STATISTICAL ANALYSIS PLAN: PROTOCOL ALN-TTRSC-005

Revusiran

An Open-Label Study to Evaluate the Efficacy and Safety of Revusiran in Patients with Transthyretin-Mediated Familial Amyloidotic Polyneuropathy with Disease Progression Post-Orthotopic Liver Transplant

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Name of Test Drug: Revusiran (ALN-TTRSC)

Phase: Phase 2

Methodology: Multicenter, multinational, open-label study

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Analysis Plan Date: 11 August 2016

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APPROVAL SIGNATURE PAGE

Protocol Title: An Open-Label Study to Evaluate the Efficacy and Safety of Revusiran in Patients with Transthyretin-mediated Familial Amyloidotic Polyneuropathy with Disease Progression Post-Orthotopic Liver Transplant

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Date: 06 Sep 2016

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 clinical study report.

Sponsor Signatory:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomic therapeutic class
ATTR	Transthyretin-mediated amyloidosis
COMPASS	Composite Autonomic Symptom Score
CI	Confidence interval
CRO	Contract research organization
CSR	Clinical study report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EQ-5D-5L	European quality of life questionnaire – 5 dimensions – 5 levels
FAP	Familial amyloidotic polyneuropathy
HP	Heat pain
ICH	International Conference on Harmonisation
ISR	Injection site reaction
KPS	Karnofsky Performance Status
LFT	Liver function test
mBMI	Modified body mass index
MedDRA®	Medical Dictionary for Regulatory Activities
mNIS	Modified neurological impairment score
NCS	Nerve conduction studies
NIS	Neurological impairment score
NYHA	New York Heart Association
OLT	Orthotopic liver transplant
PK	Pharmacokinetic(s)
PND	Polyneuropathy disability
QOL	Quality of life
QOL-DN	(Norfolk) Quality of Life Diabetic Neuropathy
QST	Quantitative sensory testing
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Standard deviation

Abbreviation	Definition
SI	International system of units
SOC	System organ class
TEAE	Treatment-emergent adverse event
TP	Touch pressure
TTR	Transthyretin
ULN	Upper limit of normal
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Refer to Protocol ALN-TTRSC-005 for details on the disease overview, overview of revusiran, and study rationale. A brief overview of the study design is provided below in Section 1.2.

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. 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 substantial differences in the currently planned analyses relative to those planned in the study protocol (see Section 5). Any substantial changes made to the planned analyses after finalization of the SAP will be described in the CSR.

1.1.2.1. Primary Objective

The primary objective of this study is to assess the efficacy of revusiran in patients with Transthyretin (TTR)-mediated Familial Amyloidotic Polyneuropathy (FAP) with disease progression post-orthotopic liver transplant (OLT) by evaluating the reduction in serum TTR level compared to baseline.

1.1.2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- Evaluate the safety and tolerability of revusiran when administered to TTR-mediated FAP patients with disease progression post-OLT;
- Characterize the pharmacokinetics (PK) of revusiran;
- Describe the effect of revusiran on neurologic impairment.

1.1.2.3. Exploratory Objective

The exploratory objectives of this study are to evaluate the effect of revusiran on various clinical activity parameters including quality of life (QOL), disease stage, modified body mass index (mBMI), and cardiac function.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a multicenter, multinational, open-label study designed to evaluate the efficacy, safety, and PK of subcutaneously (SC) administered revusiran in patients with TTR-mediated FAP with disease progression post-OLT. It is anticipated that patients from approximately 5 clinical study centers will participate in this study.

Eligible, consenting patients will receive 5 daily doses of revusiran (Days 0 through 4) and a dose at Day 7, followed by once weekly doses for the duration of the study.

Visits will be held at the clinical study center for the following visits, as stated in the schedule of assessments in the protocol: Screening Period (Day -42 to Day -1), Predose Assessments (Day 0), and Daily Dosing (Days 0 through 4) as well as each month for the first 3 months, and approximately every 3 months through Month 18 (or Early Termination), and at the End of Study (EOS) (approximately 28 days after the last dose). The remaining study visits may be conducted at the clinical study center or in the patient's home.

The primary objective of this study will be evaluated by the collection of serum samples for the measurement of total TTR levels. TTR samples will be collected prior to study drug administration, and then assessed on a monthly basis for 3 months, approximately every 3 months thereafter, and at Early Termination.

Adverse events (AEs) will be collected throughout the treatment period and at the EOS visit.

