STATISTICAL ANALYSIS PLAN

Compound: TD-9855

Study Number: Study 0145

Study Title: A Phase 2 Study to Assess the Effect and Safety of TD-9855 in Subjects with Neurogenic Orthostatic Hypotension

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CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

TD-9855, Study 0145, Part C

A Phase 2 Study to Assess the Effect and Safety of TD-9855 in Subjects with Neurogenic Orthostatic Hypotension

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ADAM	Analysis data model
AE	adverse event
BLQ	Below level of quantification
BMI	body mass index
BP	blood pressure
CI	confidence interval
CFB	Change from baseline
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
HR	heart rate
LOD	Limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
NC	non-calculable
NQ	non-quantifiable
PK	pharmacokinetic
PP	Per-protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
WHODD	World Health Organization Drug dictionary

1 INTRODUCTION

This document outlines the initial plan for the summarization and analysis of clinical data collected in STUDY 0145 for TD-9855, Part C only.

This is the proof of concept study to determine if the norepinephrine reuptake inhibitor TD-9855 produces an acute pressor effect in patients with primary forms of autonomic failure, and if this is associated with a reduction in symptoms of orthostatic intolerance. Results of this study will guide decisions about the further development.

[redacted]

This document describes the a priori plan for analysis. Once the analysis is in progress, it may become apparent from the data that the planned analysis should be modified. Any substantive modification to the original analysis plan will be identified in the clinical study report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to determine if TD-9855 has sustained pressor response and improves symptoms of orthostatic intolerance in subjects with nOH due to MSA, PAF, or Parkinson's disease.

2.2 Secondary Objectives

The secondary objectives of the study are:

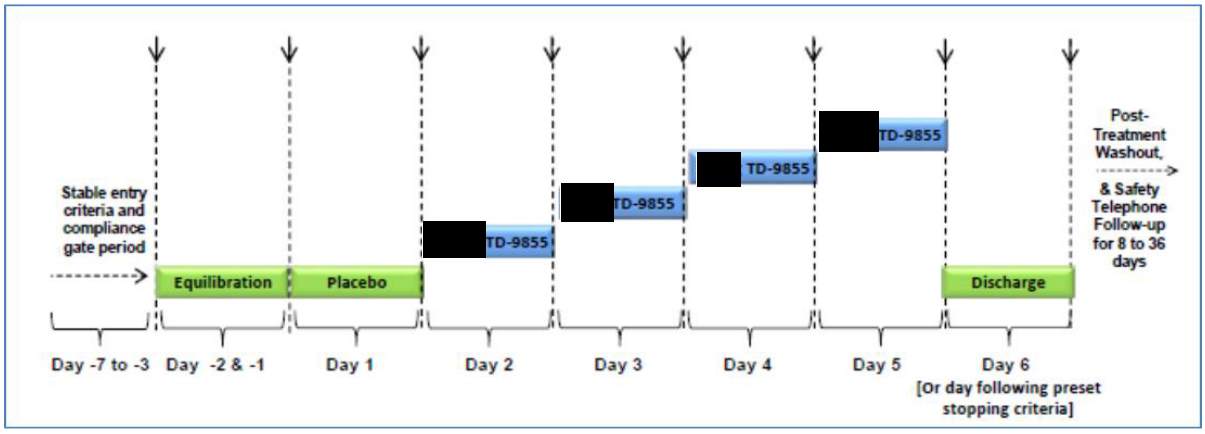
- to evaluate the safety and tolerability of TD-9855 in the control of nOH. and
- to evaluate the PK and PD (NE and DHPG) of TD-9855 after single and multiple doses in subjects with nOH.

3 OVERVIEW OF STUDY DESIGN

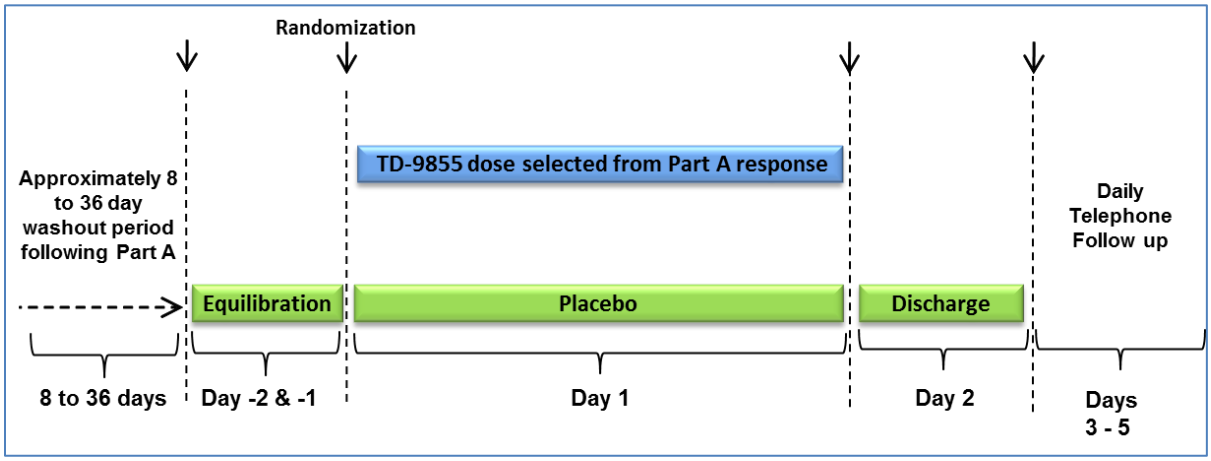
This is a multicenter, randomized, 3 part, single-blind (Part A), double-blind (Part B), and open-label multiple dose extension (Part C) study of TD-9855 versus placebo in subjects

with nOH. However, beginning with Amendment 2 of this protocol, Part B of the study has been discontinued.

This study consists of three Parts, A, B and C. Part A follows a daily, single, escalating dose design starting with placebo on Day 1, followed by a dose of [redacted] TD-9855 on Day 2, and proceeding to escalating higher doses of TD-9855 on a daily basis up to a max dose of [redacted] based on safety, tolerability, and determination of a pressor effect. Starting from protocol Amendment 2, TD-9855 escalation doses changed to [redacted] from Day 2 to Day 5.



Part B follows a randomized, placebo–controlled, parallel design evaluating a dose that was determined to be generally well tolerated and to have a pressor effect for a given subject from Part A.



In Part C, subjects who demonstrate a pressor effect in Part A, who complete Part A and remain otherwise eligible will have the option to participate in Part C and receive open-label TD-9855 by tablet once daily for up to [redacted]

[redacted]

For subjects enrolled under Amendment 2, the dose administered on Day 2 of Part C will be reduced to a dose level equal to [redacted] of the dose level administered on Day 1 of Part C (rounded up to the nearest 1 mg). Subjects will continue receiving the dose level from Day 2 of Part C for the remainder of the study. However in the case where a subject develops the presence or worsening of previously described supine hypertension or other adverse events suggesting intolerability, [redacted].

