosis or Post Serious COVID-19 AE

The primary analysis will not include assessments performed after the initiation of local standard treatment for hATTR amyloidosis or on or after onset of a serious COVID-19 AE (Section 3.5). Sensitivity analysis of mNIS+7 change from baseline including data post local standard treatment for hATTR amyloidosis or post serious COVID-19 AE from either study will be conducted using the ANCOVA method at Month 9 and MMRM method at Month 18.

4.4.2.2. Sensitivity Analysis: Propensity Score

To allow some control of more factors and covariates without saturating the model, a propensity score approach will be used to reduce the predictors to a single propensity score. The propensity score is defined as the probability of being treated with vutrisiran as obtained from a logistic regression model of treatment group [vutrisiran; placebo (APOLLO)]. The logistic regression model will include the following baseline variables:

- Continuous variables
  - NT-proBNP (log-transformed)
  - mNIS+7
  - Norfolk QoL-DN total score
- Categorical variables
  - Previous tetramer stabilizer use (tafamidis/diflunisal) [Yes; No]
  - Karnofsky Performance Status (KPS) [60; 70-80; 90-100]
  - Cardiac Subpopulation [Yes; No]
  - PND score [I; II; IIIA; IIIB/IV]
  - Age at hATTR Symptom onset [< 50; ≥ 50]
  - Neuropathy Impairment Score (NIS) [< 50; ≥ 50]
  - Genotype [V30M; non-V30M]
  - FAP stage [I; II/III]

The primary endpoint will be analyzed in this sensitivity analysis using the ANCOVA method at Month 9 and MMRM method at Month 18, including the propensity score covariate in addition to the default model factors and covariates.

4.4.2.3. Sensitivity Analysis: Pattern-Mixture Model

The primary analysis ANCOVA/MI method addresses data under missing at random (MAR) assumptions. To assess the robustness of the primary analysis results under missing not at random (MNAR) assumptions, a sensitivity analysis using a pattern-mixture model (PMM) will be conducted at Months 9 and 18 using a modified ANCOVA/MI method.

The model will be based on the following assumptions:

1. Patients who have missing data due to COVID-19, including patients who have missing assessments, who have data censored because a serious COVID-19 AE was reported before Month 9 (or 18), or who die due to COVID-19:
   a. Under the hypothetical estimand of interest where the COVID-19 pandemic did not occur, these assessments should have been obtained with no COVID-19 impact. Therefore, for patients meeting either of these criteria, assessments will be considered MAR, and will be imputed using MI estimated from all nonmissing data collected on treatment from the vutrisiran group.
2. Patients who have missing data unrelated to COVID-19 and are alive before Month 9 (or 18):
   a. Placebo-treated patients who have missing data: The missing data are considered MAR and will be imputed using MI estimated from placebo-treated patients. The

imputation is done regardless of whether a patient was on-treatment or discontinued treatment before the scheduled Month 9 (or 18) efficacy assessment.

   b. Vutrisiran-treated patients who have missing data while on treatment: Patients are expected to continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, missing data during the on-treatment period (within 126 days of the patient's last dose before the scheduled Month 9 [or 18] efficacy assessment) are considered MAR and will be imputed using MI estimated from all nonmissing data collected on treatment from the vutrisiran group. The 126-day window was selected given the long PD effect of vutrisiran.
   c. Vutrisiran-treated patients who have missing data after stopping their study treatment: Patients will no longer benefit from treatment in the future and will have trajectory similar to placebo-treated patients. Therefore, missing data after treatment discontinuation (more than 126 days after the patient's last dose of study drug before the scheduled Month 9 (or 18) efficacy assessment) will be imputed using the data from placebo-treated patients.

3. Patients who have missing data and who die before Month 9 (or 18) unrelated to COVID-19:

   a. Assuming deaths observed in the study will likely be related to worsening of disease, the missing data will be imputed by taking random samples from the worst 10% mNIS+7 change from baseline scores among vutrisiran- and placebo-treated patients at Month 9 (or 18). The imputation will be done for patients from both vutrisiran and placebo groups.

Following the procedure describe above, 100 imputed datasets will be generated, and each imputed dataset will be analyzed and estimates combined following the same ANCOVA/MI model as the primary analysis.

More details on the implementation of PMM are discussed in Section 9.2.

4.4.2.4. Other Analysis: Binary Endpoint

The number and percentage of patients with a decrease (change from baseline < 0) in total score of mNIS+7 from baseline to Month 9 and to Month 18 will be summarized. The endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) test with Mantel-Haenszel odds ratios and associated CIs presented, stratified by genotype (V30M vs. non-V30M). Patients with missing change from baseline values due to COVID-19 will be excluded; all other patients with missing change from baseline values will be considered non-responders.

4.4.2.5. Other Analysis: Efficacy PP Population

To mitigate for the impact of the COVID-19 pandemic, mNIS+7 will also be analyzed using the Efficacy PP population; full details are provided in Section 4.9.2.

4.4.2.6. Overview of Primary Endpoint Analyses

The planned analyses of the primary endpoint mNIS+7 are summarized in Table 4.

Table 4: Analysis of Primary Endpoint mNIS+7

Statistical Method
Month 9: ANCOVA/MI
Month 18: MMRM
Sensitivity analysis: Including data post local standard treatment for hATTR amyloidosis or post serious COVID-19 AE (Month 9: ANCOVA; Month 18: MMRM)
Sensitivity analysis: Propensity score (Month 9: propensity-adjusted ANCOVA; Month 18: propensity-adjusted MMRM)
Sensitivity analysis: Pattern-mixture model with modified ANCOVA/MI at Months 9 and 18
Other analysis: Binary endpoint analysis using stratified CMH
Other analysis: Efficacy PP Population (Month 9: ANCOVA; Month 18: MMRM)

4.4.3. Secondary Efficacy Evaluations

4.4.3.1. Key secondary endpoint: Norfolk QoL-DN Total Score

Change from baseline in Norfolk QoL-DN total score (primary analysis incorporating COVID-19 pandemic impact questions, described in Section 9.1.2) will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. Sensitivity, binary, and Efficacy PP Population analyses for Norfolk QoL-DN total score will also be conducted as described for mNIS+7 in Section 4.4.2.

An additional sensitivity analysis of change from baseline in Norfolk QoL-DN total score (without incorporating COVID-19 impact questions, described in Section 9.1.2) will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18.

4.4.3.2. 10-meter Walk Test Speed, mBMI, and R-ODS

For 10-meter walk test speed (Section 9.1.4), mBMI (Section 9.1.5), and R-ODS (Section 9.1.6), change from baseline will be analyzed using an ANCOVA/MI model at Month 9 (with mBMI and R-ODS analyzed at Month 9 as exploratory endpoints), and using an MMRM at Month 18. Binary analyses for 10-meter walk test speed will also be conducted as described for mNIS+7 in Section 4.4.2.4.

