Official Title: An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients With Hereditary Transthyretin-mediated Amyloidosis (hATTR Amyloidosis) With Disease Progression Post-Orthotopic Liver Transplant

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ALN-TTR02-008

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Statistical Analysis Plan, Protocol ALN-TTR02-008
08 October 2020, Amendment 1 SAP

ALN-TTR02 (patisiran)

APPROVAL SIGNATURE PAGE

Protocol Number: ALN-TTR02-008
Protocol Title: An Open-label Study to Evaluate Safety, Efficacy and Pharmacokinetics (PK) of Patisiran-LNP in Patients with Hereditary Transthyretin-mediated Amyloidosis (hATTR amyloidosis) with Disease Progression Post-Orthotopic Liver Transplant

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROVAL SIGNATURE PAGE</td>
<td>2</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>3</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>5</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS AND DEFINITION OF TERMS</td>
<td>6</td>
</tr>
<tr>
<td>1. INFORMATION FROM THE STUDY PROTOCOL</td>
<td>8</td>
</tr>
<tr>
<td>1.1. Introduction and Objectives</td>
<td>8</td>
</tr>
<tr>
<td>1.1.1. Introduction</td>
<td>8</td>
</tr>
<tr>
<td>1.1.2. Document and Study Objectives</td>
<td>8</td>
</tr>
<tr>
<td>1.1.2.1. Primary Objective</td>
<td>8</td>
</tr>
<tr>
<td>1.1.2.2. Secondary Objectives</td>
<td>9</td>
</tr>
<tr>
<td>1.1.2.3. Exploratory Objectives</td>
<td>9</td>
</tr>
<tr>
<td>1.1.2.4. Safety Objective</td>
<td>9</td>
</tr>
<tr>
<td>1.2. Study Design</td>
<td>9</td>
</tr>
<tr>
<td>1.2.1. Synopsis of Study Design</td>
<td>9</td>
</tr>
<tr>
<td>1.2.2. Study Procedures</td>
<td>10</td>
</tr>
<tr>
<td>1.2.3. Efficacy, Pharmacokinetic, Immunogenicity, and Safety Assessments</td>
<td>10</td>
</tr>
<tr>
<td>1.2.3.1. Efficacy Assessments</td>
<td>10</td>
</tr>
<tr>
<td>1.2.3.2. Pharmacokinetic Parameters</td>
<td>10</td>
</tr>
<tr>
<td>1.2.3.3. Immunogenicity Parameters</td>
<td>10</td>
</tr>
<tr>
<td>1.2.3.4. Safety Parameters</td>
<td>10</td>
</tr>
<tr>
<td>2. PATIENT POPULATION</td>
<td>11</td>
</tr>
<tr>
<td>2.1. Population Definitions</td>
<td>11</td>
</tr>
<tr>
<td>2.2. Protocol Deviations</td>
<td>11</td>
</tr>
<tr>
<td>3. GENERAL STATISTICAL METHODS</td>
<td>12</td>
</tr>
<tr>
<td>3.1. Sample Size Justification</td>
<td>12</td>
</tr>
<tr>
<td>3.2. General Methods</td>
<td>12</td>
</tr>
<tr>
<td>3.3. Computing Environment</td>
<td>12</td>
</tr>
<tr>
<td>3.4. Baseline Definitions</td>
<td>13</td>
</tr>
<tr>
<td>3.5. Adjustments for Covariates</td>
<td>13</td>
</tr>
<tr>
<td>3.6. Multiple Comparisons/Multiplicity</td>
<td>13</td>
</tr>
<tr>
<td>3.7. Subpopulations</td>
<td>13</td>
</tr>
</tbody>
</table>
3.8. Withdrawals, Dropouts, and Loss to Follow-up ........................................ 13
3.9. Onset of Serious COVID-19 Adverse Events ........................................ 13
3.10. Missing Data ......................................................................................... 13
3.10.1. Handling of Missing Data for Secondary Endpoints ..................... 14
3.10.2. Other Missing Data ......................................................................... 14
3.11. Visit Windows ...................................................................................... 15
3.12. Interim Analyses .................................................................................. 15
4.  STUDY ANALYSES ................................................................................. 16
4.1. Patient Disposition ............................................................................... 16
4.2. Demographics and Baseline Characteristics ....................................... 16
4.2.1. Demographics and Baseline Characteristics ................................... 16
4.2.2. Baseline Disease Characteristics ...................................................... 16
4.2.3. Baseline Efficacy Parameters ......................................................... 17
4.2.4. Medical History ............................................................................... 17
4.2.5. Prior Medications ........................................................................... 17
4.2.6. Baseline Cardiac Structure and Function ........................................ 17
4.3. Pharmacokinetic Evaluations .............................................................. 18
4.4. Efficacy Analyses ................................................................................ 18
4.4.1. Primary Endpoint ........................................................................... 18
4.4.2. Secondary Endpoints ...................................................................... 18
4.4.2.1. NIS ......................................................................................... 18
4.4.2.2. Norfolk QoL-DN and R-ODS ..................................................... 19
4.4.2.3. COMPASS-31 ....................................................................... 19
4.4.2.4. mBMI ..................................................................................... 19
4.4.3. Exploratory Endpoints ................................................................... 20
4.4.3.1. FAP stage and PND score ......................................................... 20
4.4.3.2. KPS ...................................................................................... 20
4.5. Safety Analyses .................................................................................... 20
4.5.1. Study Drug Exposure ..................................................................... 20
4.5.2. Adverse Events ............................................................................... 21
4.5.3. AEs of Clinical Interest (AECI) ...................................................... 22
4.5.4. Laboratory Data ............................................................................. 22
4.5.5. Vital Signs and Physical Examination .......................................... 23
4.5.6. Premedications ........................................................................................................................................... 23
4.5.7. Concomitant Medications ......................................................................................................................... 23
4.5.8. Hospitalizations/Healthcare Encounters and Outpatient Procedures .................................................... 24
4.6. Anti-Drug Antibody (ADA) ............................................................................................................................ 24
4.7. COVID-19 Global Pandemic ......................................................................................................................... 24
4.7.1. General Impact ........................................................................................................................................ 24
4.7.2. Impact on Efficacy Endpoints ................................................................................................................. 24
4.7.3. Impact on Adverse Events ........................................................................................................................ 25
4.7.4. Other Impacts .......................................................................................................................................... 25
5. CHANGES TO PLANNED ANALYSES ......................................................................................................... 26
6. REFERENCES .................................................................................................................................................... 27
7. APPENDICES .................................................................................................................................................... 28
7.1. Questionnaire/Scoring .................................................................................................................................. 28
7.1.1. Neuropathy Impairment Score (NIS) .......................................................................................................... 28
7.1.2. Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) ............................................................... 29
7.1.3. Rasch-Built Overall Disability Scale (R-ODS) .............................................................................................. 29
7.1.4. Composite Autonomic Symptom Score-31 (COMPASS-31) ................................................................... 30
7.2. Pandemic Phase Start Dates by Country ...................................................................................................... 35
8. AMENDMENT HISTORY .................................................................................................................................. 36