Patients will participate in this study for approximately 21 months (inclusive of a 42-day screening period and a follow-up visit 28 days after the last dose of study drug) and will be treated with study drug for 18 months.

An independent Data Monitoring Committee (DMC) will be implemented for the study and will operate under a prespecified charter.

1.2.2. Randomization Methodology

This is an open-label, single-arm study; therefore, randomization is not applicable.

1.2.3. Stopping Rules and Unblinding

1.2.3.1. Stopping Rules

No stopping rules are prespecified in the protocol to stop the trial early for either harm or benefit.

1.2.3.2. Unblinding

Unblinding does not apply in this open-label study.

1.2.4. Study Procedures

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

1.2.5. Efficacy, Pharmacokinetic, Safety and Exploratory Endpoints

1.2.5.1. Primary Endpoint

The primary endpoint is the percent reduction from baseline in serum TTR level at 6 months.

1.2.5.2. Secondary Endpoints

The secondary endpoints of the study are the change from baseline over 18 months for the following:

- Serum TTR;
- mNIS+7;
- Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Questionnaire;
- PND Score.

1.2.5.3. Pharmacokinetic Assessments

Blood samples will be obtained for the assessment of plasma levels of revusiran. Exploratory analyses may also be conducted on plasma samples to evaluate metabolites of revusiran.

Pharmacokinetic parameter estimates using the concentration time data will be performed by Alnylam. All tabulations of PK data will be presented in a PK and PK/PD report separate from the CSR.

1.2.5.4. Safety Assessments

The safety of revusiran will be evaluated by:

- AEs, including liver allograft rejection;
- Vital sign measurements;
- Clinical laboratory evaluations;
- 12-lead electrocardiogram (ECG);
- Physical examinations;
- Ophthalmology examinations;
- Concomitant medications, including immunosuppressive agent monitoring.

1.2.5.5. Exploratory Endpoints

The exploratory endpoints of the study are the assessment of change from baseline over 18 months for the following:

- mBMI;
- FAP stage;
- Grip strength;
- New York Heart Association (NYHA) classification;
- Karnofsky Performance Status (KPS);
- Echocardiogram parameters;
- Cardiac biomarkers;
- EuroQoL questionnaire in 5-dimensions;
- Composite Autonomic Symptom Score (COMPASS) 31 questionnaire;
- Columbia Suicide Severity Rating Scale questionnaire;
- Pharmacoeconomics questionnaire;
- Optional exploratory residual liver tissue evaluation.

2. PATIENT POPULATION

2.1. Population (Analysis Set) Definitions

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

- Evaluable Analysis Set: All patients who have received at least a single dose of study drug and have a non-missing serum TTR result at Month 6 (Week 26) visit.
- Safety Analysis Set: All patients who received at least a single dose of study drug.
- PK Analysis Set: All patients who received at least a single dose of study drug and have at least 1 postdose blood sample for PK parameters and who have evaluable PK data.

The primary efficacy endpoint will be analyzed using the Evaluable Analysis Set. All secondary and exploratory efficacy endpoints will be analyzed using the Evaluable Analysis Set and Safety Analysis Set (note: if these 2 analysis sets are identical then secondary and exploratory efficacy endpoints will be analyzed using only the Evaluable Analysis Set). Safety will be analyzed using the Safety Analysis Set. The PK Analysis Set will be used to conduct PK analyses. PK analyses are described in a separate PK analysis plan.

2.2. Protocol Violations

All protocol deviations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Approximately 12 patients will be enrolled in this study. For the estimation of sample size, a mean reduction of 88% in serum TTR has been observed from baseline to Day 35 with a standard deviation (SD) of 6% in healthy volunteers taking revusiran. If this study yields a mean reduction of 80% at 6 months with an SD of 6%, 12 patients would yield a 95% confidence interval (CI) of approximately 77% to 83%.

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days will be calculated relative to the day of the first dose of study medication which is designated as Day 0. The day preceding first dose is Day -1. The last day of study medication is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc.

All outputs will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF 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, descriptive statistics including the number of patients, mean, median, SD, minimum, and maximum values will be presented.

If assessments are collected in replicates (e.g., grip test, mNIS+7), then the average of the replicates will be used in the analyses.

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 March 2015 Version (or later).

3.4. Baseline Definitions

Baseline will be defined as the measurement closest to and prior to the first administration of study drug for all safety assessments and clinical outcomes. For TTR and Vitamin A, baseline will be defined as the average of all pre-dose values (i.e., screening, screening/baseline, and baseline, as well as any values from unscheduled visits that occur prior to dosing on Day 1).