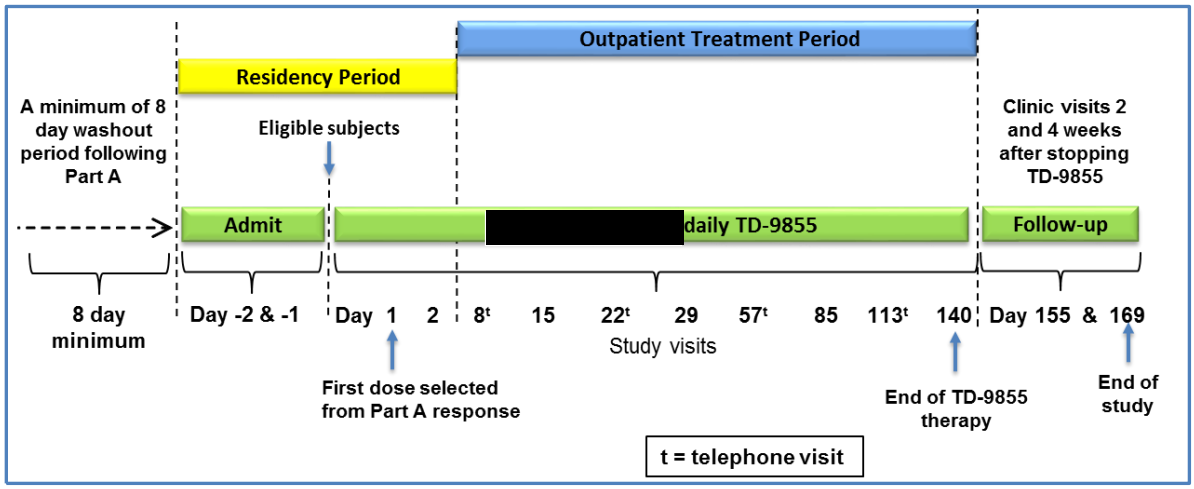
Under Amendment 3, subjects will be discharged from the research clinic on Day 2, and continue at the same dose level as Day 1 of Part C. At the subsequent scheduled visits until Day 29, the Investigator has the option to double the subject's dose level at their discretion, if in their opinion the subject will benefit from, and can tolerate, a higher dose level. After Day 29, dose increases will need to be discussed with the Sponsor. It is recommended that the subject receives at least 7 daily doses of TD-9855 at any single dose level before escalation to a higher dose to allow TD-9855 exposure to reach steady state at the lower dose. [redacted]. The schedule for potential dose increases is shown in the table below.

Part A Maximum Dose	Part C Day 1 dose	Part C Day 8 dose	Part C Day 15 dose	Part C Day 22 dose	Part C Day 29 dose
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Part A Maximum Dose	Part C Day 1 dose	Part C Day 8 dose	Part C Day 15 dose	Part C Day 22 dose	Part C Day 29 dose
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the case where a subject develops the presence or worsening of supine hypertension (as determined by the Investigator with agreement from the Sponsor) or other adverse events suggesting intolerability, [redacted]

Regardless of the protocol amendment, if supine hypertension or other adverse events persist after the dose has been reduced, dosing in that subject should be discontinued and appropriate alternative therapy and care provided to the subject as determined by the principal investigator.



4 SAMPLE SIZE AND POWER

[redacted]

[redacted]

Table 1. Sample size for Part C

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

5 STUDY ENDPOINTS

5.1 Efficacy Endpoints

For Part C, the primary endpoint is the improvement from baseline in the Likert scale "dizziness, lightheadedness, feeling faint, or feeling like you might black out" (OHSA, question 1) at week 4.

The secondary endpoints for Part C include:

- Change from baseline in the composite OHSA, OHDAS, and OHQ score
- Change from baseline in standing SBP
- Change from baseline in seated SBP
- Duration of standing during the orthostatic standing test
- Change from Supine SBP to Seated SBP

5.2 Safety Endpoints

For all Parts of the study, safety and tolerability assessments will include adverse events, laboratory abnormalities, ECGs, and vital sign measurements including supine blood pressure. [redacted].

6 GENERAL ANALYSIS CONSIDERATIONS

6.1 Global Definitions and Conventions

All data from scheduled and unscheduled visits will be presented in the subject listings; however, unless noted otherwise, only data from scheduled visits will be included in the summaries, statistical analysis, and calculation of derived parameters.

6.2 Baseline Definition

For the OHQ (OHSA and OHDAS) scores and Clinician's/Subject's Global Impression, baseline is defined as the pre-lunch measurement on Day -1. For the blood pressure, heart rate, and duration of standing, baseline is defined as the pre-breakfast measurement on Day 1. For laboratory abnormalities and ECGs, baseline is defined as the measurement on Day -1.

6.3 Analysis Windows

All assessments will be summarized using analysis windows. The terminology of unscheduled will be applied to assessments that are outside an analysis window regardless, of the nominal label associated with the assessments in the EDC system.

All data (scheduled and unscheduled visits) will be presented in the subject listings; however, unless noted otherwise, only data from assessments within analysis windows will be included in the summaries, statistical analysis, and calculation of derived parameters.

In part C, the analysis window will be +/-3 days for the scheduled visits from Day 8 through Day 29, ±7 days for scheduled visits between Day 57 through Day 169 as defined below.

Nominal Day	Start (days)	Stop (days)
8	5	11
15	12	18

Nominal Day	Start (days)	Stop (days)
22	19	25
29	26	32
57	50	64
85	78	92
113	106	120
140	133	147
155	148	162
169	163	175

If the scheduled visit is outside of the analysis window, data will not be counted in the summary tables. In each part, the summary tables by the scheduled visit will only use data recorded for the scheduled visit. Data collected at the unscheduled visit will not be counted in the summary table, however will be included in the subject listings.

General Selection Process for Multiple Records in an Analysis Window

In general, if multiple, valid, non-missing observations exist at a visit or collection time point then records will be chosen based on the following:

- The record closest to the nominal time point in question, or,
- The later record if the two visits are equidistant from the time point, or,
- The average (arithmetic mean) if there is more than one record at the time point (generally applies to assessments done in triplicate).

6.4 Missing Data

In general, missing data will not be imputed. Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

Missing data for the following specific endpoints will be handled as follows:

Primary Efficacy Endpoint

Missing data in the analysis of the primary endpoint is assumed as missing at random (MAR) and will not be imputed in the primary analysis.

Adverse Events (AE)

For graded AE summaries, subjects with an AE and no grade on the CRF will be graded as severe. AEs without assigned relationship to study drug will be counted as AEs related to study drug in the AE summaries.