LIST OF TABLES

Table 1 Pandemic Phase Start Dates by Country ............................................................................................ 35
## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AECI</td>
<td>AE of Clinical Interest</td>
</tr>
<tr>
<td>ADA</td>
<td>Anti-Drug Antibody</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Class</td>
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<tr>
<td>AUCτ</td>
<td>Area Under the Concentration-time Curve during a Dosing Interval</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CLss</td>
<td>System Clearance at Steady State</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum Plasma Concentration</td>
</tr>
<tr>
<td>COMPASS-31</td>
<td>Composite Autonomic Symptom Score</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>FAP</td>
<td>Familial Amyloidotic Polyneuropathy</td>
</tr>
<tr>
<td>hATTR</td>
<td>Hereditary Transthyretin-Mediated Amyloidosis</td>
</tr>
<tr>
<td>HLT</td>
<td>High Level Term</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>INN</td>
<td>International Nonproprietary Name</td>
</tr>
<tr>
<td>IRR</td>
<td>Infusion-Related Reaction</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky Performance Status</td>
</tr>
<tr>
<td>LLOQ</td>
<td>Lower Limit of Quantification</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
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<tr>
<td>LS</td>
<td>Least-squares</td>
</tr>
<tr>
<td>mBMI</td>
<td>Modified Body Mass Index</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing At Random</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MMRM</td>
<td>Mixed-effects Model Repeated Measures</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>NIS</td>
<td>Neuropathy Impairment Score</td>
</tr>
<tr>
<td>NIS-R</td>
<td>Neuropathy Impairment Score - Reflex</td>
</tr>
<tr>
<td>NIS-S</td>
<td>Neuropathy Impairment Score - Sensation</td>
</tr>
<tr>
<td>NIS-W</td>
<td>Neuropathy Impairment Score - Weakness</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-terminal Prohormone of B-type Natriuretic Peptide</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>OLT</td>
<td>Orthotopic Liver Transplant</td>
</tr>
<tr>
<td>PND</td>
<td>Polyneuropathy Disability</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>QoL-DN</td>
<td>Quality of Life-Diabetic Neuropathy</td>
</tr>
<tr>
<td>Ra\text{ac}</td>
<td>Accumulation Ratio</td>
</tr>
<tr>
<td>R-ODS</td>
<td>Rasch-built Overall Disability Scale</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>siRNA</td>
<td>Small Interfering Ribonucleic Acid</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>t_{\frac{1}{2}\beta}</td>
<td>Terminal Elimination Half-life</td>
</tr>
<tr>
<td>t_{max}</td>
<td>Time to Maximum Plasma Concentration</td>
</tr>
<tr>
<td>TP</td>
<td>Touch Pressure</td>
</tr>
<tr>
<td>TTR</td>
<td>Transthyretin</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>V_{ss}</td>
<td>Apparent Volume of Distribution at Steady State</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>wt</td>
<td>Wild Type</td>
</tr>
</tbody>
</table>
1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rare autosomal dominant, systemic disease caused by a mutation in the transthyretin (TTR) gene leading to the extracellular deposition of amyloid fibrils containing both mutant and wild type (wt) TTR. [Gillmore and Hawkins 2006; Yazaki 2000]

The liver is the primary source of TTR, and liver transplantation is used in some patients for treatment of hATTR amyloidosis. [Stangou and Hawkins 2004] More than 2000 patients have been transplanted in the world since 1990, however, morbidity and mortality are substantial. Patients require life-long immunosuppressive medications, with their attendant risks of infection and renal injury. One-year mortality rates of up to 10% have been reported. [Bispo 2009; Herlenius 2004; Okamoto 2009]

Liver transplantation eliminates mutant TTR from the circulation, however, wt TTR is produced by the liver allograft. Disease progression occurs in at least one third of hATTR amyloidosis patients after a liver transplant, presumably due to continued deposition of wt TTR protein from the transplanted liver. [Adams 2013; Reines 2014]

Patisiran (the International Nonproprietary Name [INN] for the drug product also referred to as ALN-TTR02) is a novel investigational agent developed for the treatment of ATTR amyloidosis. The efficacy of patisiran in adult patients with polyneuropathy caused by hATTR amyloidosis was demonstrated in a randomized, double-blind, placebo-controlled, multicenter clinical trial (NCT 01960348) [Adams 2018]. In the US, patisiran (as ONPATTRO) was approved in 2018 for the treatment of the polyneuropathy of hATTR in adults. Patisiran is continuing to be studied in clinical studies to gain additional experience.

ALN-TTR02-008 (hereinafter referred to as Study 008) is a global Phase 3b open-label study designed to evaluate the safety, efficacy, and pharmacokinetics (PK) of patisiran in patients with hATTR amyloidosis with disease progression after orthotopic liver transplant (OLT).

1.1.2. Document and Study Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to address the study objectives of Study 008. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.2.1. Primary Objective

The primary objective of the study is to evaluate the TTR reduction of patisiran in hATTR amyloidosis patients with disease progression after OLT.
1.1.2.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the effect of patisiran on neuropathy.
- Evaluate the effect of patisiran on patient reported outcomes including QoL, activities of daily living and autonomic neuropathy symptoms.
- Characterize the effect on nutritional status.

1.1.2.3. Exploratory Objectives

The exploratory objectives of the study are to:

- Characterize exploratory measures of clinical activity (disease stage, functional status).
- Evaluate PK.
- Assess for anti-drug antibodies (ADA) against patisiran.

1.1.2.4. Safety Objective

The safety objective of the study is to evaluate the safety and tolerability of patisiran in hATTR amyloidosis patients with disease progression after OLT.

1.2. Study Design

1.2.1. Synopsis of Study Design

Study 008 is a global Phase 3b open-label study designed to evaluate the safety, efficacy, and PK of patisiran in patients with hATTR amyloidosis with disease progression after liver transplant. All eligible patients will be administered open-label patisiran.

The open-label design is supported by previous studies, including a pivotal Phase 3 double-blind, placebo-controlled study (ALN-TTR02-004; hereinafter referred to as the APOLLO study). The clinical benefits seen in the APOLLO study were observed in association with an 80% reduction of TTR with patisiran within 10 to 14 days after a single dose, which was maintained over the duration of the 18-month study compared to no change with placebo. The primary efficacy endpoint in the current study, TTR reduction, is an objective measurement and not susceptible to bias of clinical study center staff or study patients and therefore does not require a blinded placebo group for accurate interpretation.

Consented eligible patients enrolled in this study will receive 0.3 mg/kg patisiran IV once every 3 weeks for 12 months. Dosing is based on actual body weight. For patients weighing 100 kg or more, patisiran will be administered at a total dose of 30 mg IV once every 3 weeks. Eligibility for this study will be confirmed before administration of the first dose on Day 1.

Safety will be assessed throughout the study. Patients will return to the clinical site for safety evaluations at Week 12, Month 6, and Month 12. Patients will be continually assessed throughout the study for adverse events (AEs). Unscheduled visits for study assessments may occur if deemed necessary by the study personnel.
Efficacy assessments will be performed at baseline, 6 and 12 months.

1.2.2. Study Procedures

The schedule of assessments is presented in Table 1 of the study protocol.

1.2.3. Efficacy, Pharmacokinetic, Immunogenicity, and Safety Assessments

1.2.3.1. Efficacy Assessments

The efficacy of patisiran will be evaluated using the following assessments:

- Serum TTR assessed using enzyme linked immunosorbent assay (ELISA).
- Neurological impairment assessed using the Neuropathy Impairment Score (NIS).
- Patient reported quality of life (QoL) using the Norfolk Quality of Life –Diabetic Neuropathy (QoL-DN) questionnaire.
- Disability reported by patients using the Rasch-built Overall Disability Scale (R-ODS).
- Autonomic neuropathy symptoms assessed using the Composite Autonomic Symptom Score (COMPASS-31).
- Nutritional status using modified body mass index (mBMI).
- Changes in ambulation and disease stage will be evaluated through Polyneuropathy disability (PND) score and familial amyloidotic polyneuropathy (FAP) stage.
- Functional impairment assessed using the Karnofsky Performance Status.