4.4.3.3. Time-averaged Trough TTR Percent Reduction

Time-averaged trough TTR percent reduction through Month 18 is defined as the average trough (ie, predose) TTR percent reduction from Month 6 to 18, which is the steady state period for both vutrisiran and patisiran. Only trough TTR assessments meeting requirements described in the TTR PP population definition (Section 2; Table 3) will be included. The Hodges-Lehmann method [Hodges and Lehmann 1962], stratified by previous TTR stabilizer use (yes vs no), where values within each stratum are first aligned by the within-stratum 1-sample Hodges-Lehmann median, will be used to estimate the 95% CI for the median difference between the vutrisiran and patisiran groups in this study. Non-inferiority of vutrisiran (versus patisiran) will be declared if the lower limit of the 95% CI for the median treatment difference in TTR percent reduction (vutrisiran – patisiran) in this study is greater than –10%.

Sensitivity analyses using the same analysis method will be conducted to compare the TTR percent reduction through Month 18 between the vutrisiran group from this study and the pooled patisiran group from this study and the APOLLO study.

4.4.3.4. Overview of Secondary Endpoint Analyses

The planned analyses of the secondary endpoints are summarized in Table 5 .

Table 5: Analysis of Secondary Endpoints

Endpoint	Statistical Method	Analysis Population	Special Notes
Norfolk QoL-DN total score	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 9.1.2 Sensitivity and binary analyses described in Section 4.4.2
10-meter walk test speed	Month 9: ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 9.1.4 Binary analyses described in Section 4.4.2.3
mBMI	Month 9 (exploratory endpoint): ANCOVA/MI Month 18: MMRM	mITT	In APOLLO study, mBMI was not assessed at Months 9 or 18. The average values of Day 189 and Day 357 will be derived as Month 9. Day 546 will be used as Month 18.
R-ODS	Month 9 (exploratory endpoint): ANCOVA/MI Month 18: MMRM	mITT	Derivation described in Section 9.1.6
TTR percent reduction through Month 18	Stratified Hodges-Lehmann	TTR PP	Sensitivity analysis comparing against patisiran (HELIOS-A + APOLLO)

4.4.4. Exploratory Efficacy Evaluations

The exploratory continuous endpoints, including change from baseline in NIS (Section 9.1.1.2), EQ-5D-5L index (Section 9.1.3), and EQ VAS, will be analyzed using an ANCOVA/MI model at Month 9, and using an MMRM at Month 18. For EQ-5D-5L, categorical descriptives for ordinal response within each EQ-5D domain will be presented at each visit.

The exploratory categorical endpoints, PND score, FAP stage, NYHA class, and KPS, will be descriptively summarized by presenting categorical descriptives for each visit. Categorical descriptives for patients with improving, no change, and worsening in PND/FAP at each postbaseline visit will also be summarized.

Cardiac structure and function will be assessed for all patients through echocardiograms. Cardiac stress and injury will be measured using serum levels of the cardiac biomarkers NT-proBNP, troponin I, and troponin T. Quantification of these biomarkers will be performed at a central laboratory. Descriptive statistics will be provided for actual values, changes, and percentage changes from baseline in echocardiogram parameters and serum levels of troponin I, troponin T, and NT-proBNP by treatment group at each visit.

For the mITT Population and Cardiac Subpopulation, select echocardiographic parameters will be analyzed using an MMRM at Month 18 with covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]), and an interaction term (treatment group by visit), including:

- Mean left ventricular (LV) wall thickness
- LV mass
- Global longitudinal strain
- LV end-diastolic volume
- Cardiac output

Cardiac biomarker NT-proBNP will be analyzed for the mITT population and Cardiac Subpopulation using an ANCOVA/MI model with covariate (baseline) and factor (treatment group) at Month 9. Additionally, NT-proBNP will be analyzed at Month 18 for the mITT population and Cardiac Subpopulation using an MMRM with covariate (baseline value), factors (treatment group; visit [Month 9; Month 18]), and an interaction term (treatment group by visit). A logarithmic transformation will be applied to both baseline and change from baselines values to normalize the data before fitting the MMRM. The adjusted geometric mean fold-change and the ratio of the fold-change (vutrisiran/placebo) from baseline will be presented.

For the mITT Population and Cardiac Subpopulation, change from baseline in heart-to-contralateral lung ratio and normalized LV total uptake of injected dose as assessed by technetium scintigraphy will be summarized at Month 18. Perugini grade as assessed by technetium scintigraphy will be descriptively summarized by presenting categorical descriptives for each visit. Additional Technetium parameters may be descriptively summarized.

All echocardiogram, cardiac, and technetium scintigraphy data will be presented in data listings.

4.4.5. Subgroup Analyses

Subgroup analyses will be conducted to assess the consistency of treatment effect within various subgroups defined by the following baseline characteristics:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Region [North America; Western Europe; Rest of World]
  - Region groups may be adjusted if <20 patients included in any category
- NIS [< 50; ≥ 50]
- Previous tetramer stabilizer use [Yes; No]
- Genotype [V30M; non-V30M]

- FAP stage [I; II & III]
- Cardiac Subpopulation [Yes; No]

Subgroup analyses will be performed for the primary endpoint, mNIS+7, and key secondary endpoint, Norfolk QoL-DN, at Month 9 using separate ANCOVA models with covariate (baseline value) and factors (treatment group; genotype [not applicable to genotype subgroup analyses]), and at Month 18 using an MMRM with covariate (baseline value), factors (treatment group; visit; genotype [not applicable to genotype subgroup analyses]), and an interaction term (treatment group by visit). A forest plot will be generated to illustrate the estimated treatment effect along with 95% CI within each subgroup.

4.4.6. Component/Domain Analyses

Component analyses will be conducted to assess the consistency of treatment effect on the change from baseline at Month 9 for each component of mNIS+7 (Section 9.1.1) and Norfolk QoL-DN domains (Section 9.1.2). The analyses will be performed at Month 9 using the ANCOVA/MI model used for the corresponding endpoint, and at Month 18 using the MMRM used for the corresponding endpoint . A forest plot will be generated to illustrate the estimated treatment effect along with 95% CIs for each component/domain.

4.5. Pharmacodynamic Analyses

The PD parameters include serum TTR and vitamin A. All summary tables and figures will be based on assessments within 21 days after last dose of patisiran or within 84 days after last dose of vutrisiran. Assessments more than 21 days after last dose of patisiran or more than 84 days after last dose of vutrisiran will be presented in listings and individual patient plots only.

