Official Title: **A MULTICENTER, OPEN-LABEL, EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF PATISIRAN IN PATIENTS WITH FAMILIAL AMYLOIDOTIC POLYNEUROPATHY WHO HAVE COMPLETED A PRIOR CLINICAL STUDY WITH PATISIRAN**

NCT Number: **NCT02510261**

Document Date: **Statistical Analysis Plan, Version 1.0, 12 July 2017**

STATISTICAL ANALYSIS PLAN: PROTOCOL ALN-TTR-006

A Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety and Efficacy of Patisiran in Patients with Familial Amyloidotic Polyneuropathy Who Have Completed a Prior Clinical Study with Patisiran

Protocol Number:	ALN-TTR02-006
Protocol Version and Date:	Amendment 2: 05 January 2017 Amendment 1: 08 September 2015 Original: 06 November 2014
Name of Test Drug:	Patisiran (ALN-TTR02)
Phase:	Phase 3
Methodology:	Multicenter, open label study
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Sponsor Representative:	PPD PPD
Analysis Plan Version and Date:	Final Version 1.0: 12 July 2017

APPROVAL SIGNATURE PAGE

Protocol Title: A Multicenter, Open-Label, Extension Study to Evaluate the Long-Term Safety and Efficacy of Patisiran in Patients with Familial Amyloidotic Polyneuropathy Who Have Completed a Prior Clinical Study with Patisiran

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Document Date / Version: 12 July 2017 / Final Version 1.0

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Date: 13 July 2017

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinic PPD

Sponsor Signatories:

PPD

Alnylam Pharmaceuticals, Inc.

Signature: PPD

Date: 13 JUL 2017 PPD

PPD

Alnylam Pharmaceuticals, Inc.

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Date: PPD 13 JUL 2017

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
Σ5	sum of 5 nerve conduction attributes
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	anatomic therapeutic class
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
COMPASS-31	Composite Autonomic Symptom Score
eCRF	electronic case report form
CRO	contract research organization
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
EQ-5D-5L	EuroQoL five dimensions, five-level scale
EQ-VAS	EuroQoL visual analog scale
EW	early withdrawal
FAP	familial amyloidotic polyneuropathy
hATTR	hereditary transthyretin-mediated amyloidosis
HLT	high level term
HP	heat pain
HRdb	heart rate response to deep breathing
ICH	International Conference on Harmonisation
IENFD	intraepidermal nerve fiber density
INN	International Nonproprietary Name
IRR	infusion-related reaction
IV	intravenous
KPS	Karnofsky performance status
LOCF	last observation carried forward
mBMI	modified body mass index
MedDRA	Medical Dictionary for Regulatory Activities
mNIS+7	Modified Neuropathy Impairment Score

Abbreviation	Definition
MR	magnetic resonance
NCS	nerve conduction studies
NIS	Neuropathy Impairment Score
NIS+7	Neuropathy Impairment Score + sum of 7 nerve tests
NIS-W	Neuropathy Impairment Score - Weakness
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PBP	postural blood pressure
PD	pharmacodynamic
PND	polyneuropathy disability
PT	preferred term
QOL	quality of life
QOL-DN	Quality of Life-Diabetic Neuropathy
QST	quantitative sensory testing
R-ODS	Rasch-built Overall Disability Scale
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGNFD	sweat gland nerve fiber density
siRNA	small interfering ribonucleic acid
SMQ	Standardized MedDRA query
SOC	system organ class
TP	touch pressure
TTR	transthyretin
ULN	upper limit of normal
V30M	Val30Met
VDT	vibration detection threshold
WHO	World Health Organization
WT	wild type

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Patisiran (the International Nonproprietary Name [INN] for the drug product also referred to as ALN-TTR02) is a novel investigational agent being developed for the treatment of polyneuropathy in patients with hereditary transthyretin-mediated (hATTR) amyloidosis. Patisiran comprises a small interfering ribonucleic acid (siRNA) which is specific for transthyretin (TTR), and is formulated in a hepatotropic lipid nanoparticle (LNP) for intravenous (IV) administration.[1] It is designed to significantly suppress liver production of both wild type (WT) and all mutant forms of TTR, thereby having the potential to reduce amyloid formation and provide clinical benefit to patients with hATTR amyloidosis.

ALN-TTR02-006 (hereinafter referred to as study 006) is a multicenter, open-label extension study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy who have completed a prior study with patisiran (ALN-TTR02-003 or ALN-TTR02-004, hereinafter referred to as Studies 003 and 004, respectively).

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 in order to address the study objectives of Study 006. 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 and will be used to guide the interim and final analyses of the study.

The objective of this study is to assess the safety and efficacy of long-term dosing with patisiran in patients with hATTR amyloidosis with polyneuropathy.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a multicenter, multinational, open-label extension study to evaluate the long-term safety and efficacy of patisiran in patients with hATTR amyloidosis with polyneuropathy who have previously completed a patisiran study.

Consented eligible patients will enroll in this study and receive 0.3 mg/kg patisiran IV once every 21 days for the duration of the study. The study inclusion and exclusion criteria are listed in Sections 4.1 and 4.2 of the study protocol. All dosing visits have a window of ± 3 days. In order to maintain the 21-day dosing schedule from the parent study, patients are expected to have their first visit (Day 1) on this study 3 weeks after their last dosing visit on the parent study. However, a patient may initiate dosing in this study up to 45 days from the time of the last dose in the parent study. The last testing visit in the parent study will serve as the baseline for this study, unless more than 45 days have elapsed, in which case the baseline tests will be repeated prior to the first dose of patisiran on Day 1. Eligibility for this study will be confirmed before administration of the first dose on Day 1.

After the Day 1 visit, patients will either return to the clinical site for the patisiran infusions or will receive the patisiran infusions at home once every 21 (±3) days. Patients who are receiving patisiran infusions at home will have phone contact with the site at least every 30 (±5) days. Patients will also have visits at the clinical site at approximately 26 and 52 weeks, and yearly thereafter.

A complete set of efficacy assessments will be performed at 52 weeks (+/-4 weeks), followed by more limited efficacy assessments yearly thereafter.

Safety will be assessed throughout the study. Patients will return to the clinical site for safety evaluations at 26 and 52 weeks during the first year and yearly thereafter. 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.

Patients rolling over into this open-label study from a previously blinded study will remain blinded to their previous treatment assignment until after database lock has occurred in that parent study.

1.2.2. Study Procedures

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

1.2.3. Efficacy, Pharmacodynamic, Safety, and Other Assessments

1.2.3.1. Efficacy Assessments

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

- Neurological impairment assessed using the Neuropathy Impairment Score (NIS), Modified NIS (mNIS +7) composite score and NIS+7.
- Patient reported quality of life (QOL) using the EuroQoL five dimensions, five-level scale (EQ-5D-5L) questionnaire and the Norfolk Quality of Life –Diabetic Neuropathy (QOL-DN) questionnaire; patients from Study 003 do not have to complete the Norfolk QOL-DN questionnaire.
- Overall health using the EuroQoL visual analog scale (EQ-VAS).
- Disability reported by patients using the Rasch-built Overall Disability Scale (R-ODS).
- Autonomic symptoms assessed using the Composite Autonomic Symptom Score (COMPASS-31).
- Motor function assessments, including timed 10-meter walk test and grip strength test.
- Polyneuropathy disability (PND) score and familial amyloidotic polyneuropathy (FAP) stage.
- Nutritional status using modified body mass index (mBMI).
- Pathologic evaluation of sensory and autonomic innervation evaluated by intraepidermal nerve fiber density (IENFD) analysis and quantitation of dermal sweat gland nerve fibers (SGNFD) via tandem 3mm skin punch biopsies taken from the leg (only for patients having this assessment in the parent study).
- Dermal amyloid content (% Congo Red staining) using the same skin punch biopsy specimens analyzed for nerve fiber density.