1.2.3.2. Pharmacokinetic Parameters

Concentrations of plasma siRNA (ALN-18328) and 2 novel lipid excipients (DLin-MC3-DMA and PEG2000-C-DMG) will be determined to estimate individual PK parameters using noncompartmental analysis methods.

1.2.3.3. Immunogenicity Parameters

Blood samples will be assessed for anti-PEG2000-C-DMG antibodies.

1.2.3.4. Safety Parameters

Safety evaluations performed during the study include monitoring of adverse events (AEs), recording of concomitant medications, physical examinations (clinically significant abnormalities observed during the physical examination are recorded on the medical history or AE electronic case report form (eCRF)), measurement of vital signs, and clinical laboratory evaluations (including hematology, serum chemistry, coagulation, liver function tests, and pregnancy testing), and liver allograft status (including checking and recording immunosuppressive drug levels every 3 months).
2. PATIENT POPULATION

2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- Safety Analysis Set: All patients who received any amount of patisiran. The Safety Analysis Set will be used for the analyses of the primary efficacy and safety assessments.

- Per Protocol Analysis Set: All patients in the Safety Analysis Set who missed $\leq 2$ doses of patisiran due to the COVID-19 pandemic during the study. The Per Protocol Analysis Set will be used for the analyses of secondary and exploratory efficacy assessments.

- Pharmacokinetic Analysis Set: All patients in the Safety Analysis Set who received at least one complete dose of patisiran (see Section 4.5.1) and who have provided at least one valid post-dose PK concentration value.

2.2. Protocol Deviations

A deviation is considered any departure from the procedures set forth in the protocol. Protocol deviations will be classified into major and minor by medical review. A major deviation includes any deviation that may impact patient safety or efficacy interpretation. Deviations not designated as major will be considered minor. COVID-19 related protocol deviations will be identified.

All protocol deviations, COVID-19 related protocol deviations, and major protocol deviations will be presented in separate data listings.
3. **GENERAL STATISTICAL METHODS**

3.1. **Sample Size Justification**

Assuming a normally distributed true TTR percent reduction from baseline of 80% with a standard deviation of 18%, a sample size of 16 patients will yield a 95% confidence interval (CI) with a half-width of approximately 10%. Assuming a 20% premature discontinuation rate, approximately 20 patients will be enrolled in the study.

3.2. **General Methods**

Formal statistical hypothesis testing will be performed on the primary efficacy endpoint conducted at the nominal 2-sided, 0.05 level of significance. All non-primary endpoint summaries will be descriptive.

All output will be incorporated into Microsoft Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Continuous data will be described using descriptive statistics such as the number of observations (n), mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum. For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. The mean, SD, SEM and median will be reported to one greater decimal place.

For laboratory data, if any value is recorded as less than the lower limit of quantification (LLOQ), then the value used for calculation will be assigned a value of LLOQ.

Categorical and ordinal data will be tabulated using the patient count and percentages in each category unless otherwise specified. When count data are presented, the percentage will not be presented when the count is zero. A percentage of 100% will be reported as 100% without any decimal places.

Study Day 1 will be defined as the day of the first dose of patisiran in this study. Study Day will be calculated relative to the first dose date of study drug for all patients:

- If the assessment date is after the date of first study drug dose, then the study day will be calculated as:
  
  \[
  \text{Study Day} = \text{Date of assessment} - \text{date of first dose of study drug} + 1, 
  \]

- If the assessment date is before the date of the first dose of study drug, then the study day will be calculated as:

  \[
  \text{Study Day} = \text{Date of assessment} - \text{date of first dose of study drug}. 
  \]

All data recorded on the eCRF will be included in data listings.

3.3. **Computing Environment**

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 (or later), unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 (or later). Premedications, prior
and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version September 2018 (or later).

### 3.4. Baseline Definitions

Unless noted otherwise, baseline will be defined as the last non-missing evaluable measurement on or prior to the first dose of patisiran in this study.

For TTR, baseline will be defined as the average of all records, including those from any unscheduled visits, prior to the date and time of first dose.

### 3.5. Adjustments for Covariates

The single hypothesis in this study will be tested using the Wilcoxon signed-rank test, a nonparametric test for paired data. Adjustment for covariates will not be performed for this analysis.

### 3.6. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a single hypothesis to be tested.

### 3.7. Subpopulations

No analyses of patient subgroups are planned.

### 3.8. Withdrawals, Dropouts, and Loss to Follow-up

A patient may stop participation in the study at any time and for any reason.

A patient considering stopping participation in the study should be informed that they can discontinue study drug and/or decline procedural assessments and remain in the study for the collection of important study data as described in the Protocol.

If a patient still chooses to discontinue study drug and stop participation in all follow-up, every effort should be made to conduct the end of study assessments within 4 weeks of the last dose.

When a patient discontinues study treatment and/or withdraws from the study, the primary reason for withdrawal must be recorded in the appropriate section of the eCRF, and all efforts will be made to complete and report the observations as thoroughly as possible.

A patient will be considered lost to follow-up if the patient repeatedly fails to return for scheduled visits and is unable to be contacted by the clinical study center.

### 3.9. Onset of Serious COVID-19 Adverse Events

Secondary and exploratory efficacy assessments on or after the onset of a serious COVID-19 AE for a patient may be censored. The sponsor will review the reported events and determine if the impacts on efficacy warrants censoring.

### 3.10. Missing Data

For efficacy endpoints, the number and percentage of patients with missing data, including due to the COVID-19 pandemic, at each scheduled visit will be summarized.
3.10.1. Handling of Missing Data for Secondary Endpoints

For NIS, Norfolk QoL-DN, R-ODS and mBMI efficacy assessments, the primary analysis will be based on the last observation carried forward (LOCF) method, which makes use of the patient’s previous observed post-baseline assessment value to impute the missing post-baseline assessment. Specifically, for NIS, Norfolk QoL-DN, and R-ODS, a missing value for the assessment at Month 12 will be imputed using the patient’s observed value at month 6; for mBMI, a missing value for a post-baseline assessment at or after month 6 will be imputed by using the patient’s most recent observed post-baseline value.

Specific algorithms will be used to impute values and/or subcomponents of particular assessments when subcomponents are missing (NIS, Norfolk QoL-DN, R-ODS, and COMPASS-31; see Section 7.1.1, Section 7.1.2, Section 7.1.3, and Section 7.1.4, respectively). The result of the partial imputation (either a non-missing or missing value) will be used in all statistical analyses.

There will be no imputation for missing data for other efficacy endpoints unless otherwise specified. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

3.10.2. Other Missing Data

For records with fully or partially missing AE onset date and/or stop date, conventions for determining whether an AE is treatment emergent and calculating start/end study day of an AE is as below:

- AE onset dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.
- AE onset dates with missing month will be assumed to occur on the first day of the non-missing year (ie, January 1), except for AEs occurring in the first year of dosing, in which case the date will be the first day of dosing.
- If year of the AE start date is missing, no date imputation will be made, but the AE will be considered treatment-emergent.
- An AE that is not ongoing and has a stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month.
- An AE that is not ongoing and has a stop date with a missing month will be assumed to occur on the last day of the non-missing year (ie, December 31).