Summary tables will be provided for observed values, changes and percentage changes from baseline for each scheduled time point by treatment group for TTR and vitamin A during the study (also see details in Section 6.1).

In addition to TTR percent reduction analyses specified in Section 4.4.3.3, the following parameters, derived using all available TTR samples within the specified windows (including nontrough and unscheduled), will be summarized using descriptive statistics:

- Maximum percentage reduction in serum TTR and vitamin A over 9 and 18 months
- Mean percentage reduction in serum TTR and vitamin A over 9 and 18 months
- Mean percentage reduction in serum TTR at steady-state from Month 6 to 9 and from Month 6 to 18

Subgroup analysis for maximum and mean percentage reduction in serum TTR described above will be provided for the following subgroups:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Previous tetramer stabilizer use [Yes; No]

- Genotype [V30M; non-V30M]
- Weight (kg) [(<65; ≥65]

Summary of TTR levels over time for patients in the patisiran group before and after the switch to vutrisiran will be presented to evaluate maintenance of serum TTR levels following switch from patisiran to vutrisiran.

All PD data will be displayed in data listings.

4.6. Pharmacokinetic Analyses

4.6.1. Study Variables

4.6.1.1. Concentration Data

For vutrisiran, plasma concentrations of ALN-TTRSC02(siRNA) will be obtained. For patisiran, plasma concentrations of ALN-18328(siRNA), Dlin-MC3-DMA and PEG_{2000}-C-DMG will be obtained. Concentration values that are below the limit of quantification (LLOQ or BLQ) will be set to zero for analysis.

4.6.1.2. Plasma Pharmacokinetic Parameters

Model independent PK parameters to be calculated and summarized descriptively include:

- Study days 1 and 253:
  - Predose levels for vutrisiran and patisiran
  - Observed concentration 3-hour, 6-hour, 24-hour postdose (Cp [3 hr, 6 hr, 24hr]) for vutrisiran and 30-min, 6 hour, 24-hour postdose (Cp [30 min, 6 hr, 24 hr]) for patisiran
  - AUC0-24 for vutrisiran
  - Observed trough concentration (Ctrough) for patisiran
  - Observed maximum concentration (Cmax) for vutrisiran
  - Time of observed maximum concentration (Tmax) for vutrisiran
- All other visits:
  - Predose levels for vutrisiran and patisiran
  - Observed concentration 3-hour postdose (Cp [3 hr]) for vutrisiran and patisiran

4.6.2. Statistical Methods

Descriptive statistics for plasma concentration will include the number of patients, mean, SD, coefficient of variation (CV), geometric mean, geometric mean CV, median, minimum, and maximum.

The plasma Cmax, AUC, Cp (predose, 3 hr, 6hr, 24 hr), and Tmax of vutrisiran will be summarized by nominal sampling day as well as the plasma Cp (predose, 30 min, 6 hr, 24 hr) and C_{trough} of ALN-18328 (siRNA), Dlin-MC3-DMA and PEG_{2000}-C-DMG for patisiran. In addition, for vutrisiran only, ratios of Day 253 vs Day 1 AUC and Cmax will be summarized. Mean concentrations (+SD) as well as individual concentrations will be plotted versus nominal sampling time.

Subgroup analysis of vutrisiran plasma Cmax, AUC, Tmax, and ratios of Day 253 vs Day 1 AUC and Cmax will be provided for the following subgroups:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Previous tetramer stabilizer use [Yes; No]
- Genotype [V30M; non-V30M]
- Weight (kg) [(<65; ≥65]

Plasma concentration data will be presented in by-patient listings.

The PK-PD relationship between the plasma concentration and the percent change from baseline in TTR protein and vitamin A will be explored graphically for vutrisiran and ALN-18328 (siRNA) of patisiran separately.

The PK exposure-response relationships for primary endpoint (mNIS+7) and incidence of relevant AEs may also be explored. These may be summarized by exposure quartiles at 9-months for vutrisiran.

Population PK and exposure-response modeling will be reported separately.

4.7. Safety Analyses

Safety analyses will be conducted using the Safety population. All safety summaries will be descriptive and will be presented by treatment group.

4.7.1. Study Drug Exposure

Last exposure date during the 18-month Treatment Period is defined as the earliest of the following dates:

- Last dose date + treatment-specific window (83 days for vutrisiran; 20 days for patisiran)
- Analysis cutoff date
- End of study date
- Week 84 dose date (start of Legacy Treatment Extension Period)
- RTE Day 1 dose date (start of RTE Period)

Duration of drug exposure will be defined as last exposure date – first dose date + 1. Duration of drug exposure, the total number of doses received, and total amount of study drug received will be summarized by descriptive statistics. Summaries of the numbers and percentages of patients with no missing dose, and the number of missing doses per patient will also be provided. The total volume infused or injected will be summarized as well.

Study drug exposure data collected in the CRFs of study drug administration will also be summarized for each dose or infusion. The numbers and percentages of patients with complete, partial, and missing dose administrations will be summarized. Complete and partial administration is defined as follows:

- Patisiran:
  - Complete: ≥80% (≥160 mL) of the planned infusion volume (200 mL)
  - Partial: >0% to <80% (>0 to <160 mL) of the planned infusion volume (200 mL)
- Vutrisiran:
  - Complete: 100% administered
  - Partial: >0% to <100% administered

For the patisiran group, the number of patients who experienced interruptions of infusions for any reason will be tabulated, as well as the number of patients with infusion interruptions due to an infusion-related reaction (IRR).

For the vutrisiran group, the above drug exposure summaries applicable to vutrisiran will also be provided by vial vs prefilled syringe dose presentations. Vutrisiran doses with missing dose presentation information before the date of first prefilled syringe administration to any patient will be treated as vial dose presentations.

Duration of exposure to vial and prefilled syringe dose presentations of vutrisiran will also be summarized.

Dosing information for each patient will be presented in a data listing.

4.7.2. Adverse Events

This Phase 3 study will use the APOLLO study as an external control. Patient-level data from this study will be compared with patient-level data from APOLLO for relevant AE summaries only.

AEs will be coded using the MedDRA coding system (version 23.0 or later) and displayed in tables and data listings using SOC and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, defined as any AE with onset during or after the administration of study drug through 28 days following the last dose of patisiran or 84 days following the last dose of vutrisiran. In addition, any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study will be considered treatment-emergent. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first administration of study drug.

Adverse events will be summarized by the numbers and percentages of patients reporting a given AE. A patient contributes only once to the count for a given AE (overall, by SOC, by preferred term). Overall event counts and event rates may also be summarized.

An overall summary of AEs will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any serious AE (SAE), any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths.