Missing dates/time for AEs and Concomitant Medications

Missing dates will be handled as follows:

- Complete missing start date will be imputed as the same as first dose date;
- Partial missing start date imputation:
  - Missing start day with same month as first dose: maximum day (1, first dose day);
  - Missing start day with different month as first dose: 1
  - Missing start month with same year as first dose: maximum (January, first dose month);
  - Missing start month with different year as first dose: January
- Complete missing stop date will be considered as ongoing and not imputed;
- Partial missing stop date imputation:
  - Missing stop day: last day of month;
  - Missing stop month with same year as last dose: minimum (December, last dose month);
  - Missing stop month with different year as last dose: December

Missing times will be handled as follows:

- If a start or stop time is missing, the start time is imputed as 1 minute after a.m. midnight (12:01) and stop time is imputed to be 1 min before p.m. midnight (23:59).

Laboratory Data

For non-efficacy laboratory data, a missing baseline value will be replaced with the last available assessment before the first dose, generally the screening assessment. A retest value will be used if the first test is invalidated, e.g., specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of "< x" (x is considered as the LOD). More specifically, x−1 is used for data summarization if the data are reported in the form of "< x"; and x.e where e = d−1, will be used for analysis if the data are reported in the form of "< x.d";
- The LOD will be used for calculation of descriptive statistics if the data is reported in the form of "≤x" or "≥x.

6.5 AEs

Recorded AEs will be mapped according to the MedDRA thesaurus by the data management CRO for this study, with Theravance Biopharma review and approval of the mappings. [redacted] will use [redacted]

6.6 Medications

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) by the data management CRO for this study with Theravance Biopharma review and approval of the mappings. The CRO will use the [redacted].

6.7 Medical History

Medical history will be mapped according to [redacted] and will be provided in listings.

6.8 General Considerations for Summaries

Analyses and tabulations will generally be prepared using SAS®, version 9.3 or later.

Ordering of Treatment Headers in Summary Tables

For the efficacy endpoints, including OHSA question 1, composite OHSA, OHDAS, and OHQ score, duration of standing, and SBP, treatment headers will be presented as subject's dose receive on the day of visit in the following order:

- TD-9855 [redacted] / TD-9855 [redacted] / TD-9855 [redacted] / TD-9855 [redacted] / TD-9855 Total

For all other endpoints and general analysis, only TD-9855 on the header of the treatment group.

Rounding

In general, the convention for rounding percentages is as follows:

- Values greater than or equal to x.x5 are rounded up,
- Values between 0 and less than x.x5 are rounded down,
- Values between –x.x5 and 0 are rounded up,
- Values less than or equal to –x.x5 are rounded down.

Significant Digits

Raw measurements will be reported the same as the data captured electronically or on the CRFs. Exceptions will be made for values reported with greater than 4 significant digits (round to 4 significant digits using a similar criterion as for percentages with the 5 in the last digit)).

- Raw measurements, Minimum, and Maximum will be reported to the same precision as the raw data captured.
- Mean, Median, Q1, Q3, 95% CI will be reported to the same number of decimal places +1 as the raw data captured.
- Standard deviation and standard error will be reported to the same number of decimal places +2 as the raw data captured.
- The number of decimal places in reporting p-value should be as follows. If more precision for the p-value is desired, it should be specified in the study TFL mock shell document.
    - Value is less than 0.001 -> <0.001
    - Value 0.001 to less than 0.10 -> round to 3 decimal places
    - Value 0.10 and greater -> round to 2 decimal places

7 ANALYSIS SETS

7.1 Intent-to-Treat

For Part C, the ITT analysis set will include all subjects who have enrolled for Part C and received at least one dose of study drug (TD-9855).

The ITT analysis set is the primary analysis set for general and efficacy analyses in each part of the study.

7.2 Safety

The Safety analysis set is the same as the ITT analysis set.

7.3 Examination of Subgroups

The following tables will be summarized by the following pre-defined subgroups in Part C:

1. MSA vs. Non-MSA
2. Symptomatic vs. Non-Symptomatic: Symptomatic and Non- Symptomatic are defined as subject with baseline (pre-lunch measurement on Day -1) OHSA question #1 scale of > 4 and ≤ 4, respectively.
3. Orthostatic hypotension vs. Non-orthostatic hypotension at baseline (pre-breakfast measurement on Day 1): Orthostatic hypotension subjects are those whose 'Change from Supine SBP to Seated SBP' ≤ - 20 mm Hg or 'Change from Supine DBP to Seated DBP' ≤ - 10 mm Hg at baseline.
4. Average daily dose of ≤ 5 mg vs. > 5 mg up to Day 29
5. Duration of Standing at Baseline - ≤ 1 min vs. > 1 min

Combination of these subgroups may also be explored, such as MSA, Symptomatic, and Average daily dose ≤ [redacted] vs. MSA, Symptomatic, and Average daily dose > [redacted]. Analysis by other subgroups may be performed if adequate number of subjects (at least 5) are enrolled in the categories.

7.4 Inclusion and Exclusion Deviations

Deviations to inclusion and exclusion criteria will be identified prior to database lock and will be summarized in a listing with the deviation and the protocol version associated with the deviation.

7.5 Major Analysis Protocol Deviations

Major analysis protocol deviations that could potentially affect the conclusions of the study will be identified prior to database lock. Major analysis protocol deviations may include, but are not limited to:

- Subjects who received an excluded concomitant treatment or medication,
- Subjects who are less than 80% compliant with study medication,
- Subjects who are out of window for the primary efficacy assessment.

Subjects with major analysis protocol deviations will be identified before the database lock and provided in a listing.

In addition, a listing of all major deviations will be provided whether they impact analysis.

8 DEFINITION OF ANALYSIS VARIABLES

8.1 Demographic and Baseline Characteristics

Age

Age will be calculated as of the date of informed consent form (ICF) and truncated to its integer value. The following formula is used:

$$age = floor\left(\frac{ICF\ Signing - Date\ of\ Birth}{365.25}\right)$$

BMI

BMI will be calculated and converted to metric units by the following:

$$BMI\left(kg/m^2\right) = \frac{weight\left(kg\right)}{height\left(m\right)^2}.$$

8.2 Efficacy Variables

Primary Efficacy Endpoint

For Part C, the primary endpoint is the improvement from baseline in the Likert scale "dizziness, lightheadedness, feeling faint, or feeling like you might black out" (OHSA, question 1) at week 4. A responder in Part C is defined as a subject who demonstrates at least a 2 unit decrease (improvement) from baseline in the OHSA question 1 at week 4. The raw data is in ordinal scale and will be treated as continuous variable to get the descriptive statistics.

Secondary Efficacy Endpoint

The secondary endpoints for Part C include:

- Change from baseline in the composite OHSA, OHDAS, and OHQ score
- Change from baseline in standing SBP
- Change from baseline in seated SBP
- Duration of standing during the orthostatic standing test
- Change from Supine SBP to Seated SBP

For the Supine and Seated blood pressure, the summary table will be based on the average value of the 5 minutes and 10 minutes measurements. The composite OHSA score is calculated by the non-missing average score of the 6 OHSA items. Similarly for the composite OHDAS score is the non-missing average of the 4 items. The composite OHQ score is the average of the OHSA and OHDAS composite scores.