- Magnetic resonance (MR) neurography (in Germany and France only).
- Cardiac assessment with echocardiograms and serum levels of terminal prohormone of B-type natriuretic peptide (NT-proBNP) and troponin I.
- New York Heart Association (NYHA) classification of heart failure.

1.2.3.2. Pharmacodynamic Parameters and Pharmacology Parameters

Pharmacodynamic (PD) markers include serum TTR assessed using enzyme linked immunosorbent assay (ELISA) and vitamin A.

Blood will be collected to evaluate anti-drug antibodies (ADA).

1.2.3.3. Safety Parameters

Safety evaluations performed during the study include monitoring of AEs and concomitant medications, physical examinations, measurement of vital signs, clinical laboratory evaluations (including hematology, clinical chemistry [including liver function tests and thyroid stimulating hormone], urinalysis, and pregnancy testing), and ophthalmology examinations.

Suicidal ideation and behavior will be assessed using the Columbia–Suicide Severity Rating Scale (C-SSRS) questionnaire.

1.2.3.4. Other Parameters

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

2. PATIENT POPULATION

2.1. Population Definitions

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

- Full Analysis Set: All patients who were enrolled will be included in the full analysis set. The full analysis set will be the primary set for the analysis of efficacy data.
- Pharmacodynamic (PD) Analysis Set: All patients who received at least 1 dose of patisiran in this study and have both baseline and at least 1 post-baseline PD assessment (either TTR or Vitamin A). For a patient who received patisiran in the parent study, if more than 45 days elapsed between the last dose of patisiran in the parent study and the first dose of patisiran in this study, the patient will be excluded from the PD analysis set.
- Safety Analysis Set: All patients who were enrolled and who received at least 1 dose of patisiran in this study. The safety analysis set will be used for the analysis of safety data.

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.

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

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

This is an open-label extension study enrolling patients who have previously completed a patisiran clinical study (Study 004 or 003); the size of the study is not determined via power analysis of particular hypotheses tests.

3.2. General Methods

As this is an extension study, formal statistical hypothesis testing will not be performed. All summaries are descriptive.

All data will be presented in by-patient data listings. The listings that contain an evaluation date will include 2 study days as described below:

1) Extension study day: the study day relative to the first dose date of patisiran in this study. The first dose date is designated as Day 1. On-treatment study days will be calculated as evaluation date – first dose date +1 and pre-treatment days will be calculated as evaluation date – first dose date. For example, the day prior to the first dose of patisiran will be Day -1 and the day after the first dose of patisiran will be Day 2, etc.
2) Parent study day: the study day relative to the day of the first dose of study drug in the parent study (Study 004 or 003).

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).

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of patients, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

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 with planned repeat assessments at a given study visit (e.g., 10-meter walk tests), the average will be calculated unless otherwise noted.

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 9.3 (or later), unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 (or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version March 2015 (or later).

3.4. Baseline Definitions

Unless noted otherwise, baseline will be defined as the last non-missing measurement on or prior to the first dose of patisiran in this study. For several procedures, the last testing visit in the parent study will serve as the baseline for this study, unless more than 45 days have elapsed, in which case the test will need to be repeated on Day 1 in this study; see Table 1 of the study

protocol for additional details. If more than 45 days have elapsed and the assessment is not repeated on Day 1, the last assessment from the parent study will serve as baseline for this study; any such occurrence will be identified as a protocol deviation.

For the mNIS+7/NIS+7 individual components, total scores and related endpoints, grip strength test, and 10-meter walk test, baseline will be calculated as the average of 2 replicates.

3.5. Study Group

Data from all sites will be summarized together. Patients will be grouped into the following 3 study groups:

1) 004 Placebo: patients in Study 006 who previously received placebo in Study 004.
2) 004 Patisiran: patients in Study 006 who previously received patisiran in Study 004.
3) 003 Patisiran: patients in Study 006 who previously received patisiran in Study 003.

Summary tables and figures will include presentations by study group and overall.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this study with a descriptive interpretation.

3.8. Subpopulations

No analyses of patient subgroups are planned.

3.9. Withdrawals, Dropouts, and Loss to Follow-up

Patients are free to withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Every effort should be made to complete the Early Withdrawal (EW) visit, if applicable. Patients who permanently discontinue treatment are to be withdrawn from the study.

In the event a patient withdraws early from the study, the contract research organization (CRO) Medical Monitor must be informed immediately. If an AE is the reason for withdrawal, the patient will remain under the supervision of the Investigator for protocol-specified safety follow up procedures.

When a patient withdraws from the study, the primary reason for withdrawal must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible.

3.10. Missing Data

3.10.1. Partially Missing Efficacy Endpoints

Specific algorithms will be used to impute values and/or subcomponents of particular assessments when subcomponents are missing (mNIS+7, NIS+7, Norfolk QOL-DN, EQ-5D-5L, R-ODS, and COMPASS-31; see Section 7.1, Section 7.2, Section 7.3, Section 7.4, and Section 7.5). The result of the partial imputation (either a non-missing or missing value) will be used in all statistical analyses.

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

3.10.2. Other Missing Data

Conventions for determining whether an AE is treatment emergent are discussed in Section 4.7.2. For the calculation of duration (e.g., 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 day and month: duration will be calculated as the simple difference in years (e.g., year of informed consent minus year of diagnosis with hATTR);
- Missing day, month, and 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. In data listings, the extension study day and parent study day will be presented.

For efficacy assessments, if the scheduled 52-week or annual visits are not performed, any evaluable visit will be grouped with the 52-week or annual assessments if it is performed within 3 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 the purpose of 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 (e.g., shift from baseline to "worst" post-baseline value).

3.12. Interim Analyses

Interim analyses will be performed to support regulatory activities and publications. These analyses will be of a descriptive nature and will not involve any formal hypothesis testing.

For an interim analysis, as this study will be ongoing, a cut-off analysis approach will be implemented to ensure data quality. The interim analysis will include data on or prior to a pre-specified cut-off date. For assessments with starting/ending dates (e.g., AEs, medications, medical history), the starting date will be compared with the pre-specified cut-off date. For any assessments consisting of multiple replicates associated with a single visit, the earliest of the dates will be compared to the cut-off; if this date is on or before the cutoff date, the replicates will be included in the analysis. In particular, for mNIS+7, NIS+7, and NIS, the date for the earliest replicate of NIS-W at the visit will be compared to the cut-off date.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated and will include the following parameters: the number of patients in each analysis population, the number of patients enrolled, the number of patients treated with patisiran, the number of patients who are ongoing, the number of patients who completed the study, and the number of patients who withdrew from the study and the primary reasons for withdrawal.

A by-patient data listing of study completion information including the reason for premature study withdrawal will be presented.

4.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics, baseline disease characteristics, baseline efficacy parameters, and medical history information will be summarized by study group and overall. No formal statistical comparisons will be performed.