For the calculation of duration (eg, time in years since diagnosis with hATTR) in the presence of an incomplete date, the following conventions will be used:

- Missing day: the first day of the month will be used;
- Missing month: duration will be calculated as the simple difference in years (eg, year of informed consent minus year of diagnosis with hATTR);
- Missing year: no duration will be calculated.
3.11. Visit Windows

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

For efficacy endpoints other than serum TTR level and mBMI, if the scheduled Month 6 or Month 12 assessments are not performed, any evaluable assessment will be grouped with the Month 6 or Month 12 assessments if it is performed within 3 months of the scheduled assessment. For mBMI, if the scheduled Week 12, Month 6, Week 36 or Month 12 assessments for mBMI are not performed, any evaluable assessment will be grouped with the scheduled assessments if it is performed within 1.5 months of the scheduled assessment.

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 by-visit summary tabulations. However, unscheduled visits will be considered for baseline values, as discussed in Section 3.4, and for inclusion in any categorical shift summaries (eg, shift from baseline to “worst” post-baseline value).

3.12. Interim Analyses

No interim analysis is planned for this study.
4. STUDY ANALYSES

4.1. Patient Disposition
The number and percentage of patients in the following categories will be summarized for the Safety Analysis Set:

- Patients in each analysis population
- Patients enrolled overall and by country and site
- Patients treated
- Patients who completed treatment
- Patients who discontinued treatment and primary reason for treatment discontinuation and discontinuation due to COVID-19
- Patients who completed study participation
- Patients who stopped study participation and primary reason for stopping study participation and stopping study participation due to COVID-19

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

4.2. Demographics and Baseline Characteristics
Demographic and baseline characteristics, baseline disease characteristics, baseline efficacy parameters, prior medications (excluding premedication), medical history information, and baseline cardiac structure and function will be summarized.

4.2.1. Demographics and Baseline Characteristics
Age, height, weight, and body mass index (BMI) will be summarized using descriptive statistics. Sex, race, ethnicity, and country will be summarized using counts and percentages.

All demographic and baseline characteristic data will be included in by-patient data listings.

4.2.2. Baseline Disease Characteristics
The following baseline disease characteristics will be summarized descriptively:

- Age at hATTR amyloidosis symptom onset
- Age at diagnosis with hATTR amyloidosis
- Genotype
- Liver Transplant History
  - Age at Liver Transplant
  - Type of liver transplant
  - Time from liver transplant to first dose of patisiran
- NYHA classification
- NT-proBNP

All baseline disease characteristic data will be included in by-patient data listings.

### 4.2.3. Baseline Efficacy Parameters

Baseline values of continuous efficacy parameters (TTR, NIS [total score and component scores], Norfolk QoL-DN, R-ODS, COMPASS-31, and mBMI) will be summarized using descriptive summary statistics. The frequency and percentage of patients in each category for baseline KPS (70, 80, 90, 100) and baseline FAP stage (0, I, II, III) will be tabulated.

A shift table will be used to summarize the historical change in polyneuropathy disability (PND) score; this table will summarize the earliest PND score (most recent PND score prior to OLT or first post-OLT PND score) versus the baseline PND score.

All baseline efficacy parameters will be included in by-patient data listings.

### 4.2.4. Medical History

Medical history will be tabulated by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). A patient contributes only once to the count for a given condition (overall, by SOC, by HLT, or by PT).

Medical history including prior surgeries will be included in a by-patient data listing. Baseline cardiac medical history will also be included in a by-patient data listing.

### 4.2.5. Prior Medications

Prior Medications will be defined as those medications that were initiated prior to first patisiran administration and are not considered premedications for patisiran administration. 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 earlier of the data cut-off date or the end of study date will be imputed.

Prior medications will be coded using the WHO Drug Dictionary (September 2018 or later). Results will be tabulated by ATC and PT; patients will only count once for each ATC or PT if they have multiple medications with the same ATC or PT.

Prior medications will be included in a by-patient data listing.

### 4.2.6. Baseline Cardiac Structure and Function

Baseline cardiac structure and function will be assessed through echocardiograms. Twelve (12)-lead electrocardiograms will also be performed. Baseline echocardiogram parameters (including wall thickness, ejection fraction, and other echo parameters) and baseline 12-lead electrocardiogram parameters in triplicate (including rhythm, ventricular rate, RR interval, PR interval QRS duration, QT interval [uncorrected], QTcB, and QTcF) will be summarized using descriptive summary statistics and will also be included in by-patient data listings.
4.3. **Pharmacokinetic Evaluations**

Pharmacokinetic analyses will be performed for ALN-18328 and 2 novel lipids (DLin-MC3-DMA and PEG2000-C-DMG) using noncompartmental analysis methods. PK analyses will be based on the Pharmacokinetic Analysis Set. Summaries will be provided for each scheduled time point. PK data will be included in by-patient data listings.

The following PK parameters will be estimated for each subject, as appropriate and if data permits: maximum plasma concentration ($C_{\text{max}}$), time to maximum plasma concentration ($t_{\text{max}}$), terminal elimination half-life ($t_{\frac{1}{2}}$), area under the concentration-time curve during a dosing interval (AUCt), systemic clearance at steady state (CLss), and apparent volume of distribution at steady state (Vss), and accumulation ratio for PK exposure parameters (Rac). Additional PK parameters may be calculated, if deemed necessary. The PK parameters will be summarized using descriptive statistics.

4.4. **Efficacy Analyses**

Primary efficacy analysis will be based on the Safety Analysis Set. Secondary and exploratory efficacy analyses will be based on the Per Protocol Analysis Set. Summaries will be provided for each scheduled time point. Efficacy data will be included in by-patient data listings.

4.4.1. **Primary Endpoint**

The primary endpoint is the average TTR percent reduction from baseline across Month 6 and Month 12.

For all analyses of post-baseline TTR data, only post-baseline TTR assessments collected within 24 days (inclusive) after receiving a complete dose of patisiran (see Section 4.5.1) will be summarized.

The median TTR percent reduction from baseline along with the 2-sided 95% distribution-free CI will be provided. The p-value for the TTR percent reduction from baseline will be obtained using the Wilcoxon signed-rank test.

A summary table will present the observed value, change from baseline, and percent change from baseline in serum TTR by visit. A boxplot will also present the percent change from baseline by visit.

Serum TTR data will be included in a by-patient listing.

4.4.2. **Secondary Endpoints**

4.4.2.1. **NIS**

Neurologic impairment will be assessed by NIS. The total NIS score is the sum of NIS-W, NIS-R, and NIS-S. Scoring algorithms for NIS score are included in Section 7.1.1. LOCF will be used for imputation for the missing NIS assessments at Month 12 as described in Section 3.10.1.

NIS absolute values and changes from baseline in the composite (total NIS score) and component scores (NIS-W, NIS-R, NIS-S) will be summarized by visit.

Observed NIS scores will be included in a by-patient listing.
4.4.2.2. Norfolk QoL-DN and R-ODS

Patient reported quality of life and disease burden will be assessed by summary statistics for the Norfolk QoL-DN total score and R-ODS. Scoring algorithms for the Norfolk QoL-DN and R-ODS are included in Section 7.1.2 and Section 7.1.3 respectively. LOCF will be used for imputation for the missing Norfolk QoL-DN and R-ODS assessments at Month 12 as described in Section 3.10.1.