Tabulations by SOC and preferred term will be produced for the following: all AEs; AEs related to treatment; severe AEs; AEs leading to infusion interruption (patisiran only); AEs leading to drug interruption; AEs leading to treatment discontinuation; AEs leading to stopping study participation; and SAEs. Adverse events and AEs related to treatment will also be tabulated by preferred term. Adverse events and SAEs will also be summarized by SOC and preferred term for the cardiac subpopulation. Subgroup tabulations by SOC and preferred term for AEs and SAEs will be provided for the following subgroups:

- Age (years) [≥65; <65]
- Sex [Male; Female]
- Race [White; All other races]
- Region [North America; Western Europe; Rest of World]
  - Region groups may be adjusted if <20 patients included in any category
- Genotype [V30M; non-V30M]
- FAP stage [I; II & III]
- Weight (kg) [<65; ≥65]

Separate tables will present the number and percentage of AEs by maximum relationship to study drug and by maximum severity. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

AEs mapping to the standardized MedDRA queries (SMQs) Depression and Suicide/Self-injury, Torsade de pointes/QT prolongation, and Cardiac failure will be summarized by preferred term. Adverse events mapping to the SMQ Drug Related Hepatic Disorder and SMQ Acute Renal Failure will be summarized by SOC and preferred term. Adverse events mapping to Cardiac Arrhythmias high level group term and the SMQ Malignant or Unspecified Tumors will be summarized by high level term and preferred term. Other SMQs or AE groupings may be evaluated.

Separate tables will be provided summarizing signs and symptoms of IRRs (overall and by premedication regimen) and AEs related to premedication by SOC and preferred term for the patisiran group. Injection site reactions will be summarized for the vutrisiran group. Summary table of ISRs by presentation (vial vs prefilled syringe) may be provided. The number and percentage of patients with AEs, ISRs, and IRRs over time will also be summarized by SOC and preferred term.

All AEs will be presented in patient data listings. Separate listings will be provided for death, SAEs, AEs leading to treatment discontinuation, AEs leading to stopping study participation, and AEs mapping to the SMQ as described above. A listing of ISRs will be provided for the vutrisiran group. Listing of IRRs and AEs related to premedications will also be provided for patisiran group. A listing of patients who underwent liver transplant will also be provided.

4.7.3. Laboratory Data

Clinical laboratory values will be expressed in SI units. Central laboratory data will be summarized. Local laboratory data will not be included for descriptive summaries by visit. Unscheduled assessments will be included in determining "worst" or potentially clinically significant values. For liver function test parameters, local laboratory data will be included in the derivation of "worst" or potentially clinically significant values under the following rules:

- Central laboratory data at both scheduled and unscheduled visits will be used
- If central laboratory data at a visit is missing, local laboratory data will be used
- If a patient has both local and central laboratory data at the same visit, the central data will be used

Summary tables and figures using central laboratory data alone and central and local laboratory data combined will be presented as applicable.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and liver function tests). Descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit.

A listing will be produced for all patients with abnormal liver function tests defined as an ALT > 3×ULN, AST > 3×ULN, and total bilirubin > 2×ULN at any time point.

A table will be produced to summarize the number and percentage of patients in each of the below categories at any postbaseline time point.

- ALT ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- AST ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- Maximum ALT or AST ≤ 1, > 1 & ≤ 3, > 3 & ≤ 5, > 5 & ≤ 10, > 10 & ≤ 20, > 20 ×ULN,
- ALP > 1.5 ×ULN,
- Total Bilirubin ≤ 1, > 1 & ≤ 1.5, > 1.5 & ≤ 2, > 2 & ≤ 3, > 3 & ≤ 5 and > 5 ×ULN,
- Total Bilirubin > 2 ×ULN concurrent with ALT or AST > 3 ×ULN.

A shift table from baseline to worst postbaseline for ALT, AST, and total bilirubin will also be provided. In separate figures, the peak total bilirubin (at any time postbaseline) will be plotted against the peak AST, the peak ALT, and the peak AST or ALT levels at any time postbaseline.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities will be provided. The results may also be graded according to the NCI CTCAE Version 5.0 or above. A shift summary of baseline to maximum postbaseline CTCAE grade may be presented, as appropriate.

The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) will be categorized as below: ≥ 90; ≥ 60 - < 90; ≥ 45 - < 60; ≥ 30 - < 45; ≥ 15 - < 30; and < 15. A shift summary of baseline to worst postbaseline eGFR category will be presented.

All laboratory data will be provided in data listings. Out-of-range laboratory results will be identified in the listings.

4.7.4. Vital Signs and Physical Examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. Summary tables of potentially clinically significant vital signs will be provided.

Vital sign measurements will be presented for each patient in a data listing.

4.7.5. Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, and QTc interval. Baseline values will be the average of measurements from the baseline triplicate ECGs for each patient recorded. Descriptive statistics will be provided for each measure over time. Change from predose to each postdose assessment will also be summarized. The number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each study visit will also be summarized.

Corrected QT interval (QTc) will be calculated using the Fridericia's (QTcF) correction formula, derived as follows:

Table 6: QTc Derivation

	Derivation	
Parameter	**If RR available**	**If RR unavailable**
QTcF	$\frac{\text{QT (msec)}}{\text{Cubic root of RR (sec)}^{a}}$	$\frac{\text{QT (msec)}}{\text{Cubic root of 60/HR (bpm)}}$

[a] RR (sec)=RR(msec)/1000.

QTcF=QTc Fridericia; HR = heart (ventricular) rate.

Categorical analyses of the QTc data will be conducted and summarized as follows:

- The number and percentage of patients with maximum increase from baseline in QTc (< 30, 30 – 60, >30, > 60 ms)
- The number and percentage of patients with maximum postbaseline QTc (< 450, 450 – < 480, 480 – 500, >480, > 500 ms)

All ECG data for each patient will be provided in a data listing. A separate listing will be provided for patients with any QTc postbaseline value > 500ms or an increase from baseline > 60 ms.

4.7.6. Premedication

Patisiran 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 histamine 1 (H1) blocker (diphenhydramine 50 mg, or equivalent)
- Intravenous histamine 1 (H2) blocker (ranitidine 50 mg, or equivalent)

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

Premedications will be coded using the WHO Drug Dictionary (March 2020 or later). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Premedication data will be listed.

4.7.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (March 2020 or later). Prior medications include medications taken ≥ 1 time before the first dose of study drug, regardless of medication end date. Concomitant medications include medications taken ≥ 1 time on or after the first dose of study drug, regardless of medication start date. Results will be tabulated by ATC level 3 (or higher if not available) and preferred term.