Age, height, weight, and body mass index (BMI) will be summarized using descriptive statistics (number of patients, mean, SD, median, minimum, and maximum). Sex, race, ethnicity, and region will be summarized by presenting the numbers and percentages of patients in each category.

The following baseline disease characteristics will be summarized by presenting the numbers and percentages of patients in each category:

- Genotype (V30M vs non-V30M)
- Karnofsky Performance Status (KPS)
- Concurrent Stabilizer Use at Study Entry (yes, no)

Concurrent stabilizer use at study entry is defined as patients who were receiving TTR tetramer stabilizers (tafamidis or diflunisal) for at least 2 weeks within the first month following the first dose of patisiran in Study 006.

Time in years since diagnosis with hATTR will be summarized using descriptive statistics.

Baseline values of continuous efficacy parameters (mNIS+7, Norfolk QOL, NIS-W, mBMI, 10-meter walk test, COMPASS-31, NIS, NIS+7, grip strength, EQ-5D-5L, EQ-VAS, R-ODS, IENFD distal thigh and distal leg, and SGNFD distal thigh and distal leg) will be summarized using descriptive summary statistics. The numbers and percentages of patients in each category for baseline PND score (I, II, IIIA, IIIB, IV), baseline FAP stage (0, I, II, III), and baseline NYHA class (I, II, III, IV) will also be summarized.

All demographic and baseline data for each patient will be provided in data listings.

Medical history will be summarized 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, by PT). Medical history including prior surgeries and pregnancy test results will be presented in data listings.

4.3. Pharmacokinetic Evaluations

No pharmacokinetic evaluations will be done for this study.

4.4. Pharmacodynamic Analyses

Pharmacodynamic analyses will be based on the PD analysis set.

The PD parameters include serum TTR (ELISA) and vitamin A. All summary tables and figures will be based on assessments within 21 days of last dose of patisiran. Assessments more than 21 days after last dose 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 study group and overall. Graphical displays will be provided for the observed values of TTR and vitamin A for each scheduled time point by study group.

All PD data will be displayed in data listings.

4.5. Efficacy Analyses

Efficacy analyses will be based on the full analysis set. Summaries will be provided for each scheduled time point by study group and overall.

Neurologic impairment will be assessed by mNIS+7, NIS+7, and NIS. The observed values and changes from baseline in the composite and component scores of mNIS+7, NIS+7, and NIS will be summarized. The mNIS+7 composite score consists of the NIS weakness (NIS-W) and reflex (NIS-R) domains, quantitative sensory testing (QST) by body surface area including touch pressure (TP) and heat pain (HP), 5 nerve conduction studies (Σ5 NCS), as well as autonomic assessment through postural blood pressure (PBP). The NIS+7 includes the NIS-W, NIS-R, NIS sensation (NIS-S), and Σ7 Nerve tests (including sum of 5 NCS which overlaps but is not identical to the Σ5 NCS calculated for mNIS+7 above, vibration detection threshold (VDT), and heart rate response to deep breathing [HRdb]). The total NIS score is the sum of NIS-W, NIS-R, and NIS-S. Scoring algorithms for mNIS+7, NIS+7, and NIS, including methods for handling missing components, are included in Section 7.1.

Patient reported QOL will be assessed by the Norfolk QOL-DN total score (Study 003 patients do not have to complete this assessment) and by the EQ-5D-5L index value (using U.S. references to calculate the index). Overall health will be assessed by the EQ-VAS and disability will be assessed by the R-ODS. Patient reported autonomic neuropathy symptoms will be assessed by the COMPASS-31 total score. The observed values and changes from baseline in these measures will be summarized. Continuous summaries of each Norfolk QOL-DN and COMPASS-31 domain score, as well as categorical summaries of each EQ-5D-5L domain will also be provided. Scoring algorithms for the Norfolk QOL-DN, EQ-5D-5L, R-ODS, and COMPASS-31 are included in Section 7.2, Section 7.3, Section 7.4, and Section 7.5.

Motor function assessments will include a timed 10-meter walk test and test of grip strength in the dominant arm, as well as an evaluation of ambulation using PND score and FAP stage. The observed values and changes from baseline in 10-meter walk test speed and grip strength will be summarized. Categorical summaries of FAP stage and PND score will also be provided.

Pathologic evaluation of sensory and autonomic innervation will be evaluated by IENFD analysis and quantitation of SGNFD via tandem 3 mm skin punch biopsies taken from the distal leg and distal thigh. In addition, the evaluation of dermal amyloid content (% Congo Red staining) using the same skin punch biopsy specimens analyzed for nerve fiber density (SGNFD and IENFD) will also be assessed. Continuous summaries of the observed values and changes

from baseline in IENFD, SGNFD, and dermal amyloid content will be provided by site (i.e., distal thigh, distal leg).

Nutritional status of patients will be evaluated using the mBMI, calculated as BMI (kg/m^2) multiplied by albumin (g/L). The observed values and changes from baseline in mBMI will be summarized.

A categorical summary of the observed values and changes from baseline in the NYHA classification of heart failure will be provided.

Cardiac structure and function will be assessed through echocardiograms as well as measurement of serum levels of the cardiac biomarkers NTproBNP and troponin I. Descriptive statistics will be provided for actual values, changes, and percentage changes from baseline in echocardiogram parameters (including wall thickness, ejection fraction, and other echo parameters), serum levels of troponin I and NT-proBNP.

Magnetic resonance (MR) neurography data will be presented in a by-patient data listing.

4.6. Healthcare Utilization Assessments

The patient-reported pharmacoeconomics questionnaire data will be presented in a data listing.

4.7. Safety Analyses

Safety analyses will be based on the safety analysis set. All safety summaries will be presented by study group and may include an overall column as specified.

4.7.1. Study Drug Exposure

The total duration of drug exposure will be defined as (the last dose of patisiran in this study – the first dose of patisiran in this study + 21)/30.44 months. Duration of drug exposure, the total number of doses received, duration of infusion (per infusion) and amount of patisiran received (per infusion and in total) will be summarized by descriptive statistics. Summaries of the numbers and percentages of patients with at least 1 missed dose, and the number of missed doses per patient will also be provided. The total amount of drug received and the total volume infused will also be summarized. The number of patients who experienced dose interruptions for any reason will be tabulated, as well as the number of patients with dose interruptions due to an infusion related reaction (IRR).

A drug exposure table summarizing the treatment duration and interruptions under the "original" and "reduced" premedication regimens (see Section 4.7.6) will be also provided. A patient who switches from "original" to "reduced" regimen during treatment will be counted in both categories. For patients switching to the reduced regimen, the duration of exposure on the original regimen is defined as (the date of regimen change – the first dose of patisiran in this study)/30.44 months, and the duration of exposure on the reduced regimen is defined as (the last dose of patisiran in this study – the date of regimen change + 21)/30.44 months.

Dosing information for each patient will be presented in a data listing. In addition, a listing will be provided to present the durations of study drug exposure under the original regimen and reduced regimen for each patient.

4.7.2. Adverse Events

All AEs will be coded using the MedDRA coding system (version 18.0 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 treatment-emergent is defined per protocol 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. 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 patisiran. For an interim analysis where a cut-off approach is used, events with a partially missing onset date will be assumed to have started prior to the cut-off date unless it can be unequivocally determined (from the partial onset date) that the event occurred after the cut-off date; events with a fully missing onset date will be assumed to have started prior to the cut-off date.