The absolute values and changes from baseline in these measures will be summarized descriptively by visit. Continuous statistical summaries of each Norfolk QoL-DN domain score will also be provided.

Observed Norfolk QoL-DN and R-ODS scores will be included in by-patient listings.

4.4.2.3. COMPASS-31

Patient reported autonomic neuropathy symptoms will be assessed by the COMPASS-31 total score. Scoring algorithms for COMPASS-31 are included in Section 7.1.4.

The observed values and changes from baseline in COMPASS-31 will be summarized descriptively by visit. Continuous statistical summaries of each COMPASS-31 domain score will also be provided.

The COMPASS-31 total score will be analyzed using a mixed-effects model for repeated measures (MMRM), which 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 (Mallinckrodt et al, 2008). MMRM also assumes data are missing at random (MAR).

In the MMRM model, the outcome variable is the change from baseline in COMPASS-31 total score; the model includes baseline COMPASS-31 total score as a continuous covariate and visit (Month 6 or Month 12) as a fixed effect term. Least-squares (LS) mean estimates, SEMs and 95% CIs at Month 6 and Month 12 will be presented. An unstructured covariance structure will be used to model the within-patient errors. If the model fails to converge, the compound symmetry covariance structure will be used. The Satterthwaite approximation will be used to estimate the degrees of freedom.

Observed COMPASS-31 scores will be included in a by-patient listing.

4.4.2.4. mBMI

mBMI is calculated as BMI (kg/m²) multiplied by albumin (g/L). LOCF will be used for imputation for the missing mBMI assessments as described in Section 3.10.1.

Descriptive statistics will be provided for absolute values and changes from baseline in nutritional status (mBMI).

Observed mBMI values will be presented in a by-patient listing.
4.4.3. Exploratory Endpoints

4.4.3.1. FAP stage and PND score
Changes in ambulation will be evaluated through the PND score and FAP stage. The actual PND score or FAP stage and their comparisons with baseline (ie, improved, no change or worsened) will be summarized by visit. Tables for shift in PND score or FAP stage from baseline to worst post-baseline assessment will also be provided.

FAP stage and PND score will be presented in separate by-patient listings.

4.4.3.2. KPS
Functional impairment is assessed by the KPS scale. The actual KPS score and changes from baseline will be summarized by visit. A listing for the KPS score by patient will also be provided.

4.5. Safety Analyses
Safety analyses will be based on the Safety Analysis Set and will consist of study drug exposure, adverse events (AEs), clinical laboratory assessments, vital signs and physical examinations, liver allograft status, premedications, prior and concomitant medications.

4.5.1. Study Drug Exposure
For the purpose of calculating the duration of study drug exposure, the last date of exposure to patisiran is defined as the earliest day of the following dates:

- Last dose date + 20 days
- Analysis cutoff date
- End of study date

Duration of exposure in months is defined as (the last date of exposure to study drug – date of the first dose +1)/30.4375.

Duration of drug exposure in months, the total number of doses received, duration of infusion (per infusion), amount of patisiran received (per infusion and in total), number and percentage of patients with any missed doses and infusion interruptions, number of missed doses, and number of infusion interruptions for any reason as well as due to an infusion related reaction (IRR) will be summarized.

Study drug exposure by visit, including duration of infusion and total infusion volume administered will be summarized.

The numbers and percentages of patients with complete and partial dose administrations will also be summarized. Complete and partial administration is defined as follows:

- 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).
Dosing information including phone contact information for home infusions will be included in a by-patient data listing.

4.5.2. Adverse Events

All Adverse Events (AEs) will be coded using the MedDRA coding system (version 23.0 or later) and displayed in tables and data listings using SOC and PT.

Summaries of AEs will be performed for those events that are considered treatment-emergent, where a treatment-emergent is defined as any AE with onset during or after the first administration of patisiran in this study through 28 days after the last dose of patisiran. 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.

An AE related to study drug is defined as an AE identified by the investigator having a reasonable possibility that the event may have been caused by the study drug. An AE without an assessment by the investigator as to whether there was or was not a reasonable possibility that the AE may have been caused by the study drug, will be considered as an AE related to study drug.

An AE with a missing severity will be considered as severe.

AEs will be tabulated by the frequency and percentage of patients reporting a given AE. A patient contributes only once to the count for a given AE (overall, by SOC, by PT).

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

Tabulations by SOC and PT will be produced for the following:

- all AEs,
- severe AEs,
- SAEs,
- AEs related to study drug,
- AEs leading to study drug interruption,
- AEs leading to treatment discontinuation,
- AEs leading to study withdrawal,
- AEs related to pre-medication,
- AEs over time.

AEs, AEs related to study drug and SAEs will also be tabulated by PT in decreasing order of frequency.
AEs and AEs related to study drug will be summarized by maximum severity; patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most severe occurrence.

AEs mapping to the Drug Related Hepatic Disorder standardized MedDRA query (SMQ) will be summarized by SOC and PT. Other SMQs or AE groupings may be evaluated.

By-patient data listings will be provided separately for each of the following:

- AEs (including both treatment emergent and non-treatment emergent AEs),
- all patient deaths (regardless of whether or not it was associated with an AE),
- SAEs,
- AEs leading to treatment discontinuation or study withdrawal,
- AEs related to premedication.

IRR signs and symptoms will be summarized by SOC and PT. The incidence and frequency of IRR signs and symptoms over time will also be summarized by SOC and PT.

A separate listing will also be provided for IRR signs and symptoms.

Additional AE considerations regarding COVID-19 are detailed in Section 4.7.3.

4.5.3. AEs of Clinical Interest (AECI)

The following events will be considered as AECI for this study: ALT or AST elevations > 3 ×ULN, or potential or confirmed events of liver transplant rejections. The number and percentage of patients and the number of events will be summarized for events of ALT or AST elevations > 3 ×ULN and potential or confirmed events of liver transplant rejections.

Separate listings will be provided for AECIs as collected in Supplemental AE of Clinical Interest (AECI) – Liver Function Test Elevations form and Liver Allograft Status form.

4.5.4. Laboratory Data

Laboratory data include hematology, serum chemistry, coagulation, liver function tests and pregnancy tests. Clinical laboratory values will be expressed in SI units.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, and liver function tests). Descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by scheduled 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” post-baseline category for selected parameters.

Coagulation parameters (collected at screening) will be descriptively summarized.

A listing will be produced for all patients with abnormal liver function tests defined as an ALT >3 ×ULN, AST >3 ×ULN, and/or 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 post-baseline 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.

The peak total bilirubin (at any time post-baseline) will be plotted against the peak AST or ALT level at any time post-baseline.

Laboratory test results will be graded according to the NCI CTCAE Version 5.0 or above, where applicable. A shift summary of baseline to maximum post-baseline CTCAE grade may be presented, as appropriate.

The eGFR (mL/min/1.73 m²) will be categorized as follows: ≥90; 60-89; 45-59; 30-44; 15-29 and <15. A shift summary of baseline to worst post-baseline eGFR category will be presented.

All laboratory data will be included in by-patient data listings. Laboratory values outside of the normal ranges will be identified in the listings.

4.5.5. Vital Signs and Physical Examination

The observed values and changes from baseline for weight and vital signs (blood pressure, pulse rate, body temperature, and respiration rate) will be summarized by scheduled visit. The frequency and percentage of patients with potentially clinically significant vital signs will also be presented.

Vital sign measurements will be included in a by-patient data listing.