3.5. Methods of Pooling Data

Pooling of data is not applicable to this study.

3.6. Adjustments for Covariates

No statistical analyses that adjust for any covariate(s) are planned.

3.7. Multiple Comparisons/Multiplicity

Not applicable.

3.8. Subpopulations

No analyses of patient subgroups are planned.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Patients who withdraw before month 6 or have a dose reduction before 6 months of study participation may be replaced.

3.10. Missing Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the electronic case report form (eCRF) will be included in data listings that will accompany the CSR. Data collected at multiple time points throughout the study will be presented in chronological order in the data listings according to assessment date/time. Data summaries and analyses will be based on observed data only.

Methods for handling incomplete or missing components of efficacy endpoints are discussed in the endpoint scoring algorithms in Section 6.

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.

Data collected at unscheduled visits will be included in by-patient data listings, 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 computation of 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).

The relative day of all dates will be presented in data listings.

3.12. Interim Analyses

No formal interim analyses are planned for early stopping for futility or efficacy, or for the purposes of sample size reassessment.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition data will be tabulated and include the number enrolled, the number treated with revusiran, and the number in each patient population for analysis. The number of patients discontinuing study drug and reason for discontinuation will be summarized. The number who withdrew prior to completing the study and reason(s) for early withdrawal will be summarized.

A by-patient data listing of study completion information including the reason for premature study withdrawal or treatment discontinuation, if applicable, will be presented.

4.2. Demographics and Baseline Characteristics

Demographics, baseline disease characteristics, and medical history information will be summarized for the Safety Analysis Set and presented overall. No formal statistical comparisons will be performed.

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

Baseline disease characteristics will be summarized by presenting the number and percentage of patients with or without the V30M genotype mutation. Descriptive statistics will be provided for time (years) from diagnosis with transthyretin amyloidosis (ATTR amyloidosis) to study enrollment (using date of informed consent) and time (years) from liver transplant to study enrollment. Baseline mNIS+7 score will be summarized using descriptive statistics. Karnofsky Performance Status, NYHA Classification and FAP stage at baseline will be summarized by presenting the numbers and percentages of patients in each category. The PND scores measured pre-OLT, post-OLT, and at baseline will be summarized with the number and percentage in each category. Medical history conditions will be coded to MedDRA system organ class (SOC) and preferred term. Tabular summaries will be produced for medical history conditions by SOC and preferred term. Immunosuppressant medications collected prior to the first dose of study drug will be summarized by WHO Drug anatomic therapeutic class (ATC) and preferred term.

All demographic and baseline disease characteristics data for each patient will be provided in data listings. By-patient listings for medical history, immunosuppressant medication, historical liver function values (prior to 6 months before screening) and pregnancy test results will be generated.

4.3. Efficacy Analysis

4.3.1. Primary Efficacy Endpoint

The primary efficacy analysis will be performed after all patients have finished 6 months of treatment with study drug. The primary efficacy analysis will be based on the Evaluable Analysis Set.

The primary efficacy endpoint is the percent change from baseline in serum TTR level at 6 months. The mean percent change in serum TTR from baseline to 6 months with the associated 95% CI will be presented. A 2-sided 80% CI will also be generated. A t-test of the null hypothesis of no change in serum TTR from baseline at 6 months will be performed at the 2-sided, 0.05 confidence level.

Sensitivity analyses will be conducted to assess the robustness of the primary analysis. The sensitivity analyses will include a bootstrap 95% CI for the median percent change from baseline to 6 months in serum TTR. The bootstrap CI will be constructed using the percentile method. That is, the lower and upper limits of the bootstrap CI are defined as the 2.5^{th} and 97.5^{th} percentiles of the median percent change from baseline estimated from 1000 bootstrap samples. In addition to the t-test described above, a sensitivity analysis will include the p-value from the Wilcoxon signed rank test.

4.3.2. Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be based on the Evaluable Analysis Set and Safety Analysis Set, except as noted in Section 2.1.

Descriptive statistics for actual values, change from baseline, and percent change from baseline at each scheduled visit will be provided for serum TTR. Eighty percent and 95% CIs will be produced for the mean change from baseline at Month 18. Individual serum TTR values over time will be plotted. Individual values of percent change from baseline in serum TTR will also be plotted. Plots of the mean (± SEM) serum TTR values and percent change in serum TTR from baseline at each scheduled visit will be generated.