AEs will be summarized by the number 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). Overall event counts and frequencies may also be summarized.

An overall summary of AEs will include the numbers and percentages of patients with any AE, any AE assessed by the Investigator as related to treatment (definite or possible relationship), any severe AE, any severe AE related to treatment, any serious AE (SAE), any SAE related to treatment, any AE leading to study withdrawal, any study drug related AE leading to study withdrawal, and any deaths.

Tabulations by SOC and PT will be produced for the following: all AEs; AEs related to treatment; severe AEs; AEs leading to study withdrawal, and SAEs. Separate tables will be provided summarizing signs and symptoms of IRRs and AEs related to premedication by SOC and PT. The incidence and frequency of AEs and IRRs over time will also be summarized by SOC and PT. AEs and AEs related to treatment will also be tabulated by PT in decreasing order of frequency over all patients.

Separate tables will present AE incidence rates by maximum relationship to study drug and by maximum severity. If a patient experiences more than 1 event in a given SOC or PT, the patient is counted once for that SOC or PT according to the most related or the most severe occurrence, respectively. AEs with a missing relationship will be considered as definitely related to study drug, and AEs with a missing severity will be considered as severe.

AEs identified by the Depression and Suicide/Self-injury standardized MedDRA query (SMQ) will be summarized by PT; these AEs will be tabulated by PT in decreasing order of frequency over all patients. AEs identified by the Drug Related Hepatic Disorder SMQ will be summarized by SOC and PT. AEs identified by the Malignant or Unspecified Tumors SMQ will be summarized by HLT and PT. Other SMQs or AE groupings may be evaluated.

All AEs occurring on-study, including both treatment emergent and non-treatment emergent events, will be listed in patient data listings. A separate listing will be provided for IRRs. Listings will be provided for any AEs assessed by the Investigator as related to premedication or any study procedure. Non-treatment emergent AEs will also be listed separately.

By-patient listings will also be provided for the following: all patient deaths, all SAEs, and AEs leading to study withdrawal.

4.7.3. Laboratory Data

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, coagulation studies, thyroid, 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, where the "worst" post-baseline category will be based on the maximum difference (in absolute value) from the upper or lower limits of the normal range.

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.

- 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 4.0 or above, where applicable. A shift summary of baseline to maximum post-baseline CTCAE grade may be presented, as appropriate.

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

All laboratory data will be provided in data listings. Laboratory values outside of the normal ranges will additionally be listed separately.

4.7.4. Vital Signs and Physical Examination

The observed values and changes from baseline in weight and vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate, will be summarized by scheduled visit. The frequency and percentage of patients with an abnormal change from baseline in pulse rate or blood pressure measures will also be presented.

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

All abnormal physical examination findings will be presented in a by-patient data listing.

4.7.5. Ophthalmology Examinations

Ophthalmology examinations include Visual Acuity, Slit Lamp Biomicroscopy, and Visual Field assessments.

Visual Acuity and Visual Field Exam Results: The actual value and change from baseline results will be summarized by scheduled visit.

Biomicroscopy (Slit Lamp) Exam Results: For the baseline results, the number and percentage of patients falling into each category of the examination status (normal, abnormal/not clinically significant, abnormal/clinically significant) will be summarized for each eye structure. For post-baseline results, the number and percentage of patients falling into each category of the examination status (new findings/worsening of finding, no change, improvement of finding) will be summarized for each eye structure.

Data for each of these assessments will be provided in a data listing.

4.7.6. Premedications

All patients will receive premedication prior to the dose of patisiran in order to reduce the potential of an IRR. The original premedication regimen as outlined below was used at the start of the study. A subset of patients experienced AEs suspected to be related to steroids (e.g., flushing) and were transitioned to a reduced premedication regimen, with a reduced dose of corticosteriod to mitigate these events, as sanctioned in the protocol. After observing that the subset of patients tolerated the lower corticosteroid dose with no increase in IRRs, the protocol was amended (Amendment 1.0) to transition the rest of the patients to the reduced premedication regimen (see below).

The following original premedication regimen was used prior to protocol amendment 1.0:

- Dexamethasone 8 mg PO or equivalent administered the evening before dosing and 20 mg PO at least 60 minutes prior to the start of the infusion of patisiran;
- Paracetamol 500 mg PO or equivalent administered the evening before dosing and at least 60 minutes prior to the start of the infusion of patisiran;
- H2 blocker PO (e.g., ranitidine 150 mg or famotidine 20 mg or equivalent other H2 blocker dose) administered the evening before dosing and at least 60 minutes prior to start of the infusion of patisiran; and
- H1 blocker PO, 10 mg cetirizine or equivalent (hydroxyzine 25 mg or fexofenadine could be substituted if patient did not tolerate cetirizine) administered the evening before dosing and at least 60 minutes prior to start of the infusion of patisiran.

The following reduced premedication regimen was instituted for all patients with protocol amendment 1.0:

- Dexamethasone 10 mg IV or equivalent, administered at least 60 minutes prior to the start of the infusion of patisiran;
- Paracetamol 500 mg PO or equivalent at least 60 minutes prior to the start of the infusion of patisiran;
- H2 blocker IV (e.g., ranitidine 50 mg, famotidine 20 mg, or equivalent other H2 blocker dose) at least 60 minutes prior to the start of the infusion of patisiran; and

- H1 blocker IV, diphenhydramine 50 mg (or equivalent other IV H1 blocker available at the study site) at least 60 minutes prior to the start of the infusion of patisiran. Hydroxyzine 25 mg PO or fexofenadine 30 or 60 mg PO or cetirizine 10 mg PO could be substituted for any patient who did not tolerate IV diphenhydramine or other IV H1 blocker.

Premedications will be coded using the WHO Drug Dictionary (March 2015 or later). Results will be tabulated by anatomic therapeutic class (ATC) and PT. Premedication data will be listed.

4.7.7. Concomitant Medications

Concomitant medications will be defined as those medications that were initiated after first patisiran administration in this extension study or those that were ongoing at the time of the first patisiran administration in this study. 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.

Concomitant medications will be coded using the WHO Drug Dictionary (March 2015 or later). Results will be tabulated by ATC and PT; patients will only count once for each ATC or PT in the event that they have multiple medications with the same ATC or PT. Medications taken as protocol-specified premedications will be summarized separately.

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

4.7.8. Suicide Questionnaire

The numbers and percentages of patients experiencing the suicidal ideation, suicidal behavior, or self-injurious behavior composite outcomes (and individual components thereof) during the treatment period will be summarized. A shift table will be employed to summarize the baseline C-SSRS category versus the worst post-baseline C-SSRS category; the categories are defined as 1) no suicidal ideation or behavior, 2) suicidal ideation, and 3) suicidal behavior. Subjects 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

Anti-drug antibody data will be presented in a data listing. Patients with positive ADA results will be presented in a separate listing.

5. CHANGES TO PLANNED ANALYSES

In the protocol, the first day of drug administration in this study was designated as Day 0. In the SAP and table/listing/figure outputs, the first dose day will be defined as Day 1, following CDISC convention. Each calculated study day after dosing is 1 day plus the reported study day following the protocol defined Schedule of Assessments.