For Change from time-matched placebo in seated SBP, calculate the area under the effect curve from 0 to 12 hours (AUC0_12) using the following trapezoidal rule. Calculation of AUC0_12 will use observed data points (actual time). If there is missing data for seated SBP, AUC will not be calculated. Here is the formula for AUC:

$$AUC_{0-t} = \frac{\sum_{i=1}^{I-1} (y_i + y_{i+1})(t_{i+1} - t_i)}{2}$$

where

y_i = the value of the parameter at the i-th time point,

t_i = the i-th time point, and

I = the number of time points used in the AUC calculation.

A hypothetical example is given below to illustrate the calculation.

			AUC Calculation			
Nominal Time Point (H)	Actual Time Point (H)	Parameter Value (Y_i)	T_diff= T_(i+1) – T_i	Y_sum= Y_(i+1) + Y_i	T_diff x Y_sum	AUC_{0_12}
0	0	1.5				
4	2.01	2.2	2.01	3.7	7.437	
7	3.91	3.4	1.9	5.6	10.64	
9	8.05	2.8	4.14	6.2	25.668	
12	23.95	2.1	11.87	4.8	56.976	50.361

8.3 Safety Variables

For all Parts of the study, safety and tolerability assessments will include adverse events, laboratory abnormalities, ECGs, and vital sign measurements.

9 ANALYSES

Table, figures and listing titles are denoted in underlined text.

9.1 General Analyses

Generally, summary statistics including N, mean, median, standard deviation, Q1, Q3, Min, and max will be generated for continuous variables. For the ordinal data such as OHSA scales, it will be treated as continuous variable for summary statistics. For categorical variables, count and % will be summarized.

Figures including serial plot, box plot, bar chart, and heatmap will be employed to depict the data. For the longitudinal data, such as vital signs, blood pressures in seated, supine, and standing positions, OHSA scales, lab data, etc., serial pot or box plot will be generated to describe the changes. Bar chart will be used to depict the changes in scales of categorical data, e.g. OHSA scales. Heatmap will be used to depict the changes in blood pressure by

individual patient, with x-dimension as visit (study days), y-dimension as time points, and the colored heatmap to represent the categories of changes from baseline.

9.1.1 Subject Disposition

Subject disposition information will be summarized for all subjects by study Part (A and C) and by dose. Summaries will include:

- Number of subjects enrolled in Part A
- Number of subjects enrolled in Part C
- Number and percentage of subjects treated with study drug (Part C)
- Number and percentage of subjects completing the study (Part C)
- Number and percentage of subjects by reason discontinuing the study drug (Part C)
- Number and percentage of subjects by reason discontinuing the study (Part C)

For Part C, the subject disposition table will include the number (%) of subjects who were rolled over from Part A into the open-label extension study.

A listing of subject disposition will include the ITT analysis set status, the date of informed consent signed, the date of first dose and last dose of study drug, primary reason for subject discontinuation of study medication, the date of last visit, study completion status, and primary reason for study termination.

9.1.2 Demographics and Baseline Characteristics

Demographics including age, sex, race, ethnicity, height, weight, and BMI will be summarized for the ITT analysis set.

The following baseline characteristics data will be summarized descriptively:

- Underlying diagnosis of nOH (MSA, PAF, Parkinson's disease)
- Symptomatic (yes or no)
- OHSA question 1 at baseline

In addition, the following baseline characteristics will also be summarized descriptively for Part C:

- OHSA composite score at baseline
- OHDAS composite score at baseline
- OHQ composite score at baseline
- Orthostatic hypotension (yes or no) at baseline
- Duration of Standing at baseline
- SBP (Seated, Supine, Standing) at baseline

A listing will be provided.

9.2 Efficacy Analyses

For all efficacy data analyses, the ITT group will be used unless otherwise specified.

9.2.1 Primary Efficacy Evaluation

For Part C, the primary endpoint is the improvement from baseline in the Likert scale "dizziness, lightheadedness, feeling faint, or feeling like you might black out" (OHSA, question 1) at week 4. The scales will be treated as continuous variable, and a summary table including descriptive statistics will be generated. A responder in Part C is defined as a subject who demonstrates at least a 2 unit decrease (improvement) from baseline in the OHSA question 1 at week 4. The proportion of subject who demonstrate ≥ 1 unit, ≥ 2 units, ≥ 3 units, ≥ 4 units improvement, no change, and worsen (by 1 and >1 unit) at each visit will be calculated with exact 90% confidence intervals and summarized by visit and dose level per each visit. In addition, OHSA question 1 improvement will be summarized by baseline value categories (baseline OHSA #1 ≥ 2).

The example SAS code for summary of proportion of responders is following:

```
proc freq data = xxx;
    by timepoint cat;
    tables yes_no / binomial(exact) alpha=.1 cl;
    ods output BinomialCLs = result_1;
run;
```

Where ‘timepoint’ is the time points for the measurements, ‘cat’ is the category of improvement (or no change, worsen) by number of unit, and ‘yes_no’ is the indicator for subjects in each category.

9.2.2 Secondary Efficacy Evaluation

For Part C, actual score and its change from baseline in composite OHSA, OHDAS, and OHQ will be generated descriptively by study visit. For Standing and Seated SBP, as well as duration of standing, the actual value (in minutes) and its change from baseline will also be summarized descriptively by time point (pre-breakfast, pre-lunch) and study visit. In addition, categorical shift (categories from 0 to 10 by 1 minute, and ≥ 10 minutes) of change from baseline for standing duration will also be summarized. For Standing SBP, number and percent of subjects with SBP > 80 mmHg by time point will also be analyzed.

For primary and secondary endpoints, graphic display of the data will be generated. Mean+/-SD line plot and boxplot will be used to depict the change over time point for vital signs and scores in OHSA, OHDAS and composite OHQ. Heatmap will be used to plot the individual change over time points on the data for vital signs (Seated, Standing, and Supine SBP and DBP). Bar chart will be used to depict the changes in scales of categorical data, e.g. OHSA scales, and in change subgroup for Seated SBP and Duration of Standing.