Descriptive statistics will be provided for actual values, change from baseline, and percent change from baseline at each scheduled visit for the mNIS+7 composite score, and the Norfolk QOL-DN total score. Both 80% and 95% CIs will be produced for the mean change from baseline at Month 18 for these endpoints.

Components of the mNIS+7 will be summarized separately, including the NIS-Weakness, NIS-Reflexes, Nerve conduction (sum of the 5 NCS), quantitative sensory testing (QST), and postural blood pressure Similar descriptive summaries will be provided for the 5 domain scores of the Norfolk QOL-DN (see Section 6.2).

Shift tables will be created for the PND score to summarize the baseline value versus post-baseline value at each scheduled visit. An additional summary of PND score will present the shift from baseline to worst post-baseline value.

4.3.3. Exploratory Endpoints

Analyses of secondary efficacy endpoints will be based on the Evaluable Analysis Set and Safety Analysis Set, except as noted in Section 2.1.

Descriptive statistics will be provided for actual values, change from baseline and percent change from baseline at each scheduled visit for continuous exploratory endpoints. For categorical values, the numbers and percentages of patients reporting each response will be generated.

For QOL questionnaires, summaries of each of the domains will also be generated.

Shift tables will be created for FAP stage to summarize the baseline value versus post-baseline value at each scheduled visit. An additional summary will present the shift from baseline to worst post-baseline value. Similar summaries will be provided for NYHA classification and KPS. For KPS, the categories will be defined as follows: 100-80 (able to carry out normal activity and to work; no special care needed), 70-50 (unable to work; able to live at home and care for most personal needs; varying amount of assistance needed) and 40-0 (unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly).

4.4. Pharmacokinetic Evaluation

Summaries of PK data will be described in a separate SAP.

4.5. Safety Analyses

Safety analyses will be conducted using the Safety Analysis Set.

4.5.1. Study Drug Exposure

Exposure to study drug will be characterized by presenting descriptive statistics for duration of exposure (in months) and amount of study drug received (per dose and in total).

Descriptive statistics will be presented for the total duration of study drug exposure in months. The number and percentage of patients exposed for less than 3 months, 3 to <6 months, and so forth, will be presented. The number and percentage of patients exposed for at least 3 months, at least 6 months, and so forth, will be presented. Similar summaries will be presented for the number of doses received. The total number of patients requiring a dose reduction to 250 mg will be presented as well. Dosing information for each patient will be presented in a data listing.

4.5.2. Adverse Events

All AEs will be summarized using the MedDRA coding system (Version 18.0 or later) and displayed in tables and data listings using SOC and preferred term.

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 after the first administration of study medication, or any event that was present at baseline but worsened in intensity. Events with a fully or partially missing onset date will be assumed to be treatment-emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first administration of study medication.

All AEs will be summarized by the numbers and percentages of patients reporting a given AE. Therefore, in any tabulation, a patient contributes only once to the count for a given AE (overall, by SOC, by preferred term).

An overall summary of AEs will include the number and percentage of patients with any treatment-emergent adverse event (TEAE), 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 adverse event (SAE), any SAE related to treatment, any AE leading to study treatment discontinuation, any AE leading to study treatment reduction, and any AE leading to death.

Tabulations by SOC and preferred term will be produced for all AEs, for all AEs related to study medication, for all SAEs, and for all AEs leading to study discontinuation. Separate tables will present AE incidence rates by maximum severity and by maximum relationship to study drug. Patients who report multiple occurrences of the same TEAE (preferred term) will be classified according to the most severe or most related occurrence, respectively. In all tables, AEs will be ordered by decreasing frequency of preferred term within SOC. AEs may also be summarized by other groups including, but not limited to, high level term (HLT), high level group term (HLGT) or standardized MedDRA query (SMQ).

Separate summaries will be provided for AEs of clinical interest, which include injection site reactions (ISRs) and hepatic AEs, including LFT abnormalities considered clinically significant by the Investigator.

The incidence of ISRs will be summarized by preferred term. A separate summary will present incidence rates by preferred term and maximum severity. Injection site reactions will be identified by the high level term of "Injection Site Reactions."

The incidence of hepatic events will be summarized by preferred term.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study will be listed in patient data listings. Adverse events of clinical interest will also be listed separately.