In addition to IENFD and SGNFD, skin punch biopsies will also be assessed for dermal amyloid content, which has been added as an efficacy parameter.

6. REFERENCES

1 Akinc A, Zumbuehl A, et al. A combinatorial library of lipid-like materials for delivery of RNAi therapeutics. Nat Biotechnol. 2008;26(5):561-569.

7. QUESTIONNAIRE/SCORING APPENDICES

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

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

Note: the mNIS+7 and NIS+7 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 below.

Assessment Tool	Total Points	Components (maximum points)

mNIS+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+7	270	• NIS-W: Weakness (192)
		• NIS-R: Reflexes (20)
		• NIS-S: Sensation (32)
		• ∑7 Nerve tests
		  • 5 Nerve conduction studies ∑5 (18.6)
		  • Peroneal compound muscle action potential (peroneal CMAP)
		  • Peroneal motor nerve conduction velocity (peroneal MNCV)
		  • Peroneal motor nerve distal latency (peroneal MNDL)
		  • Tibial motor DL
		  • Sural sensory nerve action potential (sural SNAP)
		  • Vibration detection threshold (VDT) (3.72)
		  • Heart rate response to deep breathing (HRdb) (3.72)

7.1.1. Modified Neuropathy Impairment Score + 7 (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.

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 (e.g., absent reflexes in a patient older than 60 is assessed as 0, or normal). The maximum total score for NIS-R is 20.
3. QST measures HP and TP from among 10 distributed anatomical sites on one side of the body. Scoring is based on point abnormality ($<95^{th}$ = 0 point, $\geq 95^{th}$ – $<99^{th}$ = 1 point and $\geq 99^{th}$ = 2 points). The test score is 2 times the total scores for QST of HP by body surface area ($QST\text{-}BSA_{HP}$) and QST of TP by body surface area ($QST\text{-}BSA_{TP}$). The maximum total score for QST is 80. Missing values for $QST\text{-}BSA_{HP}$ and $QST\text{-}BSA_{TP}$ will be imputed separately (see below), but only the total score will be summarized.
4. ∑5 nerve conductions include ulnar CMAP, ulnar SNAP, sural SNAP, tibial CMAP, and peroneal CMAP. Their measured values were transformed to normal deviates from percentile values correcting for applicable variables of age, gender, height or weight as based on earlier studies of a large healthy patient reference cohort. Additionally, these percentile values were expressed as points from obtained percentile values (i.e., $>5^{th}$ = 0 points; $\leq 5^{th}$ – $>1^{st}$ = 1 point and $\leq 1^{st}$ = 2 points (and similarly when abnormality is in the upper tail of the normal distribution). The total score is calculated as the mean point scores of the non-missing 5 nerve tests and multiply this value by 5. The maximum total score for ∑5 NC is 10.
5. Postural BP test measures autonomic function to address risk of orthostasis. The points are assigned based on change in PBP (> -20 mmHg = 0 points; > -30 - ≤ -20 mmHg = 1 point; and ≤ -30 mmHg = 2 points).

If at least 1 value at a time point and (replicate) assessment is missing then do the following:

- Missing items within the ∑5 NCs component (e.g., missing tibial CMAP) are handled in Step 4 above.

- If 1 of the following components or subcomponents of mNIS+7 (NIS-W, NIS-S, QST-BSA_{TP}, QST-BSA_{HP}, the entire ∑5 NCs, or postural BP) is missing from 1 of the assessments at a time point ("replicate A"), then impute via substituting the component from the other assessment at that time point ("replicate B") → recover 2 complete replicate mNIS+7 measures A and B at that particular time point.
- If both replicates A and B are incomplete at different components, insert replicate A components into replicate B and replicate B components into replicate A as necessary → allow recovery of 2 complete replicate mNIS+7 measures A and B.
- If NIS-W component is missing from both replicates A & B, mNIS+7 score is considered as missing. If 1 of the other mNIS+7 components or subcomponents (NIS-R, the entire ∑5 NCs, QST-BSA_{TP}, QST-BSA_{HP}, or postural BP) is missing from both replicates A and B, impute this component as the average of the component using data from any of the patients who had non-missing data for that component at the time point.
- If 1 entire mNIS+7 replicate is missing, do not impute the missing replicate; just use the singular (other) replicate rather than the average of the 2 in subsequent calculations.
- If no single complete mNIS+7 measure can be found or recovered, mNIS+7 score is considered as missing.

In 006, if the last mNIS+7 assessment in the parent study was done more than 45 days before the first dose in 006, mNIS+7 will be reassessed on Day 1 in 006. It is expected that very few patients will have this Day 1 assessment; therefore, the imputation algorithm for missing components in mNIS+7 will be slightly different from the general algorithm. If NIS-W is missing from both replicates, the mNIS+7 total score will be considered as missing, similar to the general algorithm. If any other component is missing from both replicates, the component score will be imputed by last observation carried forward (LOCF) using the imputed average component score from the last assessment in the parent study.

7.1.2. Neuropathy Impairment Score + 7 (NIS+7)

The components of NIS+7 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 (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.
4. ∑7 nerve tests normal deviates include the following:
    - ∑5 nerve conductions:
        - For peroneal DL and tibial DL, using normal deviate.
        - For peroneal CMAP, peroneal CV and sural SNAP, using (-1) × normal deviate.
    - Vibration detection threshold (VDT): using normal deviate.
    - Heart rate response to deep breathing (HRdb): using (-1) × normal deviate.

Each normal deviate ranges from -3.72 to +3.72. The total score is calculated as the mean normal deviates of the non-missing 7 nerve tests multiplied by 7. The total score ranges from -26 to +26.

Missing values will be handled as follows:

- Missing items within the 7 nerve tests are handled in Step 4 above.
- If a component of NIS+7 (NIS-W, NIS-R, NIS-S, and 7 nerve tests) is missing from replicate A, then impute the component from replicate B → recover 2 complete replicate NIS+7 measures A and B.
- If both replicates A and B are incomplete at *different* components, insert A components into B and B components into A as necessary → recover 2 complete replicate NIS+7 measures A and B.
- If NIS-W component is missing from both replicates A & B, NIS+7 score is considered as missing. If 1 of the other NIS+7 components (NIS-R, NIS-S, and 7 nerve tests) is missing from both replicates A and B, impute this component as the average of the other patients at this time point who had non-missing data.
- If 1 entire NIS+7 replicate is missing, use the singular (other) replicate rather than the average of the 2 in subsequent calculations.
- If no single complete NIS+7 measure can be found or recovered, NIS+7 score is considered as missing.

In 006, if the last NIS+7 assessment in the parent study was done more than 45 days before the first dose in 006, NIS+7 will be reassessed on Day 1 in 006. It is expected that very few patients will have this Day 1 assessment; therefore, the imputation algorithm for missing components in NIS+7 will be slightly different from the general algorithm. If NIS-W is missing from both replicates, the NIS+7 total score will be considered as missing, similar to the general algorithm. If any other component is missing from both replicates, the component score will be imputed by LOCF using the imputed average component score from the last assessment in the parent study.

7.1.3. NIS Total Score

NIS total score is the sum of NIS-W, NIS-R, and NIS-S. The handling of missing data is similar as the steps described for mNIS+7. If NIS-W is missing from both replicates, NIS score is considered as missing.