When there are partial or missing dates, imputed dates will be used to determine 1) if a medication is prior or concomitant, and 2) duration of exposure of local standard treatment for hATTR amyloidosis. Imputed dates will not be presented in the listings.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date. For medications with a completely missing start date, the medications will be considered as started prior to the first dose of study drug; medications will be classified as prior, concomitant or both depending on the medication stop dates. For medications with a completely missing stop date, the end of study date will be imputed.

For patients who receive local standard treatment (including liver transplant) for hATTR amyloidosis during the study, the type of treatment will be summarized categorically.

Prior and concomitant medications will be presented in data listings.

4.7.8. Suicidality Questionnaire

The number and percentage of patients experiencing the suicidal ideation, suicidal behavior, or self-injurious behavior composite outcomes (and individual components) will be summarized by visit. A shift table will be employed to summarize the baseline C-SSRS category versus the worst postbaseline C-SSRS category; the categories are defined as 1) no suicidal ideation or behavior, 2) suicidal ideation, and 3) suicidal behavior. Patients experiencing both suicidal ideation and suicidal behavior are included in the suicidal behavior category.

Data from the C-SSRS questionnaire will be provided in a data listing.

4.8. Anti-Drug Antibody

The number and percentage of patients with confirmed positive anti-drug antibody (ADA) assay results at baseline and at any time during the Treatment Period, as well as treatment-emergent ADA during the Treatment Period, will be summarized. Treatment-emergent ADA consist of treatment-induced ADA and treatment-boosted ADA, defined as the following:

- Treatment-induced ADA: Confirmed positive ADA developed de novo after drug administration in patients without preexisting (baseline) confirmed positive ADA
- Treatment-boosted ADA: Confirmed positive ADA after drug administration with ADA titer > 4 x baseline ADA titer in patients with preexisting (baseline) confirmed positive ADA

The titer results for patients with confirmed positive ADA and treatment-emergent ADA results will also be summarized using descriptive statistics.

For patients with confirmed positive ADA results, spaghetti plots for the serum TTR (ELISA) over time and the plasma concentration of vutrisiran and ALN-18328, Dlin-MC3-DMA, and PEG2000-C-DMG for patisiran over time will be presented. Effect of positive ADA on efficacy and safety may also be explored.

ADA data and patients with confirmed positive ADA results will be presented in data listings.

4.9. COVID-19 Pandemic Impact Analyses

Additional data were collected to characterize the impact of the COVID-19 pandemic on general study conduct, disposition, and quality of life, and subsequently, additional analyses and summaries will be provided in acknowledgement of multiple regulatory guidances (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards, US Food and Drug Administration, 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, 2020).

4.9.1. General Impact

Patients who discontinue treatment or stop study participation due to COVID-19 will be included in patient disposition summaries as described in Section 4.1.

Impact on study participation due to COVID-19, including visit completion, visit location changes, and study drug dosing changes, will be summarized overall on the patient level with both continuous and categorical descriptives, and overall and by visit on the event level with categorical descriptives, based on the above categories.

4.9.2. Impact on Efficacy

Per protocol amendment 3 (17 July 2020), efficacy assessments that may be missed due to COVID-19 may be delayed up to 6 months after the scheduled timepoint to minimize missed endpoint ascertainment. Such delayed efficacy assessments due to COVID-19 will be included in analyses as described in Section 3.7.

Additional analyses of the primary and key secondary endpoints during the 18-month Treatment period will be conducted based on the Month 9 Efficacy PP population using an ANCOVA model at Month 9, and based on the Month 18 Efficacy PP population using an MMRM at Month 18. The Month 9 and Month 18 Efficacy PP populations are defined in Section 2. These analyses represent the initial visit windows for the efficacy assessments in place prior to the COVID-19 pandemic.

Additional descriptive summaries for the primary and secondary endpoints by pandemic phase will be provided for Month 9 analysis only. Pandemic phase definitions may vary over time given the evolving nature of the COVID-19 pandemic; potential definitions may include the following:

- Before and during pandemic, where assessments will be considered during the pandemic if the event occurs on or after first confirmed case of COVID-19 based on the country where the study site is located, described in Section 9.3.
- Before March 2020, between March 2020 and June 2020, and after June 2020.

Due to the potential impact on aspects of quality of life in multiple ways (eg, infection, anxiety and stress from the pandemic, the potential for loss of employment, and the disruptions in physical activity and social interactions due to social distancing and the closure of public gathering places), additional information on specific impacts on quality of life associated with the COVID-19 pandemic will be collected. The derivation of Norfolk QoL-DN total score and Physical Functioning/Large Fiber domains will be modified for patients reporting any impacts of COVID-19 on quality of life; these modifications are described in Section 9.1.2.

Summaries of missing efficacy data due to the COVID-19 pandemic will be included in missing efficacy data summaries as described in Section 3.6.2.

Given the measures specified in the protocol designed to ensure data integrity and the additional and modified efficacy analyses describe above, analyses excluding patients with COVID-19-related protocol deviations will not be prespecified, but may be considered post hoc if warranted.

4.9.3. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will include the number and percentage of patients, as well as events and event rates, with any AE, any severe AE, any SAE, any AE leading to treatment discontinuation, any AE leading to study discontinuation, and any deaths. AEs mapping to the COVID-19 custom query will be summarized by high level term and preferred term. Due to the evolving nature of COVID-19-related MedDRA terminology, the COVID-19 custom query will be based on the latest information available at the specified analysis timepoint.

An overall summary of AEs by pandemic phase will include the number and percentage of patients, as well as events and event rates, with any AE, any AE assessed by the Investigator as related to treatment, any severe AE, any severe AE related to treatment, any SAE, any SAE related to treatment, any AE leading to treatment discontinuation, any study drug related AE leading to treatment discontinuation, any AE leading to study discontinuation, any study drug related AE leading to study discontinuation, and any deaths. AEs and SAEs will be summarized by pandemic phase, SOC, and preferred term. The number and percentage of patients with AEs during the pandemic will also be summarized over time by SOC and preferred term.

4.9.4. Other Impacts

Treatment duration will also be summarized by pandemic phase. Adverse event, study drug exposure, and efficacy listings will include identification of assessments occurring during the pandemic.

For patients reporting an AE mapped to the COVID-19 custom query, AEs and prior and concomitant medications will also be presented in separate data listings. Additionally, patient profiles will be provided.

5. ANALYSIS OF THE RANDOMIZED TREATMENT EXTENSION (RTE) PERIOD

[redacted]

[redacted] [redacted]

[redacted]

- [redacted] [redacted]
- [redacted] [redacted]
- [redacted] [redacted]
    - [redacted] [redacted]
- [redacted] [redacted]
- [redacted] [redacted]
    - [redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

6. SUMMARY OF THE ENTIRE STUDY

The study design includes an 18-month Treatment Period, where patients will be randomized to either vutrisiran or patisiran treatment, followed by the Treatment Extension Periods (Legacy Extension and/or Randomized Treatment Extension Periods) [redacted]. Efficacy and safety assessments will be descriptively summarized over time for the mITT population and Safety populations respectively. The long-term period-based safety of vutrisiran will be characterized for the All Vutrisiran-Treated Population, including all data for patients while receiving vutrisiran treatment in any treatment period.

