Protocol Number: 0169

Official Title: A Phase 3, 4-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects With Primary Autonomic Failure

NCT Number: NCT03750552

Document Date: 19 July 2021

STATISTICAL ANALYSIS PLAN
PHASE 3

VERSION: 1.0

DATE OF PLAN:

July 19, 2021

BASED ON:

Protocol [redacted] 05 August 2020

STUDY DRUG:

TD-9855

PROTOCOL NUMBER:

0169

STUDY TITLE:

A Phase 3, 4-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects With Primary Autonomic Failure

SPONSOR:

Theravance Biopharma R&D, Inc.

c/o Theravance Biopharma US, Inc.

901 Gateway Boulevard

South San Francisco, CA 94080

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

TD-9855 (ampreloxetine), Study 0169 Statistical Analysis Plan

A Phase 3, 4-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects With Primary Autonomic Failure

Plan Version: 19JULY2021

Author: [redacted]

c.

Reviewer: [redacted]

Theravance Biopharma US, Inc.

Reviewer: [redacted]

Theravance Biopharma US, Inc.

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DOB	date of birth
dy	days
FAS	full analysis set
GCP	Good Clinical Practice
IRB	Institutional Review Board
KM	Kaplan-Meier
LLN	lower limit of normal
LS	least squares
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model repeated measures
mo	months
MSA	multiple system atrophy
NE	norepinephrine level
OTC	over-the-counter medication
PAF	pure autonomic failure
PD	Parkinson's disease
PP	per protocol
QTcF	corrected QT interval, Fridericia correction
RR	respiratory rate
SAE	serious adverse event

Abbreviation	Term
SAP	statistical analysis plan
SAS	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell count
WHO	World Health Organization
yr	years

2. INTRODUCTION

This document describes the plan for the summarization and analysis of clinical data collected in Study 0169 for ampreloxetine (TD-9855). It serves as the final authority regarding data analyses.

[redacted]

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of the study is:

- To evaluate the efficacy of ampreloxetine (TD-9855) in subjects with multiple system atrophy (MSA), Parkinson's disease (PD), or pure autonomic failure (PAF) experiencing symptomatic neurogenic orthostatic hypotension (nOH) compared with placebo at Week 4, as measured by the change from baseline of the Orthostatic Hypotension Symptom Assessment (OHSA) Question 1 (OHSA#1) score.

3.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of ampreloxetine (TD-9855) by symptom and activity assessments using OHSA and the Orthostatic Hypotension Daily Activities Scale (OHDAS).
- To evaluate the efficacy of ampreloxetine (TD-9855) using the Patient Global Impression of Change (PGI-C).
- To evaluate the efficacy of ampreloxetine (TD-9855) in preventing incidence of falls.
- To evaluate the safety and tolerability of ampreloxetine (TD-9855), including adverse events (AEs) and changes in blood pressure (BP), heart rate (HR), electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS) and laboratory tests.

3.1.3. Exploratory Objectives

[redacted]

[redacted]

3.2. Study Endpoints

3.2.1. Primary Study Endpoint

The primary study endpoint is:

- Change from baseline in OHSA#1 (dizziness, lightheadedness, feeling faint, or feeling like blacking out) at Week 4

3.2.2. Secondary Study Endpoints

- Change from baseline in OHSA composite score in Weeks 1 to 4
- Change from baseline in OHDAS composite score in Weeks 1 to 4
- PGI-C at Week 4
- Incidence of falls

3.2.3. Exploratory Study Endpoints

[redacted]

[redacted]