7.1.4. Algorithms for Setting Normal Deviates and Points

For nerve conductions and HRdb tests, raw values are provided by the Mayo Clinic. Each raw value is first converted to a z-score which is then used to set either normal deviate or point score.

Z-scores are calculated using the following equations provided by the Mayo Clinic:

Parameter (abbreviation, units)	**Z-score Equation**
Heart Rate Response to Deep Breathing (HRdb, beats/min)	HRdbz = HRdb - (28.87292939 + -0.24448047*age)
Ulnar CMAP (UMAE, mV)	UMAEz = UMAE - (12.34105776660360 + -0.04413566229394*age)
Peroneal CMAP (PMAK, mV)	PMAKz = PMAK - (7.26194271992764 + -0.04324792361150*age)
Peroneal MNCV (PMCVK, m/sec)	PMCVKz = PMCVK - (87.98055432974630 + 0.01685327077581*age + -0.00134262390616*age^2 + -0.21761114034235*height)
Peroneal MNDL (PMLA, msec)	PMLAz = PMLA - (4.97158112197395 + -0.36990514432031*sex)
Tibial CMAP (TMAK, mV)	TMAKz = TMAK - (11.91330602787780 + 0.79541113237729*age + -0.01622568048284*age^2 + 0.00008722708244*age^3 + -5.49838000227032*bsa)
Tibial MNDL (TMLA, msec)	TMLAz = TMLA - (4.00321823725368 + 0.00588241012995*age + -0.25248993385258*sex)
Sural SNAP (SSAB, uV)	y = ln(1+SSAB) - (5.58389110852732 + 0.01546531508256*age + -0.01693664229181*height + -0.00034198271691*age^2) if y > 0 then SSABz = y/(0.7001926549587 + -0.20662093194825*bsa) else if y ≤ 0 then SSABz = y
Wrist-Fifth Ulnar SNAP (USAW, uV)	y = ln(1+USAW) - (3.38461614473185 + -0.01702085210501*age + 0.59463420483099*sex) if y > 0 then USAWz = y else if y ≤ 0 then USAWz = y/(0.16695910921534 + 0.00291051555416*age)
Notes: 1) sex is coded 1 = male, 2 = female 2) height is in cm 3) weight is in kg 4) bsa = body surface area (m^2) = weight$^{0.425}$ × height$^{0.725}$ × 0.007184 5) age is an integer rounded down to the nearest year	

For a given parameter, the calculated z-score is then compared to 2 lookup tables (see below) using the following procedure to assign the normal deviate score:

1. If the calculated z-score value is less than the lower z-score value (ZLOWER) in the Extended Percentiles (EP) table, then the normal deviate value is the maximum of (-3.72, (z-score – ZLOWER + WLOWER)).
2. If the calculated z-score value is greater than or equal to ZLOWER and less than the minimum z-score value in the All Percentiles (AP) table, then the normal deviate value = -2.75.
3. If the calculated z-score value is greater than upper z-score value (ZUPPER) in the EP table, then the normal deviate value is the minimum of (3.72, (z-score – ZUPPER + WUPPER)).
4. If the calculated z-score value is less than or equal to ZUPPER and greater than the maximum z-score value in the AP table, then the normal deviate value = 2.75.

5. If the calculated z-score falls between 2 values in the AP table, select the z-score with the normal deviate value closer to 0 (i.e., the 50th percentile). The normal deviate value is the value from the Normal Deviate column corresponding to the selected z-score. For example, if PMLAZ = -0.8 then the PMLA normal deviate (PMLAND) value = -1.65. If PMLAZ = 2.2 then PMLAND = 2.37.
6. If the calculated z-score is less than or equal to the z-score corresponding to the 50th percentile and exactly matches a z-score for that parameter in the AP table, then select the row with the next highest z-score value. The normal deviate value is the value from the Normal Deviate column corresponding to the selected z-score. For example, if PMLAZ = -0.9017 then PMLAND = -1.88.
7. If the calculated z-score is greater than the z-score corresponding to the 50th percentile and exactly matches a z-score for that parameter in the AP table, then select the row with the next lowest z-score value. The normal deviate value is the value from the Normal Deviate column corresponding to the selected z-score. For example, if PMLAZ = 2.2682 then PMLAND = 2.37.

The points for the parameters are calculated as follows:

1. For PMLA, TMLA, and VDT: z-scores <1.65 are assigned 0 points, z-scores ≥1.65 but <2.33 are assigned 1 point, and z-scores ≥2.33 are assigned 2 points.
2. For HRdb, UMAE, PMAK, PMCVK, TMAK, SSAB, and USAW: z-scores > -1.65 are assigned 0 points, z-scores ≤ -1.65 but < -2.33 are assigned 1 point, and z-scores ≤ -2.33 are assigned 2 points.