6.1. During the Entire Study

Clinical efficacy and PD parameters will be summarized descriptively by visit throughout the entire study, including the18-month treatment period and the extension periods, to characterize the long-term effect of vutrisiran treatment as well as vutrisiran following patisiran treatment.

For clinical efficacy parameters, the visits will be presented by baseline, Month 9, Month 18, [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]

6.2. During Vutrisiran Treatment

Data in the vutrisiran-treatment period will consist of all data on or after the first administration of vutrisiran treatment:

- For patients randomized to vutrisiran, all data in the Treatment and Treatment Extension periods will be included
- For patients randomized to patisiran, all data in the Treatment Extension periods will be included; data in the Treatment Period while on patisiran treatment will be excluded

Where applicable, baseline will be defined as described in Section 3.3.2. Summaries will be presented by vutrisiran/vutrisiran, patisiran/vutrisiran, and overall, and will be based on the All Vutrisiran-Treated Population.

Duration of drug exposure will be defined as last vutrisiran date – first vutrisiran dose date + 1, with last vutrisiran date during vutrisiran treatment defined as the earliest of the following dates:

- Last vutrisiran dose date + treatment-specific window (83 days if last vutrisiran dose received is [redacted]; 167 days if last dose received is [redacted])
- Analysis cutoff date
- End of study date

AE and ISR summaries described in Section 4.7.2 will be provided for vutrisiran-emergent adverse events, defined as treatment-emergent adverse events occurring on or after the first dose of vutrisiran treatment through a treatment-specific window following the last dose of vutrisiran (84 days if last vutrisiran dose received is [redacted]; 168 days if last dose received is [redacted]). Potentially clinically significant postbaseline abnormalities and shift from baseline to the worst postbaseline status for laboratory, vital signs, and ECG parameters, ADA, concomitant medications, and overall study drug exposure, during the vutrisiran-treatment period will be summarized.

7. CHANGES TO PLANNED ANALYSES

Modifications to planned analysis specifications from the protocol are documented below:

1. Section 2: The Safety population definition was modified to include all patients who received any amount of study drug, regardless of randomization status. The updated definition is consistent with the APOLLO study.
2. Section 1.3.1 and Section 1.3.2: Language was added to specify US-specific positive trial criteria in accordance with FDA advice (received 14 September 2020), ie, both the primary and key secondary endpoints are deemed statistically significant. Additional language was added to clarify the implicit positive trial criteria for other regions.

8. REFERENCES

de Souza Cavalcanti J, de Paula Ferreira JL, Vidal JE, de Souza Guimaraes PM, Moreira DH, de Macedo Brigido LF, et al. HIV-1-infected patients with advanced disease failing a raltegravir-containing salvage regimen in Sao Paulo, Brazil. Int J Antimicrob Agents. 2014 Mar;43(3):287-91.

Hodges JL,Lehmann EL. Rank Methods for Combination of Indepdendent Experiments in Analysis of Variance. Annals of Mathematical Statistics. 1962;33(2):482-97.

Rubin D. Multiple Imputation after 18+ Years. Journal of the American Statistical Association. 1996;91(434):473-89.

9. APPENDICES

9.1. Questionnaire/Scoring

In questionnaires, if multiple responses are provided to a single-response question, the question is deemed as missing.

9.1.1. Modified Neuropathy Impairment Score (mNIS+7) and Neuropathy Impairment Score (NIS)

Note: the mNIS+7 and NIS measurements are conducted in duplicate per time point. The average of 2 complete duplicate values will be reported, except in cases of missing or partially missing data as described in the table below.

Assessment Tool	**Total Points**	**Components (maximum points)**
Modified NIS+7	304	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • Quantitative sensory testing by body surface area including touch pressure (TP) and heat as pain (HP): QST-BSA$_{TP+HP5}$ (80) • $\sum$5 nerve conduction studies (10) – Ulnar compound muscle action potential (ulnar CMAP) – Ulnar sensory nerve action potential (ulnar SNAP) – Sural sensory nerve action potential (sural SNAP) – Tibial compound muscle action potential (tibial CMAP) – Peroneal compound muscle action potential (peroneal CMAP) • Postural blood pressure (BP) (2)
NIS	244	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • NIS-S: Sensation (32)

9.1.1.1. Modified Neuropathy Impairment Score (mNIS+7)

There are 5 components within mNIS+7 total score including NIS-W, NIS-R, QST, $\sum$5 NC, and postural BP, as described in detail below.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.1.1.2. Neuropathy Impairment Score (NIS)

The components of NIS include the following:

1. NIS-W as described in previous section.
2. NIS-R as described in previous section.
3. NIS-S is the sum of the finger and toe sensation components (touch pressure, pin-prick, vibration, joint position). Assessments are performed separately for the right- and left-hand side of the body. Scoring for the sensory assessment is 0 (normal), 1 (decreased) and 2 (absent). The maximum total score for NIS-S is 32.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

Norfolk QoL-DN is a tool for assessing patients' perception of the effects of diabetes and diabetic neuropathy. There are 35 questions divided into 5 domains. The range of possible total scores is -4 to 136.

Part I: Symptoms

Items 1-7 (Part I) are a simple inventory of symptoms of neuropathy. The presence of the symptom is checked in whichever box applies, and an absence of a symptom is checked under "none." Positive responses are scored as 1; and negative responses, as 0.

Part II: Activities of Daily Life

Items 8-35 (Part II) pertain to Activities of Daily Life, and most of these are scaled on a 5-point Likert scale ranging from 0 (“Not a problem”) to 4 (“Severe problem”). However, Questions 31 and 32 are scored differently. In Question 31, “Good”, the middle item, is scored as 0. “Very Good” is scored as –1, “Excellent” is scored as –2. “Fair” is scored as 1, and “Poor” is scored as 2. In Question 32, “About the Same,” the middle item, is scored as 0. “Somewhat better” is scored as –1, “Much better” is scored as -2. “Somewhat worse” is scored as 1, and “Much worse” is scored as 2.