9.2.3 Other Efficacy Evaluation

The following efficacy endpoints will also be explored:

- Physician Global Assessment - descriptive summary on actual score and change from baseline over time, and number (%) of subjects by level of score and study visit
- Subject Global Assessment - descriptive summary on actual score and change from baseline over time, and number (%) of subjects by level of score and study visit
- Subject Satisfaction Survey - number (%) of subjects by level of score and study visit
- Supine SBP - descriptive summary on actual value and change from baseline by study visit

- Change from Seated SBP to Standing SBP, Change from Supine SBP to Standing SBP, Change from Supine to Seated SBP - descriptive summary on actual value and change from baseline by time point and visit
- 24 Hour Blood Pressure monitoring – including number (%) of subjects with outliers in 24 Hours SBP, subject listing of 24 Hour BP monitoring

Additional graphic display of the following efficacy endpoints will be generated:

- Individual plots in subject's actual scales over time in OHSA question 1, composite scores in OHSA, OHDAS, and OHQ. Plots for both all subjects enrolled in Part C and only the Part C completers will be generated.
- Individual plots in subject's actual values by time point and visit in Seated SBP, Supine SBP, Standing SBP, Change from Seated SBP to Standing SBP, Change from Supine SBP to Standing SBP, Change from Supine to Seated SBP, and Duration of Standing. For Change from Seated SBP to Standing SBP and Duration of Standing, plots for both all subjects enrolled in Part C and only the Part C completers will be generated.
- Mean+/-SD (from descriptive summary) line plot and boxplot for actual values over time in Seated SBP, Supine SBP, and Standing SBP.
- Mean+/-SD (from descriptive summary) line plot and boxplot for change from baseline over time in Change from Supine SBP to Seated SBP.
- Mean+/-SD (from descriptive summary) line plot for the percent change from baseline over time - Duration of Standing.
- Bar chart for the percent change from baseline in Duration of Standing.
- Individual plots in 24 Hours Vital Signs Monitor in SBP, DBP, HR, and Mean Arterial Pressure

9.2.4 Multiplicity Adjustment

Multiplicity adjustment is not applicable since only descriptive summaries are provided.

9.3 Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), and quantitative parameters from 12-lead ECGs. Vital signs will be summarized in terms of observed values and changes from baseline.

9.3.1 Exposure

A subject's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual subjects will be listed. Extent of exposure will be summarized by number of days on TD-9855 and cumulative doses of TD-9855 in Part C.

In Part C, the following will be summarized as an analysis of exposure:

- Number and percent of subjects with at least one dose of TD-9855 by dose level ([redacted]) (overall and by visits)
- Individual subject's change of dose level over time (graph)
- Descriptive summary of dose by visits
- Study drug compliance using the categories (100%; 95%; 90%; 80%; < 80%)

Study drug compliance (as percentage) can be derived as (Number of doses taken / Total expected dose) x 100, where,

- Number of doses taken = total number of doses released (number of pills x dose level) - total number of doses returned (number of pills x dose level)
- Total expected dose = dose level x number of days

Study drug administration (date/time and study day) will be provided in a data listing.

9.3.2 Adverse Events

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will be presented by system organ class (SOC),

preferred term (PT) and severity, and the frequency and percentage of subjects reporting each observed event.

A TEAE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject. AEs will also be summarized by relationship to treatment (study drug) and severity.

Data listings will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for a SAE.

9.3.3 Prior and Concomitant Medications

Medications will be summarized both prior and during the treatment period. Listing will be provided for prior and concomitant medications overall.

9.3.4 Vital Signs

Vital signs will be summarized in terms of observed values (by time point), changes from baseline (by time point). When multiple values exist for the same nominal time point (e.g., duplicate reading), the average of the readings taken for vital signs will be used in the data analysis. All recorded values for vital signs data will be presented in a by-subject listing. Vital signs outliers will be flagged in the listing (Table 2).

Table 2. Vital Signs Outlier Thresholds

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
<40 >110	<85 >160	<45 >100

A sustained elevation in supine vital signs (the mean value of BP or HR) is defined as the elevation above a given threshold at three or more consecutive on-treatment measurements. For example, elevation at pre-breakfast, pre-lunch measurement on one visit as well as pre-breakfast measurement at the subsequent visit will be considered as

sustained elevation; on the other hand, elevation at pre-breakfast but not at pre-lunch for 3 consecutive visits will not constitute as “sustained” elevation.

Categorical elevated vital signs are defined in Table 3 and Table 4. Number of subjects with elevated vital signs will be summarized by visits in Part C.

Table 3. Threshold for Elevated Supine Vital Sign

Measurements	Threshold	
Increase from Baseline in SBP (mmHg)	≥ 20	≥ 30
Increase from Baseline in DBP (mmHg)	≥ 10	≥ 20
Increase from Baseline in HR (bpm)	≥ 10	≥ 20
Post-baseline value SBP (mmHg)	≥ 140	≥ 160
Post-baseline value DBP (mmHg)	≥ 90	≥ 100
Post-baseline value HR (bpm)	≥ 100	≥ 120

Table 4. Combined Criteria for Elevated Supine Vital Sign

Combined Criteria
SBP ≥ 140 and Increase from Baseline ≥ 20
DBP ≥ 90 and Increase from Baseline ≥ 10
HR ≥ 100 and Increase from Baseline ≥ 20
SBP ≥ 160 and Increase from Baseline ≥ 20
DBP ≥ 100 and Increase from Baseline ≥ 10
HR ≥ 120 and Increase from Baseline ≥ 20

In addition, the following will also be summarized.

- a decrease in systolic blood pressure (a mean value of SBP) from supine to standing of ≥ 20 (and 30) mmHg and/or
- a decrease in diastolic blood pressure (a mean value of DBP) from supine to standing of ≥ 10 mmHg
- an increase in heart rate (a mean value of HR) from supine to standing of ≥ 30 bpm and/or
- an observed HR ≥ 120 bpm upon standing

9.3.5 ECG

The QTcF, PR interval, QT interval, QRS duration, and HR from standard digital ECGs will be summarized by study visit in terms of observed values, changes from baseline, and counts and percentages within appropriately defined categories Table 5.

Table 5. Vital Sign and ECG Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change From Baseline (%)	QRS Interval (msec)	QTcF (msec)	QTcF change from Baseline (msec)
>120	≥20	≥ 200	≥ 15	≥ 120	Males:	
>130	≥30	≥ 220	≥ 25			>30, ≤ 60
		Optional:			≥ 430	> 60
		≥ *240*			≥ 450	
		≥ *260*			≥ 470	
		≥ *280*			≥ 480	
		≥ *300*			≥ 500	
					Females:	
					≥ 450	
					≥ 470	
					≥ 480	
					≥ 500	

Treatment emergent ECG abnormalities are defined as those not present at baseline, or those that worsened after treatment, e.g., borderline at baseline, but were prolonged after treatment.

When multiple values exist for the same nominal time point (eg, triplicate reading), the average of the readings taken for ECG parameters will be used in the data analysis, including the outlier analysis stated above in table 4.

All recorded values for the ECG parameters will be presented in a by-subject listing. A listing of subjects with outliers will also be provided.

9.3.6 Clinical Laboratory Results

The study used a mixture of local and central labs, lab units, normal ranges will be converted using the Standard International lab unit if possible. Lab data will be counted as Low, Normal, and High for each visit by applying the local lab normal ranges. Lab shift tables from baseline to discharge/follow-up will be summarized.

Clinical laboratory test results will be listed by subject. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings. Abnormalities in clinical laboratory test results will be listed in a separate listing.

Cumulative urine volume over the 24-hour period for each dosing day will be summarized by Study Day and dose.