All Percentiles Table

Percentile	Normal Deviate	HRdb	UMAE	PMAK	PMCVK	PMLA	TMAK	TMLA	USAW	SSAB
0.3	-2.75	-12.783	-5.5287	-4.6320	-9.3076	-1.0017	-7.6549	-0.9448	-4.5129	-2.3235
0.4	-2.65	-12.4944	-5.5287	-4.6320	-9.3076	-1.0017	-7.6549	-0.9448	-4.5129	-2.3235
0.5	-2.58	-12.4944	-5.5287	-4.6320	-9.3076	-1.0017	-7.6549	-0.9448	-4.5129	-2.3235
0.6	-2.51	-12.4944	-5.1192	-4.3753	-8.8001	-1.0017	-7.2749	-0.9037	-4.1808	-2.2050
0.7	-2.46	-12.2499	-5.1192	-4.3753	-8.8001	-1.0017	-7.2749	-0.9037	-4.1808	-2.2050
0.8	-2.41	-12.2499	-4.8488	-4.3712	-8.8001	-1.0017	-7.2270	-0.8394	-3.9289	-2.1063
0.9	-2.37	-12.2499	-4.8488	-4.3671	-8.7164	-0.9017	-7.2270	-0.8394	-3.9289	-2.1063
1	-2.33	-11.4044	-4.8488	-4.3671	-8.7164	-0.9017	-7.2270	-0.8394	-3.9289	-2.1063
2	-2.05	-10.6489	-4.0722	-3.8807	-6.9587	-0.9017	-7.0107	-0.7982	-2.7648	-1.0013
3	-1.88	-10.2499	-3.6577	-3.1211	-6.3385	-0.8017	-6.2660	-0.7159	-2.4600	-0.9160
4	-1.75	-10.0054	-3.4371	-3.0279	-5.5293	-0.8017	-5.7380	-0.6688	-2.0958	-0.7910
5	-1.65	-9.7388	-3.2846	-2.9915	-4.9611	-0.7318	-5.5688	-0.6335	-2.0534	-0.7595
6	-1.56	-9.3603	-3.1142	-2.9481	-4.7403	-0.7318	-5.0376	-0.5982	-1.9855	-0.7098
7	-1.48	-9.2041	-2.9929	-2.8510	-4.3695	-0.7017	-4.7452	-0.5625	-1.8139	-0.6757
8	-1.41	-8.3161	-2.9192	-2.7860	-4.3445	-0.6318	-4.4486	-0.5448	-1.7251	-0.6156
9	-1.34	-7.8272	-2.7729	-2.6320	-3.9685	-0.6318	-4.3632	-0.5037	-1.6250	-0.5995
10	-1.28	-7.2262	-2.6901	-2.4320	-3.7034	-0.6017	-4.2040	-0.4865	-1.6014	-0.5764
11	-1.23	-7.0496	-2.5750	-2.3156	-3.4907	-0.6017	-4.0853	-0.4743	-1.4781	-0.5648
12	-1.18	-6.9596	-2.4377	-2.2738	-3.2399	-0.6017	-3.9092	-0.4512	-1.4231	-0.5289
13	-1.13	-6.783	-2.3142	-2.1563	-2.9994	-0.5318	-3.8051	-0.4394	-1.3393	-0.5133
14	-1.08	-6.6489	-2.1605	-2.0428	-2.9135	-0.5318	-3.6773	-0.4277	-1.2372	-0.4995
15	-1.04	-6.3603	-2.0225	-1.9645	-2.8256	-0.5318	-3.5900	-0.4100	-1.1589	-0.4773
16	-0.99	-6.2041	-1.9701	-1.8968	-2.7349	-0.5318	-3.4409	-0.4037	-1.1203	-0.4555
17	-0.95	-5.9833	-1.9080	-1.8590	-2.6739	-0.5318	-3.2858	-0.3865	-1.0880	-0.4279
18	-0.92	-5.9596	-1.8577	-1.8346	-2.4869	-0.5017	-3.1555	-0.3860	-1.0282	-0.4215
19	-0.88	-5.8713	-1.7605	-1.7293	-2.3484	-0.5017	-3.0824	-0.3684	-0.9673	-0.3858
20	-0.84	-5.7593	-1.7019	-1.6495	-2.2547	-0.5017	-2.9948	-0.3512	-0.9323	-0.3752
21	-0.81	-5.5827	-1.6695	-1.6238	-2.1736	-0.4318	-2.8392	-0.3448	-0.9115	-0.3611
22	-0.77	-5.4707	-1.6377	-1.5266	-2.1275	-0.4318	-2.6699	-0.3394	-0.8764	-0.3578
23	-0.74	-5.3382	-1.5426	-1.4375	-2.0479	-0.4017	-2.6461	-0.3218	-0.8461	-0.3288
24	-0.71	-5.2703	-1.4818	-1.3954	-1.9541	-0.4017	-2.5639	-0.3213	-0.8201	-0.3198
25	-0.67	-4.9817	-1.3633	-1.3401	-1.8102	-0.3318	-2.4213	-0.3159	-0.8141	-0.3080
26	-0.64	-4.9596	-1.3102	-1.2428	-1.6411	-0.3318	-2.3032	-0.3037	-0.7693	-0.2923
27	-0.61	-4.6268	-1.2259	-1.1266	-1.5417	-0.3318	-2.2417	-0.2978	-0.7567	-0.2861
28	-0.58	-4.4486	-1.1722	-1.0847	-1.4258	-0.3318	-2.1872	-0.2688	-0.7011	-0.2745
29	-0.55	-4.2041	-1.0840	-1.0103	-1.3566	-0.3017	-2.0659	-0.2453	-0.6843	-0.2657
30	-0.52	-4.0937	-1.0488	-1.0021	-1.2907	-0.3017	-2.0309	-0.2335	-0.6642	-0.2466
31	-0.5	-4.0038	-1.0142	-0.9508	-1.2377	-0.3017	-1.9931	-0.2277	-0.6416	-0.2374
32	-0.47	-3.7814	-0.9253	-0.9198	-1.0846	-0.3017	-1.9077	-0.2218	-0.5357	-0.2242
33	-0.44	-3.6268	-0.8750	-0.8671	-0.9904	-0.2318	-1.7583	-0.2159	-0.5096	-0.1981
34	-0.41	-3.4707	-0.7778	-0.8158	-0.9556	-0.2318	-1.6953	-0.2096	-0.4527	-0.1894

35	-0.39	-3.2924	-0.7371	-0.7618	-0.8822	-0.2318	-1.6426	-0.1924	-0.3916	-0.1858
36	-0.36	-3.182	-0.7074	-0.7523	-0.8417	-0.2318	-1.6022	-0.1860	-0.3633	-0.1721
37	-0.33	-3.0479	-0.6701	-0.6942	-0.7822	-0.2318	-1.5846	-0.1747	-0.3306	-0.1566
38	-0.31	-3.0259	-0.6287	-0.6483	-0.6634	-0.2017	-1.5418	-0.1688	-0.2903	-0.1415
39	-0.28	-2.9596	-0.5661	-0.6078	-0.6256	-0.2017	-1.3820	-0.1566	-0.2631	-0.1236
40	-0.25	-2.8272	-0.4846	-0.5467	-0.5417	-0.2017	-1.3434	-0.1507	-0.2465	-0.1043
41	-0.23	-2.7388	-0.4074	-0.5348	-0.4421	-0.1318	-1.2323	-0.1390	-0.2363	-0.0878
42	-0.2	-2.671	-0.3633	-0.4346	-0.3655	-0.1318	-1.2023	-0.1277	-0.2028	-0.0774
43	-0.18	-2.2041	-0.2985	-0.3995	-0.3276	-0.1318	-1.0807	-0.1213	-0.1897	-0.0668
44	-0.15	-2.1599	-0.2516	-0.3077	-0.2133	-0.1318	-0.8723	-0.1154	-0.1189	-0.0559
45	-0.13	-2.0038	-0.1454	-0.2103	-0.1076	-0.1017	-0.8126	-0.1096	-0.0814	-0.0369
46	-0.1	-1.8713	-0.1019	-0.1778	-0.0405	-0.1017	-0.7094	-0.0924	-0.0478	-0.0225
47	-0.08	-1.6489	-0.0343	-0.1373	-0.0001	-0.1017	-0.5876	-0.0801	-0.0218	-0.0129
48	-0.05	-1.6047	-0.0170	-0.1143	0.0387	-0.1017	-0.5527	-0.0743	0.0061	-0.0013
49	-0.03	-1.3382	0.0160	-0.1048	0.0957	-0.0318	-0.4625	-0.0629	0.0136	0.0217
50	0	-1.0937	0.0623	-0.0618	0.1549	-0.0318	-0.3295	-0.0512	0.0188	0.0689
51	0.03	-1.0275	0.0830	0.0032	0.2071	-0.0318	-0.2915	-0.0448	0.0190	0.1077
52	0.05	-0.7814	0.1278	0.0654	0.2973	-0.0017	-0.1557	-0.0390	0.0248	0.1716
53	0.08	-0.7593	0.1602	0.1059	0.3555	-0.0017	-0.1220	-0.0331	0.0348	0.1897
54	0.1	-0.4944	0.1802	0.1572	0.3712	-0.0017	-0.0486	-0.0213	0.0413	0.2291
55	0.13	-0.0937	0.2484	0.2032	0.4167	-0.0017	0.1142	-0.0096	0.0479	0.2536
56	0.15	0.217	0.2947	0.2220	0.4744	0.0682	0.2349	-0.0041	0.0566	0.2940
57	0.18	0.4173	0.3299	0.2490	0.5896	0.0682	0.3547	0.0253	0.0679	0.3011
58	0.2	0.5735	0.4133	0.3410	0.6710	0.0682	0.4620	0.0316	0.0888	0.3257
59	0.23	0.6618	0.4568	0.4220	0.7195	0.0682	0.5717	0.0547	0.0932	0.3661
60	0.25	0.8842	0.5222	0.4734	0.7472	0.0682	0.6988	0.0665	0.1035	0.3965
61	0.28	1.0404	0.5747	0.4950	0.7809	0.0682	0.8750	0.0669	0.1171	0.4216
62	0.31	1.1949	0.6574	0.5681	0.8423	0.0682	0.9640	0.0782	0.1228	0.4373
63	0.33	1.2612	0.7423	0.6625	0.9056	0.0983	1.1068	0.0841	0.1330	0.4770
64	0.36	1.5293	0.7830	0.6869	0.9563	0.0983	1.1252	0.0963	0.1398	0.4957
65	0.39	1.706	0.8250	0.7114	1.0163	0.0983	1.2375	0.1140	0.1501	0.5152
66	0.41	1.8621	0.8540	0.7681	1.0514	0.0983	1.2980	0.1199	0.1575	0.5415
67	0.44	1.9962	0.8892	0.8490	1.1319	0.1682	1.5574	0.1316	0.1721	0.5839
68	0.47	2.1287	0.9389	0.9058	1.2285	0.1682	1.6796	0.1493	0.1822	0.6237
69	0.5	2.2612	1.0037	0.9463	1.3007	0.1682	1.8460	0.1669	0.1872	0.6942
70	0.52	2.7738	1.0629	0.9627	1.4587	0.1983	1.8750	0.1782	0.1953	0.7186
71	0.55	3.3511	1.1305	1.0895	1.5916	0.1983	1.9733	0.1841	0.2049	0.7646
72	0.58	3.706	1.1484	1.1613	1.6512	0.2682	2.0584	0.1904	0.2115	0.8278
73	0.61	4.0167	1.2271	1.1922	1.7069	0.2682	2.1753	0.2194	0.2320	0.8722
74	0.64	4.2407	1.2808	1.2355	1.7460	0.2682	2.2577	0.2257	0.2492	0.9115
75	0.67	4.4836	1.3802	1.2762	1.7924	0.2983	2.3567	0.2434	0.2622	0.9370
76	0.71	4.6839	1.4719	1.3398	1.8449	0.2983	2.6142	0.2665	0.2779	0.9709
77	0.74	5.1508	1.5133	1.3922	1.9352	0.2983	2.7013	0.2846	0.2955	0.9916
78	0.77	5.5514	1.5747	1.4815	2.2061	0.3682	2.7523	0.3081	0.3004	1.0341
79	0.81	5.7297	1.6099	1.5627	2.3972	0.3682	2.8504	0.3199	0.3205	1.0512