Subscales and Scoring Algorithm

The Total QOL and 5 domains should be summed as follows:

- Total QOL (35 items) [redacted]
- Physical Functioning/Large Fiber (15 items) [redacted]
- Activities of Daily Living (ADLs) (5 items) [redacted]
- Symptoms (8 items) [redacted]
- Small Fiber (4 items) [redacted]
- Autonomic (3 items) [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

9.1.3. EuroQol-5-Dimension 5-Level (EQ-5D-5L)

Each of the 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) is scored on a 5-point Likert scale from 1 ("I have no problems/pain/anxiety") to 5 ("I am unable to…," "I have extreme anxiety/depression").

The 5 scores are concatenated together (in the order of Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) to create an EQ-5D-5L profile (e.g., 11111, 55555). The profile is then used to obtain an index value using the United States value set. The index values range from –0.109, associated with a profile of 55555, to 1.0, associated with a profile of 11111. Smaller index values indicate greater impairment.

Missing values are handled as follows:

- Missing items are coded as "9" in creating patient profiles.
- The index value is deemed as missing when responses are missing for 1 or more of the 5 dimensions.
- If the entire instrument is missing, the EQ-5D-5L index value is considered as missing.

9.1.4. 10-Meter Walk Test (10-MWT)

Two replicate assessments are expected to be performed approximately 24 hours apart and no more than 7 days apart per protocol. At baseline and for each postbaseline visit, the walk speed (m/s) analysis value is derived as follows:

Table 7: 10-MWT Derivation Scenarios

Scenario	Derivation
Both replicate assessments nonmissing	
Patient able to walk for both assessments	10/mean(time 1, time 2)
Patient unable to walk for 1 of the 2 assessments	mean(0, 10/assessable time)
Patient unable to walk for both assessments	0
One replicate assessment nonmissing	
Patient able to walk	10/assessable time
Patient unable to walk	0

9.1.5. Modified Body Mass Index (mBMI)

In the APOLLO study, mBMI was not assessed at Months 9 or 18. For the placebo (APOLLO) group, these assessments are derived as follows:

- Month 9 = mean of Day 190 (Week 27) and Day 358 (Week 51) assessments
- Month 18 = Day 547 (Week 78) assessment

9.1.6. Rasch-Built Overall Disability Scale (R-ODS)

The R-ODS consists of 24 items scored on a scale of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty). A total score will be calculated as the average of all nonmissing items multiplied by 24 if at least 90% of the items are nonmissing. The total score will be deemed as missing if more than 10% of the items (3 or more items) are missing.

9.2. Pattern-Mixture Model Details

Similar to the primary analysis methods, assessments after initiation of local standard treatment will be treated as missing and thus imputed following the PMM procedure.

9.2.1. Month 9 Analysis

As an initial step, separate intermediate datasets for mNIS+7 and Norfolk QoL-DN total score will be prepared, which will include the key variables listed in Table 8.

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

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

[redacted]

[redacted]

[redacted]

[redacted]

9.2.2. Month 18 Analysis

As an initial step, separate intermediate datasets for mNIS+7 and Norfolk QoL-DN total score will be prepared, which will include the key variables listed in Table 9. For nonmonotone missingness (patients who miss Month 9 but have Month 18 data available), the missing Month 9 change from baseline score will be imputed with the group mean of the specific treatment and considered as ‘nonmissing’ in the intermediate datasets. Nonmonotone missing data are expected to be rare.

[redacted]

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.3. Pandemic Phase Start Dates by Country

Table 10: Pandemic Phase Start Dates by Country

Country	Date of 1st Confirmed Case
Argentina	2020-03-03
Australia	2020-01-25
Belgium	2020-02-04
Brazil	2020-02-26
Bulgaria	2020-03-08
Canada	2020-01-26
Cyprus	2020-03-09
France	2020-01-24
Germany	2020-01-28
Greece	2020-02-26
Italy	2020-01-29
Japan	2020-01-14
Korea	2020-01-19
Malaysia	2020-01-25
Mexico	2020-02-28
Netherlands	2020-02-27
Portugal	2020-03-02
Spain	2020-01-31
Sweden	2020-01-31
Taiwan	2020-01-22
United Kingdom	2020-01-31
United States	2020-01-20

As reported by the World Health Organization and the Taiwan Centers for Disease Control.

10. AMENDMENT HISTORY

10.1. Amendment 1: 17 July 2020

The Sponsor developed this SAP amendment without knowledge of postbaseline efficacy data in accordance with the Data Integrity Plan. Key changes include:

- Updates reflecting cumulative changes made after the original ALN-TTRSC02-002 protocol (11 October 2018) [amendment 1 (10 October 2019), amendment 2 (06 May 2020), and amendment 3 (17 July 2020)], including:
  - Changes to primary and secondary endpoints and associated MCP
  - Changes and/or additions to derivations, summaries, and analyses to account for and/or characterize the impact of the COVID-19 pandemic
- Updates reflecting feedback received from the FDA on the original statistical analysis plan and data submission plan
- Addition of summaries to characterize the long-term efficacy and safety of vutrisiran
- Addition of prefilled syringe vs vial summaries

Section	Description	Rationale
Throughout document	Updated co-primary endpoint language to primary and key secondary	To align with protocol amendment 3 revised endpoints
Section 1	Updated study design and objectives	To align with protocol amendment 3 updated language
Section 1.3.1 Section 1.3.2	Updated MCP and add MCP for EU/other regions	To align with updated primary/secondary endpoints; to specify a separate MCP reflecting EMA/SAWP's preference to evaluate efficacy through Month 18, which will be used for potential future submissions in other regions
Section 2 Section 4.4.3.3	Updated TTR percent reduction definition and associated TTR PP population and analyses	To reflect protocol amendment 2 change to analyze TTR percent reduction at Month 18 instead of Month 9 per protocol amendment 3; name revised to make distinct from added efficacy PP population
Section 2	Added efficacy PP population	To support analyses related to COVID-19 pandemic impact on efficacy to estimate treatment effects in an 'unimpacted' population
Section 2	Added all vutrisiran-treated population	To support long-term safety analyses during vutrisiran treatment
Section 3.2	Updated presented treatment groups	To clarify planned presentations with respect to data submission plan
Section 3.6.2	Updated missing efficacy data summary	To account for missingness associated with COVID-19 pandemic
Section 3.7	Added extended efficacy analysis windows	To allow inclusion of efficacy visit data delayed due to COVID-19 pandemic