By-patient listings will also be provided for the following: all AEs leading to death, all SAEs, AEs leading to study discontinuation, AEs leading to dose reduction, AEs leading to dose interruption, and AEs leading to withdrawal from drug. In addition, by-patient listings for any AEs leading to dose reduction, dose interruption, or withdrawal from study drug will be provided for those AEs mapped to the hepatic SMQ.

4.5.3. Liver Allograft Rejections

The number and percentage of patients with evidence of liver allograft rejection will be presented. Banff grade will also be summarized. In the event that more than one Banff grade is reported, the most severe will be reported in summary tables.

Details of liver allograft rejections, including biopsy findings as applicable and changes noted in immunosuppressant regimen(s) will be included in a by-patient listing. A listing of local liver function tests (LFTs) will be generated for patients with elevated LFTs associated with liver allograft rejection.

4.5.4. 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 assessments, thyroid function tests, and LFTs). Descriptive statistics will be presented for the actual values and change from baseline at each scheduled visit. Percent change from baseline will also be summarized at each scheduled visit.

A shift table of LFT parameters (alanine transaminase [ALT], aspartate transaminase [AST], alkaline phosphatase and bilirubin) at baseline to worst-post baseline (collected at scheduled or unscheduled visits) will be summarized. The summaries for the shift tables will be based upon categories defined by the upper limit of normal range (ULN). In addition, the number and percentage of patients with ALT or AST values greater than 3 or more times the ULN will be presented. There will be separate summaries for mutually exclusive and cumulative categories. In addition, the number and percentage of patients with any ALT or AST elevations 3 or more times the ULN with concurrently elevated bilirubin (>1.5 × ULN, > 2 × ULN) will also be presented. Per-patient plots of the LFT parameters (AST, ALT, alkaline phosphatase, and total bilirubin [TB]) will be presented as value/ULN over time. Boxplots of the observed values/ULN at each scheduled visit will be presented for LFT parameters. Evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to examine post-baseline peak ALT

versus concurrent TB. Plots will also be provided for peak AST versus TB, and for peak (AST or ALT) versus TB.

All laboratory data will be provided in data listings. Laboratory values outside of the normal ranges will be listed separately, with indication as to their clinical significance. All out-of-range and clinically significant laboratory results will be identified in patient data listings.

4.5.5. Vital Signs and Physical Examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate.

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

All physical examination findings will be presented in a by-patient data listing. Abnormal physical examination findings will be presented in an additional, separate listing.

4.5.6. Electrocardiogram

Electrocardiogram results will be summarized descriptively, including the number and percentage of patients with normal, abnormal, and clinically significant abnormal results at baseline and each study visit. Descriptive statistics will be provided for ECG interval data.

The numbers and percentages of patients with QTc interval values (corrected accorded to Fridericia's formula) or changes from baseline meeting the following criteria at any time post-baseline will be presented:

- QTc interval >450 msec.
- QTc interval >480 msec.
- QTc interval >500 msec.
- QTc interval increases from baseline >30 msec.
- QTc interval increases from baseline >60 msec.

Electrocardiogram data for each patient will be provided in a data listing.

4.5.7. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary March 2015 Version (or later). Results will be tabulated by ATC and preferred term.

Concomitant medications will be tabulated overall, where any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of concomitant medications will be included in a by-patient data listing. A separate listing will be provided for immunosuppression therapy while on study.

5. CHANGES TO PLANNED ANALYSES

All substantial changes from procedures outlined in the protocol and procedures outlined in this SAP will be summarized in the study report. Decisions to deviate from planned analyses will be documented at the time they are made.

6. QUESTIONNAIRE/SCORING APPENDICES

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

6.1. Modified Neuropathy Impairment Score (mNIS+7)

[redacted]

Assessment Tool	Total Points	Components (maximum points)
Modified NIS+7	304	• NIS-W: Weakness (192) • NIS-R: Reflexes (20) • Nerve conduction studies ∑5 (10) [redacted] • Quantitative sensory testing [redacted] (80) • Postural blood pressure (BP) (2)

MODIFIED NIS + 7 (mNIS+7) Scoring Method

There are five components within mNIS+7 total score: NIS-W, NIS-R, ∑5 NCS, QST, and postural BP. The total score will be calculated as follows:

[redacted]

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

QOL-DN is a tool for assessing subjects' 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

[redacted]

Part II: Activities of Daily Life

[redacted]