4.5.6. Premedications

Premedications will be coded using the WHO Drug Dictionary (September 2018 or later). Results will be tabulated by anatomic therapeutic class (ATC) and PT. Premedication data will be presented in a by-patient data listing.

4.5.7. Concomitant Medications

Concomitant medications will be defined as those medications that were initiated after first patisiran administration or those that were ongoing at the time of the first patisiran administration. For medications with partial start or stop dates: the first day/month of the specified month/year will be imputed for start date, and the last day/month of the specified month/year 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 used.

Concomitant medications will be tabulated by ATC and PT; a patient will only be counted once for each ATC or PT if they have multiple medications with the same ATC or PT.

Concomitant medications will be included in a by-patient data listing.
4.5.8. Hospitalizations/Healthcare Encounters and Outpatient Procedures

Hospitalizations/healthcare encounters and outpatient procedures data will be included in by-patient listings.

4.6. Anti-Drug Antibody (ADA)

Serum blood samples will be collected to evaluate antidrug antibodies. Anti-PEG2000-C-DMG antibody measurements will be taken predose on scheduled infusion days.

Anti-drug antibody data including the confirmed ADA positive results flag will be included in a by-patient data listing.

4.7. COVID-19 Global Pandemic

Additional data were collected to characterize the impact of the COVID-19 pandemic on general study conduct, disposition, 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, July 2020; Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, European Medicines Agency, April 2020; Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, European Medicines Agency, June 2020; Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency, US Food and Drug Administration, June 2020).

4.7.1. General Impact

Patients who discontinue treatment or discontinue 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. Patient- and event-level summaries of the impact on study participation due to COVID-19 may also be generated by site and/or region.

Impact on study participation due to COVID-19 will be presented in data listings by patient and by visit within patient.

Protocol deviations due to COVID-19 will be presented in a patient data listing as described in Section 2.2.

4.7.2. Impact on Efficacy Endpoints

The Per Protocol Analysis Set as defined in Section 2.1 will be used for secondary and exploratory efficacy endpoints analyses.

Secondary and exploratory efficacy assessments on or after the onset of a serious COVID-19 AE for a patient may be censored (see Section 3.9).
Summaries of missing efficacy data due to COVID-19 pandemic will be included in a missing efficacy data summary table as described in Section 3.10.

4.7.3. Impact on Adverse Events

An overall summary of AEs mapping to a COVID-19 custom query will include the number and percentage of patients with at least one AE, AE assessed by the Investigator as related to treatment, severe AE, severe AE related to treatment, SAE, any SAE related to treatment, AE leading to study drug interruption, study drug related AE leading to study drug interruption, AE leading to treatment discontinuation, study drug related AE leading to treatment discontinuation, AE leading to study withdrawal, study drug related AE leading to study withdrawal, and deaths. AEs mapping to the COVID-19 custom query will be summarized by HLT and PT. 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 (see Section 7.2) will include the number and percentage of patients with at least one AE, AE assessed by the Investigator as related to treatment, severe AE, severe AE related to treatment, SAE, any SAE related to treatment, AE leading to study drug interruption, study drug related AE leading to study drug interruption, AE leading to treatment discontinuation, study drug related AE leading to treatment discontinuation, AE leading to study withdrawal, study drug related AE leading to study withdrawal, and deaths. AEs and SAEs will be summarized by pandemic phase, SOC, and PT.

AEs mapping to the COVID-19 custom query will be presented in a data listing.

Events will be considered during the pandemic if the event occurs on or after confirmed case of COVID-19 based on the country where the study site is located, described in Section 7.2.

4.7.4. Other Impacts

Adverse event, study drug exposure, and efficacy listings will include identification of assessments occurring during the pandemic.

For patients reporting any AEs mapping to the COVID-19 custom query, AEs and prior and concomitant medications will also be presented in separate data listings.
## 5. CHANGES TO PLANNED ANALYSES

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

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 2.1</td>
<td>Per Protocol Analysis Set was added.</td>
<td>The Per Protocol Analysis Set was added to support primary analyses of estimating treatment effects of secondary and exploratory efficacy endpoints in patients who did not miss or missed less than or equal to 2 doses of patisiran due to COVID-19.</td>
</tr>
<tr>
<td>Section 4.4.1</td>
<td>The Hodges-Lehmann method’s estimates of median TTR percent reduction and its 2-sided 95% CI were modified to standard median TTR percent reduction and its 2-sided 95% distribution-free CI, respectively.</td>
<td>The reason of the change is because there is no available SAS procedure in most current SAS version for one-sample Hodges-Lehmann method. Based on simulations, the estimated medians and the 2-sided 95% CIs are similar for the two methods.</td>
</tr>
<tr>
<td>Section 3.10.1 Section 4.4.2.1 Section 4.4.2.2 Section 4.4.2.4</td>
<td>The primary analysis for the NIS, Norfolk QOL-DN, R-ODS and mBMI efficacy endpoints was updated to use LOCF to impute missing post-baseline values.</td>
<td>The changes from baseline in NIS, Norfolk QOL-DN, R-ODS and mBMI assessments between Months 9 and 18 were relatively stable in the patisiran arm of the APOLLO study. Thus, the LOCF method was adopted to account for the potential missingness (including missingness related to COVID-19) in NIS, Norfolk QOL-DN, R-ODS and mBMI efficacy endpoints during this study.</td>
</tr>
<tr>
<td>Section 4.4.2.3</td>
<td>The primary analysis for the COMPASS-31 efficacy endpoint was changed to MMRM.</td>
<td>The changes from baseline in COMPASS-31 total score showed improvement from Month 9 to Month 18 in the patisiran arm of the APOLLO study. Thus, the MMRM method was adopted to account for potential missingness (including missingness related to COVID-19) in COMPASS-31 total score, which assumes data are Missing at Random (MAR).</td>
</tr>
</tbody>
</table>
6. REFERENCES


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. **Neuropathy Impairment Score (NIS)**

NIS total score is the sum of NIS-W, NIS-R, and NIS-S, these are described in detail below.

<table>
<thead>
<tr>
<th>Assessment Tool</th>
<th>Maximum Total Points</th>
<th>Components (maximum points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIS</td>
<td>244</td>
<td>• NIS-W: Weakness (192)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NIS-R: Reflexes (20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NIS-S: Sensation (32)</td>
</tr>
</tbody>
</table>

1. NIS-W is the sum of the cranial nerve components (3rd nerve, 6th nerve, facial weakness, palate weakness, tongue weakness) and muscle weakness components (respiratory, neck flexion, shoulder abduction, elbow flexion, brachioradialis, elbow extension, wrist flexion, wrist extension, finger flexion, finger spread, thumb abduction, hip flexion, hip extension, knee flexion, knee extension, ankle dorsiflexors, ankle plantar flexors, toe extensors, toe flexors). Assessments are performed separately for the right- and left-hand side of the body. Scoring for each component is 0 (normal), 1 (25% weak), 2 (50% weak), 3 (75% weak), 3.25 (move against gravity), 3.5 (movement, gravity eliminated), 3.75 (muscle flicker, no movement), and 4 (paralysis). The maximum total score for NIS-W is 192.

2. NIS-R is the sum of the reflex components (biceps brachii, triceps brachii, brachioradialis, quadriceps femoris, and triceps surae). Assessments are performed separately for the right and left foot. Scoring for each component is 0 (normal), 1 (decreased) and 2 (absent). Adjustments are made for the age of the patient (eg, absent reflexes in a patient older than 60 is assessed as 0, or normal). The maximum total score for NIS-R is 20.