Section	Description	Rationale
Section 4.1	Updated patient disposition summaries	To clarify time windows to align with efficacy analysis timepoints; to account for discontinuations associated with COVID-19 pandemic
Section 4.2	Added summary of COVID-19-related protocol deviations	To align with regulatory guidance recommendations
Section 4.4	Added details on Month 9 and 18 analyses	To clarify data intended to be cleaned and included in planned analysis submissions
Section 4.4.1.1	Added details on handling of patients with missing model covariates and factors Specify KPS to be included as continuous covariate	To clarify and align with approach used in APOLLO (ALN-TTR02-004) study
Section 4.4.1.3 Section 4.4.2.1 Section 4.4.2.2 Section 4.4.5	Added ANCOVA model for use in select sensitivity and subgroup analyses	To simplify models used for non-primary analyses
Section 4.4.2.2	Updated propensity score model covariates and factors	To incorporate FDA feedback on initial SAP to include additional potential sources of differences in treatment assignment propensity to achieve the best predictive model
Section 4.4.2.3	Added pattern-mixture model sensitivity analysis	To incorporate FDA feedback on original SAP to assess the robustness of results under MNAR assumptions
Section 4.4.3.1 Former Section 7.1.2	Added key secondary endpoint section Updated primary Norfolk derivation and added sensitivity analysis using original derivation	To align with protocol amendment 3 revised endpoints (Norfolk changed from co-primary to key secondary) To mitigate for potential COVID-19 pandemic impact on quality of life on select Norfolk items in the primary analysis
Section 4.4.4	Changed all-cause deaths and/or all-cause hospitalization analyses to exploratory	To align with protocol amendment 3 revised endpoints
Section 4.4.5 Section 4.4.6	Added Month 18 subgroup and component analyses	To support characterization of efficacy profile at Month 18 for consistency with the APOLLO study
Section 4.7.1	Added definitions of complete vs partial dose administrations	To clarify definitions aligning with CRF data collection instructions
Section 4.7.1 Section 4.7.2	Added prefilled syringe vs vial summaries	To support regulatory assessment of vutrisiran administration via prefilled syringe
Section 4.7.2	Added inclusion of external placebo comparison group	To incorporate FDA feedback on data submission plan to facilitate AE safety comparisons to the APOLLO study
Former Section 4.9	Added analyses of data in the Treatment Extension Period	To support long-term efficacy and safety objectives

Section	Description	Rationale
Former Section 4.10 Section 4.4.2.5	Added summaries of COVID-19 pandemic general impact and related impacts on efficacy and safety	To assess the impact of COVID-19 in acknowledgement of regulatory guidances
Former Section 6	Updated references and added in-text citations where appropriate	To document sources
Throughout document	Added minor definition details, summaries, and protocol-amendment updates Removed selected analyses Aligned tables with related in-text revisions Corrected general typographic and formatting errors Updated abbreviations	To streamline and clarify planned analyses needed to support overall objectives and address minor errors

10.2. Amendment 2: 15 October 2020

The Sponsor developed this SAP amendment primarily to address feedback received from the FDA regarding Norfolk QoL-DN total score in relation to criteria to declare a positive trial.

Section	Description	Rationale
Section 1.3.1 Section 1.3.2 Former Section 5	Define positive trial criteria within different regions	To address FDA feedback regarding the importance of Norfolk QoL-DN total score in declaring a positive trial To document this change from protocol language
Section 3.9	Moved database lock and cutoff date content from Section 4.4 into standalone subsection and removed content to be defined in the Data Management Plan	To improve organizational flow and streamline content
Section 4.5 Section 4.6	Updated PK/PD parameters Added PK/PD subgroup analyses	To support PK/PD data interpretation
Section 4.7.1	Updated duration of drug exposure definition	To account for treatment period and cutoff date definitions
Section 4.7.2	Added AE subgroup analyses	To support AE data interpretation
Section 4.7.3	Updated local laboratory data inclusion and summaries	To clarify rules for including local laboratory data
Section 4.8	Added treatment-emergent ADA definition	To align with ADA summaries from recent submissions
Former Section 4.10.2	Added efficacy summaries by pandemic phase	To incorporate FDA guidance on assessing impact of pandemic on efficacy
Former Section 7.1.1.3	Removed algorithms for transforming to normal deviates and points and moved to programming specifications	To prevent disclosure of information proprietary to [redacted]

Section	Description	Rationale
Former Section 7.1.5	Updated corresponding APOLLO assessment days	To align with HELIOS-A study design with first dose date = Day 1 rather than Day 0 in APOLLO
Throughout document	Corrected general typographic and formatting errors Updated minor details	To address minor errors and clarifications

10.3. Amendment 3: 24 August 2021

The Sponsor developed this SAP amendment to reflect changes made in ALN-TTRSC02-002 protocol amendment 4 (19 February 2021), which primarily pertain to the evaluation of safety, PD, and efficacy [redacted]

Section	Description	Rationale
Section 1.1	Updated study design text Added Figure 2	To align with relevant changes to study design per protocol amendment 4
Section 2	Added Re-randomized Population Updated All Vutrisiran-Treated Population	To support RTE Period summarization and reflect study design changes per protocol amendment 4
Section 3.2 Section 3.3 Section 3.4	Added content regarding for All Vutrisiran-Treated and Re-randomized populations, including treatment arm specifications, baseline definitions, RTE randomization stratification factors	To clarify important details and derivations for new summaries
Section 3.7	Added details for visit window for the RTE efficacy visit	To allow inclusion of efficacy visit data delayed due to COVID-19 pandemic for the RTE efficacy assessment
Section 3.9	[redacted]	To clarify planned analysis for the RTE period
Section 4	Relabeled Study Analysis as Analysis of the 18-Month Treatment Period	To clarify analyses and summaries for the 18-month treatment period
Section 4.4.2.3 Section 4.4.2.6 Section 9.2	Added Month 18 pattern-mixture model specifications	To support sensitivity evaluation of EU primary Month 18 efficacy endpoints
Section 4.4.3.3	Relabeled TTR Percent Reduction as Time-averaged trough TTR Percent Reduction	To distinguish from similarly named PD endpoints
Section 4.4.4	Updated NT-proBNP and echocardiogram model details Added additional scintigraphy parameters	To clarify and support cardiac efficacy evaluation
Section 4.4.4	Removed death/hospitalization endpoint	To align with relevant changes of death /hospitalization endpoint per amendment 4
Section 4.7.1	Added duration of vial and prefilled syringe exposure	To support vial vs prefilled syringe evaluation

Section	Description	Rationale
Section 5	Added summaries of RTE Period data	[redacted]
Section 6	Moved summaries of Treatment Extension Period data from Section 4 into standalone section and updated the content	To improve organizational flow and align with relevant changes to study design per protocol amendment 4
Throughout document	Corrected general typographic and formatting errors Updated minor details	To address minor errors and clarifications

Signature Page for VV-CLIN-005562 v1.0
ALN-TTRSC02-002 SAP Amend3

Task: Approval Verdict: Approve	[redacted] T+0000

Task: Approval Verdict: Approve	[redacted] 31:50 GMT+0000

Signature Page for VV-CLIN-005562 v1.0
ALN-TTRSC02-002 SAP Amend3