Subscales and Scoring Algorithm

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

- Total QOL [redacted]
- Physical Functioning/Large Fiber [redacted]
- Activities of Daily Living (ADLs) [redacted]
- Symptoms [redacted]
- Small Fiber [redacted]
- Autonomic [redacted]

[redacted]

6.3. Polyneuropathy Disability (PND) Score

Stage	Description
0	No symptoms
I	Sensory disturbances but preserved walking capability
II	Impaired walking capacity, but ability to walk without a stick or crutches
IIIA **IIIB**	Walking with the help of 1 stick or crutch Walking with the help of 2 sticks or crutches
IV	Confined to a wheelchair or bedridden

6.4. Familial Amyloidotic Polyneuropathy (FAP) Stage

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

6.5. New York Heart Association (NYHA) Classification of Heart Failure

Class	Symptomology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind, or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking 1 to 2 blocks on the level and climbing more than 1 flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

6.6. Karnofsky Performance Status (KPS)

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

6.7. 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 five 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.

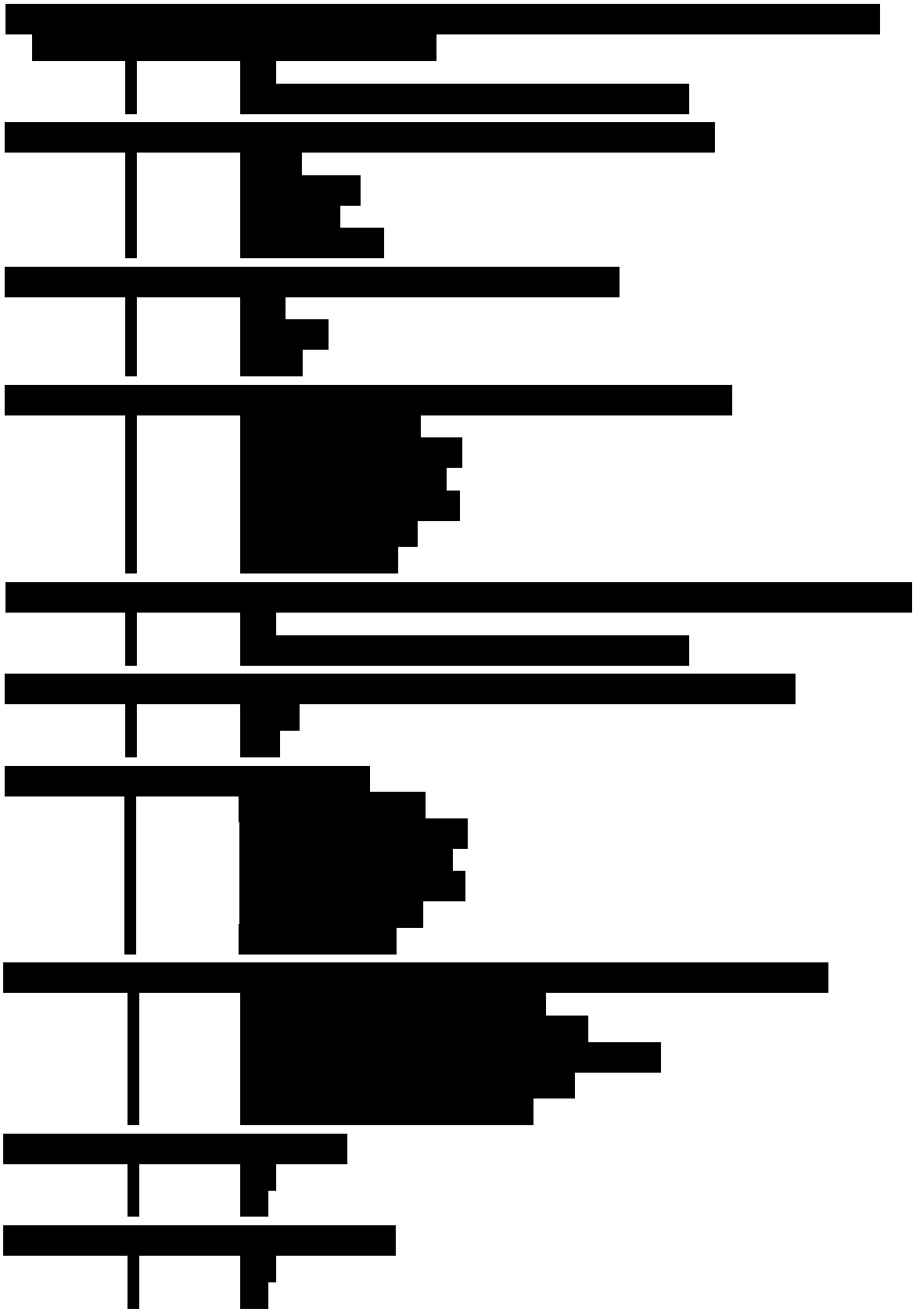
6.8. Composite Autonomic Symptom Score (COMPASS-31)