9.4 Interim Analyses

This interim analysis will be performed after all enrolled subjects have completed 4 weeks of study in Part C. The interim will include the analyses for primary, secondary, additional efficacy endpoints, and safety endpoints. The final analysis (includes all visits) will be performed after all subjects have completed Part C.

Appendix 1: Reporting Structures for Data Summary

Reporting Structures

C: Continuous endpoints will be presented with an 8-point summary using the following reporting structure, unless otherwise noted,

N	x
Mean (SD)	x.xx (x.xx)
Median	x
Q1, Q3	xx.x, xx.x
Minimum, Maximum	xx.x, xx.x

F: Frequency endpoints will be presented by a 3-point summary using the following reporting structure, unless otherwise noted,

n	X
Count (%)	x (xx.x)

MF Categorical variables (multiple frequency) will be presented by a 3-point summary using the following reporting structure, unless otherwise noted, where the sum of the category n's is the total n

n	X
Category 1 count (%)	x (x.x)
Category 2 count (%)	x (x.x)

NLSM: Normal distribution (continuous) endpoint least-square mean (LS mean) summaries will be presented using the following structure, unless otherwise noted:

Evaluable n	xx
LS Mean (SE)	xxx.x (xx.xx)
LS Mean Difference (SE)	xxx.x (xx.xx)
95% CI for LS Mean Difference	(xxx.x, xxx.x)
P-value vs. {Placebo}	0.xxx

BLSM: Binomial distribution (binary/proportion) endpoint generalized least-square mean (LS mean) summaries will be presented using the following structure, unless otherwise noted:

Count / Evaluable n	xx / xx
LS Proportion (SE)	0.xx (xx.x)
Odds Ratio (TD-XXXX / {Placebo}	xx.x
95% CI for Odds Ratio	(xx.x, xx.x)
P-value vs. {Placebo}	0.xxx

PLSM: Poisson distribution (count) endpoint generalized least-square mean (LS mean) summaries will be presented using the following structure, unless otherwise noted:

Evaluable n	xx
LS Mean Count (SE)	xxx.x (xx.xx)

```
LS Mean Difference (SE)          xxx.x (xx.xx)
95% CI for LS Mean Difference    (xxx.x, xxx.x)

P-value vs. {Placebo}            0.xxx
```

NBLSM: Negative binomial distribution (rate/ratio) endpoint generalized least-square mean (LS mean) summaries will be presented using the following structure, unless otherwise noted:

```
Evaluable n                      xx
LS Mean Annual Rate              x.xx
Ratio (TD-XXXX / {placebo})      x.xx
95% CI for Ratio                 (x.xx, x.xx)

Percent Reduction vs. {Placebo}  0.xx
95% CI for Percent Reduction     (0.xx, 0.xx)

P-value vs. {Placebo}            0.xxx
```

KM: Time to event summaries will be summarized with the following reporting structure:

```
Time to First Event
Median (95% CI)                 xx.x (xx.x, xx.x)
Q1, Q3                          xx.x, xx.x
Minimum, Maximum                xx.x, xx.x
Total Number Censored           x

P-Value vs. Placebo             0.xxxx
```

For the primary endpoint and secondary endpoints under multiplicity control, an additional p-value line will be included in the reporting summary:

```
Adjusted P-value vs. Placebo     0.xxx
```

Appendix 2: List of TFLs (Part C only)

Table Number	Table Name
14.1	**Subject Disposition, Demographic and Baseline Characteristics**
14.1.1	Subject disposition
14.1.2	Demographics and Baseline Characteristics
14.1.2.2	Baseline Characteristics (additional)
14.1.3	Medical History
14.1.4	Summary of Exposure
14.1.4.1	Prior medications by ATC class and preferred term
14.1.4.2	Concomitant medications by ATC class and preferred term
14.2	**Efficacy**
14.2.1	Summary of Change in the Likert Scale Post Study Drug Administration by Visit
14.2.1.1	Summary of Change in the Likert Scale Post Study Drug Administration by Visit and Dose
14.2.1.2	Summary of Change in the Likert Scale Post Study Drug Administration by Subgroups (over time and at Day 29 only)
14.2.2	Summary of Change in Composite OHSA Score Post Study Drug Administration by Visit
14.2.2.1	Summary of Change in Composite OHSA Score Post Study Drug Administration by Visit and Dose
14.2.2.2	Summary of Change in Composite OHSA Score Post Study Drug Administration by Subgroups
14.2.3.1	Summary of Change in Physician Global Assessment Post Study Drug Administration
14.2.3.2	Summary of Change in Subject Global Assessment Post Study Drug Administration

14.2.3.3	Summary of Physician Global Assessment Post Study Drug Administration
14.2.3.4	Summary of Subject Global Assessment Post Study Drug Administration
14.2.4	Summary of Change in OH Daily Activity Scale Post Study Drug Administration
14.2.5	Summary of Change in Composite OHDAS Score Post Study Drug Administration by Visit
14.2.5.1	Summary of Change in Composite OHDAS Score Post Study Drug Administration by Visit and Dose
14.2.5.2	Summary of Change in Composite OHDAS Score Post Study Drug Administration by Subgroups
14.2.14	Summary of Change in Composite OHQ Score Post Study Drug Administration by Visit
14.2.14.1	Summary of Change in Composite OHQ Score Post Study Drug Administration by Visit and Dose
14.2.14.2	Summary of Change in Composite OHQ Score Post Study Drug Administration by Subgroups
14.2.6	Summary of Subject Satisfaction Survey Post Study Drug Administration
14.2.13	Summary of proportion of responders on OHSA #1 by Visit
14.2.13.1	Summary of proportion of responders on OHSA #1 by Visit and Dose
14.2.13.2	Summary of proportion of responders on OHSA #1 by Visit (and at Day 29) and Dose and Subgroups
14.2.7	Summary of Change in Standing Duration Post Study Drug Administration by Visit
14.2.7.1	Summary of Change in Standing Duration Post Study Drug Administration by Visit and Dose
14.2.7.2	Summary of Change in Standing Duration Post Study Drug Administration by Subgroups