3. NIS-S is the sum of the finger and toe sensation components (TP, 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.

Missing values will not be imputed. If a component score (NIS-W, NIS-R or NIS-S) is missing, then the NIS total score is considered as missing.
7.1.2. **Norfolk Quality of Life-Diabetic Neuropathy (Norfolk 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) \(\Sigma(1-7, 8-35)\)
- Physical Functioning/Large Fiber (15 items) \(\Sigma(8, 11, 13-15, 24, 27-35)\)
- Activities of Daily Living (ADLs) (5 items) \(\Sigma(12, 22, 23, 25, 26)\)
- Symptoms (8 items) \(\Sigma(1-7, 9)\)
- Small Fiber (4 items) \(\Sigma(10, 16, 17, 18)\)
- Autonomic (3 items) \(\Sigma(19, 20, 21)\)

If at least 50% of the items are non-missing, domain scores are calculated as the average scores of non-missing included items multiplied by the number of items in the domain, rounded to the nearest integer. A domain score is missing if more than 50% of the included items are missing.

If the scores for all 5 domains are non-missing, then Total QoL is the sum of scores of the 5 domains; however, if at least 1 of the domains is missing and at least 50% of the items (18 items) are non-missing, then Total QoL is calculated as 35 times the mean of the non-missing items, rounded to the nearest integer. Otherwise, Total QoL is deemed as missing.

**7.1.3. 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 non-missing items multiplied by 24 if at least 90% of the items are non-missing. The total score will be deemed as missing if more than 10% of the items (3 or more items) are missing.
7.1.4. Composite Autonomic Symptom Score-31 (COMPASS-31)

The COMPASS-31 questionnaire comprises 6 domains: Orthostatic intolerance, Vasomotor, Secretomotor, Gastrointestinal, Bladder, and Pupillomotor. Within each domain, individual questions are scored as follows: Simple yes or no questions are scored as 0 points for no and 1 point for yes. Questions about a specific site of symptoms or symptoms under specific circumstances are scored as 0 if not present and as 1 if present for each site or circumstance. All questions regarding the frequency of symptoms are scored as 0 points for rarely or never, 1 point for occasionally or sometimes, 2 points for frequently or “a lot of the time,” and 3 points for almost always or constantly. All questions regarding the severity of symptoms are scored as 1 point for mild, 2 points for moderate, and 3 points for severe. Questions assessing the time course of a symptom are scored 0 points for responses such as “gotten somewhat better,” “gotten much better,” “completely gone,” and “I have not had any of these symptoms,” 1 point for “stayed about the same,” 2 points for “gotten somewhat worse,” and 3 points for “gotten much worse.” The scores for changes in bodily functions depend on the individual question asked. For example, “I get full a lot more quickly than I used to when eating a meal” is scored 2 points and “I get full a lot less quickly than I used to” is scored 0 points, while the answer “I sweat much more than I used to” is given 1 point and “I sweat much less than I used to” is scored 2 points.

The overall scoring proceeds as follows:

- Sum the numerical values associated with responses in each domain
- Apply the following weighting factors to the domain sums:
  - Orthostatic intolerance, 4.0
  - Vasomotor, 0.83333333
  - Secretomotor, 2.1428571
  - Gastrointestinal, 0.8928571
  - Bladder, 1.1111111
  - Pupillomotor, 0.3333333
- Sum the weighted domain scores to obtain a total weighted score (maximum of 100)

Within each domain, there are “gatekeeper” questions. For example, consider questions 5-7:

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?
   1. Yes
   2. No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)
   1. Hands
   2. Feet
7. Are these changes in your skin color:
   1. Getting much worse
   2. Getting somewhat worse
   3. Staying about the same
   4. Getting somewhat better
   5. Getting much better
   6. Completely gone

Answering “No” to question 5 obviates questions 6-7. Similarly, answering “Yes” to question 5 causes the responses to questions 6-7 to be summed in the resulting overall score. A failure to answer question 5 would render responses to questions 6-7 problematic. Question 5 is the gatekeeper question and question 6-7 will be referred as subsequent questions.

The full list of gatekeeper questions is:

- Question 1: Gatekeeper to questions, 2, 3, 4
- Question 5: Gatekeeper to question 6, 7
- Question 16: Gatekeeper to questions 17, 18, 19
- Question 20: Gatekeeper to questions, 21, 22, 23
- Question 27: Gatekeeper to question 28
- Question 29: Gatekeeper to question 30

A domain score will be deemed as missing if:

1. Answering “No” or “Never” to gatekeeper question but non-missing responses to any of the subsequent questions.
2. Answering “Yes” to gatekeeper question but 1 or more missing responses to subsequent questions, with the exception of missing responses to question 6 which will be scored as 0.
3. Missing response to gatekeeper question and 1 or more missing responses to subsequent questions.
4. Multiple responses to the same question within a domain, with the exception of question 6 that says, “check all.”
5. Missing response to a question within a domain that is not part of a gatekeeper/subsequent question set. These questions are: 8, 9, 10, 11, 12, 13, 14, 15, 24, 25, 26, 31. The exception is when both questions 9 & 10 are answered as “No” and question 11 is missing, the score will be 0.

When a gatekeeper question is missing response, but all subsequent questions are non-missing, the gatekeeper question will be imputed as “Yes” or the max impairment (example: “Constantly” for questions 27 and 29). For questions 9, 10, and 11, if both questions 9 and 10 are missing responses and the response to question 11 is “1,” question 9 & 10 will be imputed as “No.” For all other responses, question 9 & 10 will be imputed as “Yes.”

For each patient, if ≤2 domain scores are missing, the total score will be calculated by imputing the missing domain score by the average domain score using data from any of the patients who
had non-missing score for that domain at the time point. If more than 2 domain scores are missing, the total score will be deemed as missing.

The full text of the COMPASS-31 is below.

1. In the past year, have you ever felt faint, dizzy, “goofy”, or had difficulty thinking soon after standing up from a sitting or lying position?
   1. Yes
   2. No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?
   1. Rarely
   2. Occasionally
   3. Frequently
   4. Almost Always

3. How would you rate the severity of these feelings or symptoms?
   1. Mild
   2. Moderate
   3. Severe

4. In the past year, have these feelings or symptoms that you have experienced:
   1. Gotten much worse
   2. Gotten somewhat worse
   3. Stayed about the same
   4. Gotten somewhat better
   5. Gotten much better
   6. Completely gone

5. In the past year, have you ever noticed color changes in your skin, such as red, white, or purple?
   1. Yes
   2. No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)
   1. Hands
   2. Feet

7. Are these changes in your skin color:
   1. Getting much worse
   2. Getting somewhat worse
   3. Staying about the same
   4. Getting somewhat better
   5. Getting much better
   6. Completely gone

8. In the past 5 years, what changes, if any, have occurred in your general body sweating?
   1. I sweat much more than I used to
   2. I sweat somewhat more than I used to
   3. I haven’t noticed any changes in my sweating
   4. I sweat somewhat less than I used to
   5. I sweat much less than I used to

9. Do your eyes feel excessively dry?
   1. Yes
   2. No
10. Does your mouth feel excessively dry?
   1 Yes
   2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:
   1 I have not had any of these symptoms
   2 Getting much worse
   3 Getting somewhat worse
   4 Staying about the same
   5 Getting somewhat better
   6 Getting much better
   7 Completely gone