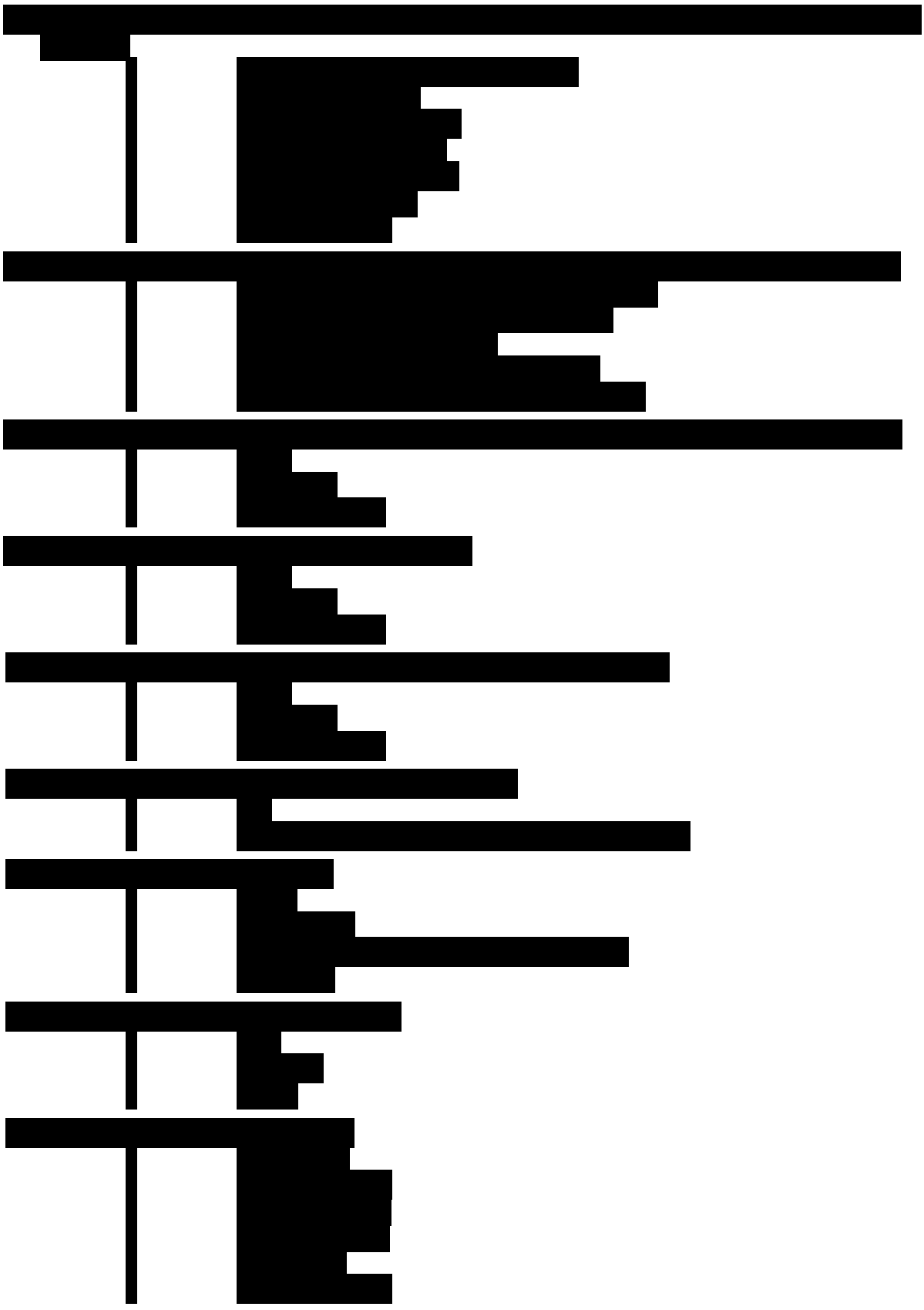
The COMPASS-31 questionnaire comprises 6 domains: Orthostatic intolerance, Vasomotor, Secretomotor, Gastrointestinal, Bladder, and Pupillomotor. Within each domain, individual questions are scored as follows: Simple yes or no questions are scored as 0 points for no and 1 point for yes. Questions about 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.