14.2.7.3	Summary of Actual Value in Standing Duration Post Study Drug Administration
14.2.7.4	Shift from Baseline to Day 29 on Actual Value - Standing Duration
14.2.8.1	Summary of Change in Seated SBP Post Study Drug Administration by Visit
14.2.8.1.1	Summary of Change in Seated SBP Post Study Drug Administration by Visit and Dose
14.2.8.1.2	Summary of Change in Seated SBP Post Study Drug Administration by Subgroups
14.2.8.2	Summary of Change in Seated DBP Post Study Drug Administration
14.2.9.1	Summary of Change in Supine SBP Post Study Drug Administration by Visit
14.2.9.1.1	Summary of Change in Supine SBP Post Study Drug Administration by Visit and Dose
14.2.9.1.2	Summary of Change in Supine SBP Post Study Drug Administration by Subgroups
14.2.9.2	Summary of Change in Supine DBP Post Study Drug Administration
14.2.10.1 – 14.2.10.4	Summary of Change in 1 min Standing SBP Post Study Drug Administration (and 3 min, 5 min, 10 min) by Visit
14.2.10.1.1 – 14.2.10.4.1	Summary of Change in 1 min Standing SBP Post Study Drug Administration (and 3 min, 5 min, 10 min) by Visit and Dose
14.2.10.1.2 – 14.2.10.4.2	Summary of Change in 1 min Standing SBP Post Study Drug Administration by Subgroups (and 3 min, 5 min, 10 min)
14.2.11.1 – 14.2.11.4	Summary of Change from Seated SBP to 1 min Standing SBP Post Study Drug Administration (and 3 min, 5 min, 10 min)
14.2.12.1 – 14.2.12.4	Summary of Change from Supine SBP to 1 min Standing SBP Post Study Drug Administration (and 3 min, 5 min, 10 min)
14.2.15.1	Summary of Change from Supine SBP to Seated SBP Post Study Drug Administration by Visit
14.2.15.1.1	Summary of Change from Supine SBP to Seated SBP Post Study Drug Administration by Visit and Dose

Figure 15.2.1.1	Individual Change from Baseline in Vital Signs - Seated SBP over Time
Figure 15.2.1.2	Mean+/-SD Change from Baseline in Vital Signs - Seated SBP over Time
Figure 15.2.1.2.1	Mean+/-SD Change from Baseline in Vital Signs - Seated SBP over Time by Subgroups
Figure 15.2.1.3	Individual Actual Value in Vital Signs - Seated SBP over Time
Figure 15.2.1.4	Mean +/ SD Actual Value in Vital Signs - Seated SBP over Time
Figure 15.2.2.1	Individual Change from Baseline in Vital Signs - Seated DBP over Time
Figure 15.2.2.2	Mean+/-SD Change from Baseline in Vital Signs - Seated DBP over Time
Figure 15.2.3.1.1	Individual Change from Baseline in Vital Signs - 1 min Standing SBP over Time
Figure 15.2.3.1.2	Mean+/-SD Change from Baseline in Vital Signs - 1 min Standing SBP over Time
Figure 15.2.3.1.2.1	Mean+/-SD Change from Baseline in Vital Signs - 1 min Standing SBP over Time by Subgroups
Figure 15.2.3.1.3	Individual Actual Value in Vital Signs - 1 min Standing SBP over Time
Figure 15.2.3.1.4	Mean +/ SD Actual Value in Vital Signs - 1 min Standing SBP over Time
Figure 15.2.3.2.1	Individual Change from Baseline in Vital Signs - 3 min Standing SBP over Time
Figure 15.2.3.2.2	Mean+/-SD Change from Baseline in Vital Signs - 3 min Standing SBP over Time

Figure 15.2.3.2.2.1	Mean+/-SD Change from Baseline in Vital Signs - 3 min Standing SBP over Time by Subgroups
Figure 15.2.3.2.3	Individual Actual Value in Vital Signs - 3 min Standing SBP over Time
Figure 15.2.3.2.4	Mean +/ SD Actual Value in Vital Signs – 3 min Standing SBP over Time
Figure 15.2.3.3.1	Individual Change from Baseline in Vital Signs - 5 min Standing SBP over Time
Figure 15.2.3.3.2	Mean+/-SD Change from Baseline in Vital Signs - 5 min Standing SBP over Time
Figure 15.2.3.3.2.1	Mean+/-SD Change from Baseline in Vital Signs - 5 min Standing SBP over Time by Subgroups
Figure 15.2.3.3.3	Individual Actual Value in Vital Signs - 5 min Standing SBP over Time
Figure 15.2.3.3.4	Mean +/ SD Actual Value in Vital Signs – 5 min Standing SBP over Time
Figure 15.2.3.4.1	Individual Change from Baseline in Vital Signs - 10 min Standing SBP over Time
Figure 15.2.3.4.2	Mean+/-SD Change from Baseline in Vital Signs - 10 min Standing SBP over Time
Figure 15.2.3.4.2.1	Mean+/-SD Change from Baseline in Vital Signs - 10 min Standing SBP over Time by Subgroups
Figure 15.2.3.4.3	Individual Actual Value in Vital Signs - 10 min Standing SBP over Time
Figure 15.2.3.4.4	Mean +/ SD Actual Value in Vital Signs – 10 min Standing SBP over Time
Figure 15.2.4.1.1	Individual Change from Baseline in Vital Signs - Change from Seated SBP to 1 min Standing SBP over Time
Figure 15.2.4.1.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Seated SBP to 1 min Standing SBP over Time

Figure 15.2.4.2.1	Individual Change from Baseline in Vital Signs - Change from Seated SBP to 3 min Standing SBP over Time
Figure 15.2.4.2.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Seated SBP to 3 min Standing SBP over Time
Figure 15.2.4.3.1	Individual Change from Baseline in Vital Signs - Change from Seated SBP to 5 min Standing SBP over Time
Figure 15.2.4.3.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Seated SBP to 5 min Standing SBP over Time
Figure 15.2.4.4.1	Individual Change from Baseline in Vital Signs - Change from Seated SBP to 10 min Standing SBP over Time
Figure 15.2.4.4.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Seated SBP to 10 min Standing SBP over Time
Figure 15.2.5.1.1	Individual Change from Baseline in Vital Signs - Change from Supine SBP to 1 min Standing SBP over Time
Figure 15.2.5.1.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Supine SBP to 1 min Standing SBP over Time
Figure 15.2.5.2.1	Individual Change from Baseline in Vital Signs - Change from Supine SBP to 3 min Standing SBP over Time
Figure 15.2.5.2.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Supine SBP to 3 min Standing SBP over Time
Figure 15.2.5.3.1	Individual Change from Baseline in Vital Signs - Change from Supine SBP to 5 min Standing SBP over Time
Figure 15.2.5.3.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Supine SBP to 5 min Standing SBP over Time
Figure 15.2.5.4.1	Individual Change from Baseline in Vital Signs - Change from Supine SBP to 10 min Standing SBP over Time
Figure 15.2.5.4.2	Mean+/-SD Change from Baseline in Vital Signs - Change from Supine SBP to 10 min Standing SBP over Time
Figure 15.2.6.1	Individual Change from Baseline in Vital Signs - Supine SBP over Time
Figure 15.2.6.2	Mean+/-SD Change from Baseline in Vital Signs - Supine SBP over Time