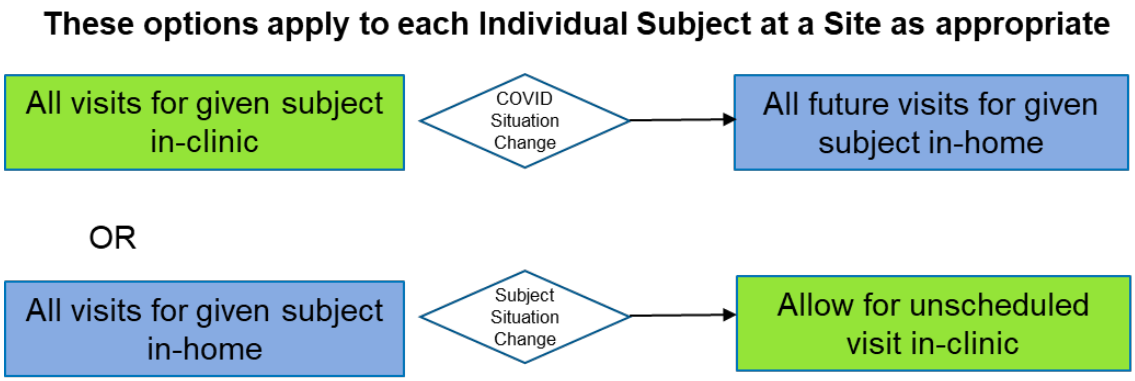
3.2.4. Safety and Tolerability Endpoints

- Physical examination
- Neurological examination
- Vital signs including ambulatory BP
- Resting ECGs
- Clinical laboratory tests, including biochemistry, hematology, urinalysis
- Concomitant medication
- AEs
- Subject compliance to study treatment
- C-SSRS

4. STUDY DESIGN

4.1. Summary of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate efficacy, safety, and tolerability of ampreloxetine (TD-9855) in subjects with primary autonomic failures (MSA, PD, or PAF) and symptomatic neurogenic orthostatic hypotension (nOH) after 4 weeks of treatment. Given the challenges presented by the COVID-19 pandemic the trial utilizes an operational design featuring the ability to conduct protocol required visits as either in clinic or remote visits. Investigators must conduct all study visits for Study 0169 for a given subject in a consistent manner for each subject to reduce the possibility of variability in data collection and reporting. Therefore, Investigators, in discussion with each individual subject at their site, will be required to elect to conduct all visits either in the clinic or remotely for each individual subject at their site. Regardless of which election an Investigator and subject make, the Screening visit (V1) must be conducted in clinic for all subjects. Tools and systems are available to sites and subjects to support remote visits (e.g., direct to subject shipping of study medication and other study supplies, standardized HIPAA/GDPR compliant telemedicine platform, in-home health nurses).



Due to the potential for resurgence of COVID-19 and its impact on both sites and subjects, the Sponsor will allow Investigators to request exceptions to the selected type of study visit modality due to COVID-19 or COVID-19 related circumstances. Approved exceptions will be recorded as COVID-19 related protocol deviations.

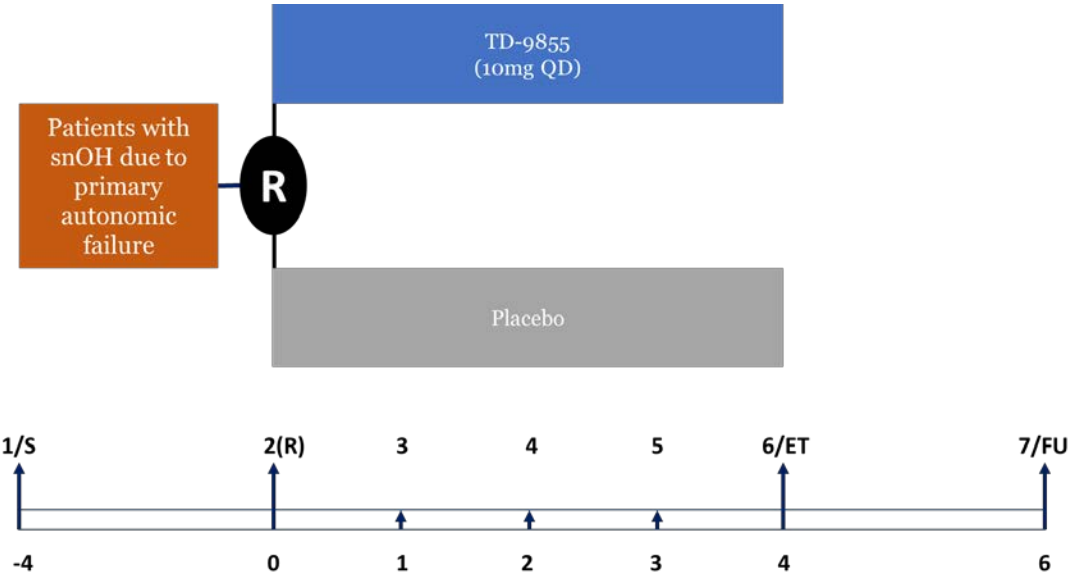
All sites are allowed at Investigator discretion to conduct either in-clinic or remote unscheduled visit(s) for subject safety or unexpected subject medical needs outside of the regular visit schedule. In this case, unscheduled visits are not considered protocol deviations and the Investigator is not required to obtain preapproval from the Sponsor. Data collected during these visits may include any protocol-specified assessments which will be captured in the clinical database.