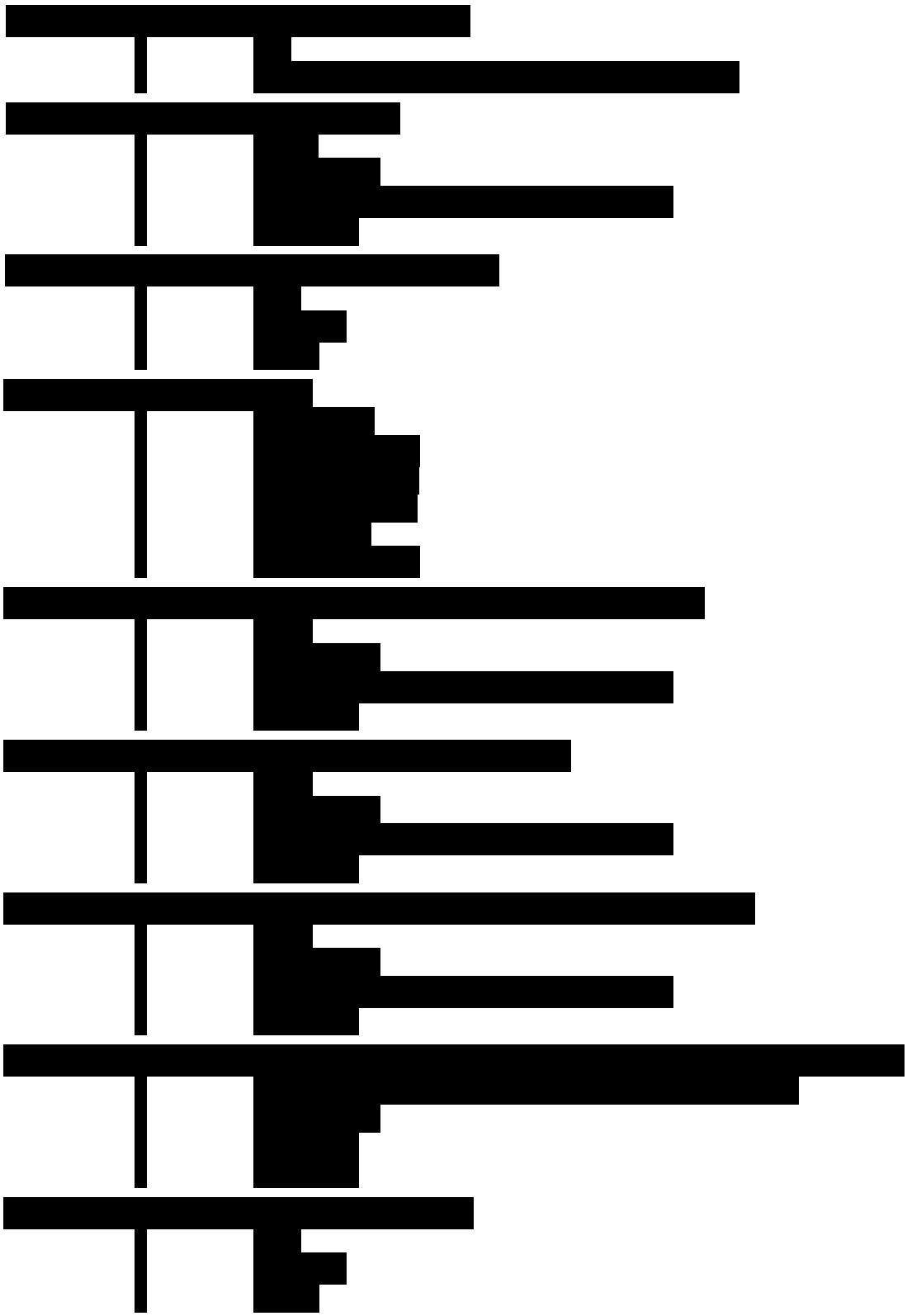
The overall scoring proceeds as follows:

- 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)

[redacted]







7. CLINICAL STUDY REPORT APPENDICES

7.1. Statistical Tables to be Generated

7.2. Figures to be Generated

7.3. Data Listings to be Generated

7.4. Statistical Table Shells

7.5. Figure Shells

7.6. Data Listing Shells