12. In the past year, have you noticed any changes in how quickly you get full when eating a meal?
   1 I get full a lot more quickly now than I used to
   2 I get full more quickly now than I used to
   3 I haven’t noticed any change
   4 I get full less quickly now than I used to
   5 I get full a lot less quickly now than I used to

13. In the past year, have you felt excessively full or persistently full (bloated feeling) after a meal?
   1 Never
   2 Sometimes
   3 A lot of the time

14. In the past year, have you vomited after a meal?
   1 Never
   2 Sometimes
   3 A lot of the time

15. In the past year, have you had a cramping or colicky abdominal pain?
   1 Never
   2 Sometimes
   3 A lot of the time

16. In the past year, have you had any bouts of diarrhea?
   1 Yes
   2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?
   1 Rarely
   2 Occasionally
   3 Frequently ____________ times per month
   4 Constantly

18. How severe are these bouts of diarrhea?
   1 Mild
   2 Moderate
   3 Severe
19. Are your bouts of diarrhea getting:
   1. Much worse
   2. Somewhat worse
   3. Staying the same
   4. Somewhat better
   5. Much better
   6. Completely gone

20. In the past year, have you been constipated?
   1. Yes
   2. No (if you marked No, please skip to question 24)

21. How frequently are you constipated?
   1. Rarely
   2. Occasionally
   3. Frequently ________ times per month
   4. Constantly

22. How severe are these episodes of constipation?
   1. Mild
   2. Moderate
   3. Severe

23. Is your constipation getting:
   1. Much worse
   2. Somewhat worse
   3. Staying the same
   4. Somewhat better
   5. Much better
   6. Completely gone

24. In the past year, have you ever lost control of your bladder function?
   1. Never
   2. Occasionally
   3. Frequently ________ times per month
   4. Constantly

25. In the past year, have you had difficulty passing urine?
   1. Never
   2. Occasionally
   3. Frequently ________ times per month
   4. Constantly

26. In the past year, have you had trouble completely emptying your bladder?
   1. Never
   2. Occasionally
   3. Frequently ________ times per month
   4. Constantly

27. In the past year, without sunglasses or tinted glasses, has bright light bothered your eyes?
   1. Never (if you marked Never, please skip to question 29)
   2. Occasionally
   3. Frequently
   4. Constantly
28. How severe is this sensitivity to bright light?
1. Mild
2. Moderate
3. Severe

29. In the past year, have you had trouble focusing your eyes?
1. Never (if you marked Never, please skip to question 31)
2. Occasionally
3. Frequently
4. Constantly

30. How severe is this focusing problem?
1. Mild
2. Moderate
3. Severe

31. Is the most troublesome symptom with your eyes (ie, sensitivity to bright light or trouble focusing) getting:
1. I have not had any of these symptoms
2. Much worse
3. Somewhat worse
4. Staying about the same
5. Somewhat better
6. Much better
7. Completely gone

7.2. Pandemic Phase Start Dates by Country

Table 1 Pandemic Phase Start Dates by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Date of 1st Confirmed Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>2020-01-24</td>
</tr>
<tr>
<td>Germany</td>
<td>2020-01-28</td>
</tr>
<tr>
<td>Italy</td>
<td>2020-01-29</td>
</tr>
<tr>
<td>Portugal</td>
<td>2020-03-02</td>
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<tr>
<td>Spain</td>
<td>2020-01-31</td>
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<tr>
<td>Sweden</td>
<td>2020-01-31</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2020-01-31</td>
</tr>
</tbody>
</table>

As reported by the World Health Organization and the Taiwan Centers for Disease Control.
8. **AMENDMENT HISTORY**

Amendment 1: 08 October 2020

Key changes were made to the original SAP to address the impact of the COVID-19 pandemic, including:

- Addition of Per Protocol Analysis Set.
- Updates of using LOCF method for the analyses of NIS, Norfolk QoL-DN, R-ODS and mBMI efficacy endpoints, and using MMRM method for the analysis of COMPASS-31 efficacy endpoint.
- Addition of summaries and analyses to characterize the impact of the COVID-19 pandemic.

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 2.1</td>
<td>Per Protocol Analysis Set was added.</td>
<td>The Per Protocol Analysis Set was added to support primary analyses of estimating treatment effects of secondary and exploratory efficacy endpoints in patients who did not miss or missed less than or equal to 2 doses of patisiran due to COVID-19.</td>
</tr>
<tr>
<td>Section 2.2</td>
<td>A data listing of COVID-19 related protocol deviations was added.</td>
<td>The data listing of COVID-19 related protocol deviations was added to align with regulatory guidance recommendations.</td>
</tr>
<tr>
<td>Section 3.9</td>
<td>The potential data censoring for secondary and exploratory efficacy endpoints on or after the onset of a serious COVID-19 AE was added.</td>
<td>This was to account for the potential impact of COVID-19 on secondary and exploratory efficacy endpoints in addition to the update of using Per Protocol Analysis Set for primary analyses of secondary and exploratory efficacy endpoints.</td>
</tr>
<tr>
<td>Section 3.10</td>
<td>Missing efficacy data summaries were added.</td>
<td>This was to account for potential missingness in efficacy data, including missingness due to COVID-19.</td>
</tr>
<tr>
<td>Section 4.1</td>
<td>Patient disposition summaries were updated.</td>
<td>Patient disposition summaries were updated to account for discontinuations associated with COVID-19 pandemic.</td>
</tr>
<tr>
<td>Section 3.10.1</td>
<td>The primary analysis for the NIS, Norfolk QOL-DN, R-ODS and mBMI efficacy endpoints was updated to use LOCF to impute missing post-baseline values.</td>
<td>The changes from baseline in NIS, Norfolk QOL-DN and R-ODS assessments between Months 9 and 18 and mBMI assessments between Months 3 and 18 were relatively stable in the patisiran arm of the APOLLO study. Thus, the LOCF method was adopted to account for the potential missingness (including missingness related to COVID-19) in NIS, Norfolk QOL-DN, R-ODS and mBMI efficacy endpoints during this study.</td>
</tr>
<tr>
<td>Section</td>
<td>Description</td>
<td>Rationale</td>
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<tr>
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<tr>
<td>Section 4.4.2.3</td>
<td>The primary analysis for the COMPASS-31 efficacy endpoint was changed to MMRM.</td>
<td>The changes from baseline in COMPASS-31 total score showed improvement from Month 9 to Month 18 in the patisiran arm of the APOLLO study. Thus, the MMRM method was adopted to account for potential missingness (including missingness related to COVID-19) in COMPASS-31 total score, which assumes data are Missing at Random (MAR).</td>
</tr>
<tr>
<td>Section 4.7</td>
<td>Summaries of COVID-19 pandemic general impact and related impacts on efficacy and safety were added.</td>
<td>The summaries were added to assess the impact of COVID-19 in acknowledgement of regulatory guidance.</td>
</tr>
<tr>
<td>Section 7.2</td>
<td>A table for the pandemic phase start dates by country was added.</td>
<td>The table was added to support the related by-pandemic-phase analyses.</td>
</tr>
<tr>
<td>Throughout document</td>
<td>General data presentation rules were corrected; Wording of selected analyses were updated; MedDRA version was updated to 23.0 or later; CTCAE version was updated to 5.0 or above; Abbreviation list was updated.</td>
<td>The updates were to streamline and clarify planned analyses needed to support overall objectives and address minor errors.</td>
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