80	0.84	6.1066	1.7065	1.6491	2.5217	0.3682	3.0249	0.3312	0.3330	1.0760
81	0.88	6.4173	1.7802	1.7247	2.5986	0.3983	3.1374	0.3434	0.3382	1.1249
82	0.92	6.5293	1.8802	1.8599	2.7346	0.3983	3.2372	0.3547	0.3524	1.1720
83	0.95	6.7076	1.9395	1.9140	2.8123	0.4682	3.3970	0.3846	0.3572	1.2310
84	0.99	7.2391	2.0244	1.9801	2.9923	0.4983	3.5065	0.4199	0.3732	1.2883
85	1.04	7.6177	2.1450	1.9924	3.0338	0.4983	3.6598	0.4547	0.3822	1.3203
86	1.08	8.0845	2.2395	2.0627	3.1704	0.5682	3.8320	0.4782	0.3962	1.3679
87	1.13	8.217	2.3305	2.1275	3.2896	0.5983	3.8959	0.4959	0.4054	1.3814
88	1.18	8.5514	2.5574	2.1924	3.4144	0.5983	4.2745	0.5900	0.4366	1.5034
89	1.23	9.0404	2.6361	2.2815	3.5946	0.6682	4.4199	0.6076	0.4498	1.5338
90	1.28	9.1949	2.7657	2.3654	3.7666	0.6983	4.4980	0.6257	0.4756	1.6781
91	1.34	9.5073	2.9512	2.4599	3.8362	0.7682	4.7815	0.6488	0.4876	1.7277
92	1.41	9.7297	3.0596	2.5342	3.9685	0.8682	4.9848	0.6552	0.4995	1.7787
93	1.48	9.9741	3.2333	2.7005	4.1271	0.9682	5.3345	0.6787	0.5271	1.8612
94	1.56	10.9521	3.4389	2.7815	4.3815	0.9983	5.5661	0.7665	0.5548	1.9634
95	1.65	11.728	3.6568	2.9652	4.6629	1.0682	6.1351	0.7963	0.5886	2.0163
96	1.75	12.4836	3.7333	3.1627	5.0363	1.1682	6.3302	0.8199	0.6115	2.1509
97	1.88	13.8401	3.9250	3.8382	5.1400	1.2983	6.9363	0.9140	0.6422	2.2184
98	2.05	14.6618	4.3540	4.0519	5.5861	1.5983	7.9601	1.1959	0.7477	2.4046
99	2.33	17.728	5.1216	4.3517	7.3224	1.8983	9.8583	1.3963	0.8782	2.8233
99.1	2.37	20.0845	5.1216	4.3517	7.3224	1.8983	9.8583	1.3963	0.8782	2.8233
99.2	2.41	20.0845	5.1216	4.4761	7.4064	2.2682	9.8583	1.3963	0.8782	2.8233
99.3	2.46	20.0845	5.1685	4.6005	7.4064	2.2682	10.0358	1.4371	0.8803	2.9923
99.4	2.51	21.1728	5.1685	4.6005	7.4064	2.2682	10.0358	1.4371	0.8803	2.9923
99.5	2.58	21.1728	7.4830	6.2977	7.6495	2.5983	10.3303	1.6728	0.8973	3.0371
99.6	2.65	21.1728	7.4830	6.2977	7.6495	2.5983	10.3303	1.6728	0.8973	3.0371
99.7	2.75	25.7517	7.4830	6.2977	7.6495	2.5983	10.3303	1.6728	0.8973	3.0371

Extended Percentiles Table

Variable	WLOWER	WUPPER	ZLOWER	ZUPPER
HRdb	-2.65	2.65	-12.6387	23.4623
UMAE	-2.75	2.75	-7.4715	7.5668
PMAK	-2.75	2.75	-5.1036	6.4342
PMCVK	-2.75	2.75	-9.3393	8.1941
PMLA	-2.75	2.75	-1.0517	3.0833
TMAK	-2.75	2.75	-7.7785	10.6018
TMLA	-2.75	2.75	-0.9831	3.414
USAW	-2.75	2.75	-6.5249	0.9233
SSAB	-2.75	2.75	-2.3692	3.2713

7.2. 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) $\Sigma(1\text{-}7, 8\text{-}35)$
- Physical Functioning/Large Fiber (15 items) $\Sigma(8, 11, 13\text{-}15, 24, 27\text{-}35)$
- Activities of Daily Living (ADLs) (5 items) $\Sigma(12, 22, 23, 25, 26)$
- Symptoms (8 items) $\Sigma(1\text{-}7, 9)$
- Small Fiber (4 items) $\Sigma(10, 16, 17, 18)$
- Autonomic (3 items) $\Sigma(19, 20, 21)$

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

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.

7.3. 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.

7.4. 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.

7.5. 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 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.
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 (i.e. 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