Figure 15.2.6.2.1	Mean+/-SD Change from Baseline in Vital Signs - Supine SBP over Time by Subgroups
Figure 15.2.6.3	Individual Actual Value in Vital Signs - Supine SBP over Time
Figure 15.2.6.4	Actual Value in Vital Signs - Supine SBP over Time
Figure 15.2.7.1	Individual Change from Baseline in Vital Signs - Supine DBP over Time
Figure 15.2.7.2	Mean+/-SD Change from Baseline in Vital Signs - Supine DBP over Time
Figure 15.2.8.1	Individual Change from Baseline in Vital Signs - Standing Duration over Time
Figure 15.2.8.2	Mean+/-SD Change from Baseline in Vital Signs - Standing Duration over Time
Figure 15.2.8.2.1	Mean+/-SD Change from Baseline in Vital Signs - Standing Duration over Time by Subgroups
Figure 15.2.8.3	Individual Percent Change from Baseline in Vital Signs - Standing Duration over Time
Figure 15.2.8.4	Individual Percent Change from Baseline in Vital Signs - Standing Duration over Time – All Subjects
Figure 15.2.8.5	Mean+/-SD Percent Change from Baseline in Vital Signs - Standing Duration over Time
Figure 15.2.8.6	Individual Actual Value in Vital Signs - Standing Duration over Time
Figure 15.2.8.7	Individual Actual Value in Vital Signs - Standing Duration over Time – All Subjects and Part C Completers
Figure 15.2.8.8	Mean+/-SD Actual Value in Vital Signs - Standing Duration over Time
Figure 15.2.9.1	Individual Vital Signs - Seated and Standing SBP Heatmap
Figure 15.2.10.1	Individual Vital Signs - Seated and Standing DBP Heatmap

Figure 15.2.11.1	Individual Vital Signs - Supine SBP Heatmap
Figure 15.2.12.1	Individual Vital Signs - Supine DBP Heatmap
Figure 15.2.13.1	Bar Plot of Change from Baseline in Vital Signs - Seated SBP by Dose and Change Subgroup
Figure 15.2.14.1	Bar Plot of Change from Baseline in Vital Signs - Standing Duration by Dose and Change Subgroup
Figure 15.2.14.2	Bar Plot of Percent Change from Baseline in Vital Signs - Standing Duration by Dose and Percent Change Subgroup
Figure 15.2.15.1	Bar Plot of OHSA Question 1 Change from Baseline Pre-Lunch
Figure 15.2.15.2	Bar Plot of OHSA Question 1 Change from Baseline Pre-Lunch for Baseline Value > 2
Figure 15.2.15.3	OHSA Question 1 - Actual Value for Individual Subject over Time
Figure 15.2.15.4	OHSA Question 1 - Actual Value for Individual Subject over Time - All Subjects and Part C Completers
Figure 15.2.15.5	Mean +/ SD Change from Baseline in OHSA Question 1 over Time
Figure 15.2.15.6	OHSA Composite Score - Actual Value for Individual Subject over Time
Figure 15.2.15.7	OHSA Composite Score - Actual Value for Individual Subject over Time - All Subjects and Part C Completers
Figure 15.2.15.8	Mean +/ SD Change from Baseline in OHSA Composite Score over Time
Figure 15.2.15.9	OHDAS Composite Score - Actual Value for Individual Subject over Time
Figure 15.2.15.10	OHDAS Composite Score - Actual Value for Individual Subject over Time - All Subjects an Part C Completers
Figure 15.2.15.11	Mean +/ SD Change from Baseline in OHDAS Composite Score over Time

Figure 15.2.15.12	OHQ Composite Score - Actual Value for Individual Subject over Time
Figure 15.2.15.13	OHQ Composite Score - Actual Value for Individual Subject over Time - All Subjects and Part C Completers
Figure 15.2.15.14	Mean +/ SD Change from Baseline in OHQ Composite Score over Time
Figure 15.2.16.1	Individual Plots in 24 Hours Vital Signs Monitor - Systolic Blood Pressure over Time
Figure 15.2.16.2	Individual Plots in 24 Hours Vital Signs Monitor - Diastolic Blood Pressure over Time
Figure 15.2.16.3	Individual Plots in 24 Hours Vital Signs Monitor - Heart Rate over Time
Figure 15.2.16.4	Individual Plots in 24 Hours Vital Signs Monitor - Mean Arterial Pressure over Time
Figure 15.2.17.1	Individual Change from Baseline in Vital Signs - Change from Supine SBP to Seated SBP over Time
Figure 15.2.17.2	Mean +/ SD Change from Baseline in Vital Signs - Change from Supine SBP to Seated SBP over Time
Figure 15.2.17.3	Mean +/ SD Change from Baseline in Vital Signs - Change from Supine SBP to Seated SBP over Time by Subgroups
Figure 15.2.17.4	Individual Actual Value in Vital Signs - Change from Supine SBP to Seated SBP over Time for All Subjects and Part C Completers
Figure 15.2.17.5	Mean +/ SD Actual Value in Vital Signs - Change from Supine SBP to Seated SBP over Time
14.3	**Safety**
14.3.1	Extent of Exposure
14.3.1.1	Study Drug compliance
14.3.1.2	Summary of Exposure by Visit
14.3.1.3	Number (%) of Subjects with Exposure by Visit
13.3.2	Overview of adverse events
14.3.3.1	Treatment-emergent adverse events by system organ class and preferred term

14.3.3.2	Treatment-emergent adverse events by preferred term
14.3.4	Treatment-emergent adverse events occurring in >2% subjects by preferred term and sorted by decreasing frequency
14.3.5	Treatment-emergent adverse events by system organ Class, preferred term, and maximum severity
14.3.6	Treatment-emergent adverse events by system organ Class, preferred term, and Treatment Relationship
14.3.7	Study drug related treatment emergent adverse events by system organ class and preferred term
14.3.8.1	Serious adverse events by preferred term
14.3.8.2	Serious adverse events by system organ class and preferred term
14.3.10.1	Shift Table of Laboratory values from baseline to Worst Increase by laboratory test group, lab parameters
14.3.10.2	Shift Table of Laboratory values from baseline to Worst Decrease by laboratory test group, lab parameters
14.3.11.1	Summary of vital signs and Change from baseline by parameter and visit
14.3.11.2	Number (%) of patients with potentially clinically significant Changes in vital signs by visit
14.3.12.1	Summary of ECG and Change from Baseline by parameters and visit
14.3.12.2	Number (%) of patients with abnormal ECG and Changes by categories by parameters and visit
Figure 14.3.1	Individual Change of Exposure over Time - All Subjects

Listings

Number	Title
16.2.1	Subject disposition
16.2.2	Demographic and baseline characteristics
16.2.4	Prior and concomitant medications
16.2.5	OHSA score
16.2.6	OHDAS score
16.2.7	Clinical global impression (Global Assessment Score from Physician and Subject)
16.2.8	Extent of exposure (including duration between Part A and Part C)
16.2.9.1	Adverse events
16.2.9.2	Serious adverse events
14.2.9.3	Adverse events leading to drug discontinuation
14.2.9.4	Treatment Emergent Adverse Events with Concomitant Medications
16.2.10	Vital signs (Seated BP, Standing BP, Supine BP, Standing Duration)
16.2.10.2	24 Hours Vital Signs Monitor
16.2.11	ECGs
16.2.12	Clinical laboratory results (hematology, chemistry, urinalysis)
16.2.13	Study Drug Accountability
16.2.14	Major Protocol Deviation