For subjects that have previously completed the Screening visit at the time regulatory and ethics approval for [redacted] is received, sites must reconsent the subject using the most recently approved version of the Informed Consent Form to obtain subject consent for remote study visits, if that visit modality is selected by the Investigator and the subject. For those subjects who are already randomized to study treatment and active in the study at the time regulatory and ethics approval for [redacted] is received, the Investigator and subject should continue the remaining study visits in the same visit modality as the Randomization Visit.

Symptomatic neurogenic orthostatic hypotension is defined as:

- A sustained reduction of BP of ≥20 mm Hg (systolic) or ≥10 mm Hg (diastolic) within 3 minutes of standing or tilted-up to ≥60^{o} elevation from a supine position.
- A score of at least a 4 on the Orthostatic Hypotension Symptom Assessment Question #1

The study consists of 3 periods: (i) 4-week screening, (ii) 4-week randomized treatment, and (iii) 2-week follow up. The schematic representation is as shown below:



After signing the informed consent, the subject will enter a screening period of up to 4 weeks to confirm eligibility. At the screening visit, which must be performed in the clinic for all subjects, the subject will provide a comprehensive medical history of their disease and treatments. The subject's disease will be characterized and documented by the investigator.

The subject will receive an assessment of their physical condition, including safety and laboratory evaluations and related aspects of their disease states according to the Schedule of Study Procedures (Table 2). The presence of nOH symptoms and reported sensation of dizziness, lightheadedness, feeling faint, or feeling like blacking out (OHSA#1) must be confirmed by the application of a tilt-table test. This tilt-table test serves 2 purposes: (i) determination of the systolic/diastolic BP changes, and (ii) training the subjects to recognize the sensations associated with OHSA#1.

Eligible subjects will undergo training of accurate scoring of their sensation of dizziness, lightheadedness, feeling faint, or feeling like blacking out as outlined by the OHSA#1.

Following the screening period, the subject will proceed to Visit 2 to further confirm the additional eligibility criteria prior to randomization. This includes the completion of the Orthostatic Hypotension Questionnaire (OHQ) in which a minimum score of 4 points in OHSA#1 is required. Subjects meeting all applicable inclusion criteria and none of the applicable exclusion criteria, including confirmation of relevant criteria by the independent Enrollment Steering Committee (ESC), will be randomized to receive either ampreloxetine (TD-9855) or matching placebo for the next 4 weeks.

Following randomization and completion of study assessments, the subject will receive a [redacted] of ampreloxetine (TD-9855) (or matching placebo) [redacted] for the remaining double-blind treatment period.

Subjects completing the 4-week double-blind treatment period will be eligible to enroll and continue receiving study medication in Study 0170. The final visit for those subjects who do not complete the 4-week double-blind treatment period or who choose not to continue into Study 0170 will be the follow-up visit (V7). This visit must be completed two weeks from the date of the last dose.

The subject will return for weekly assessments as outlined in the Schedule of Study Procedures (Table 2).

4.2. Definition of Study Drugs

Study drug includes the following (placebo and ampreloxetine [TD-9855]):

- Ampreloxetine (TD-9855) [redacted]: Taken orally for 4 weeks without regard to food at approximately the same time each morning with approximately 8 ounces of water
- Placebo once daily: Taken orally for 4 weeks without regard to food at approximately the same time each morning with approximately 8 ounces of water

[redacted]

4.3. Sample Size Considerations

[redacted]

4.4. Randomization

Central randomization for treatment allocation will be implemented. A computer-generated randomization schedule will be prepared for this study under the supervision of the sponsor.

Subjects will be randomized at Visit 2 in a 1:1 ratio to ampreloxetine (TD-9855) or placebo using a randomization schedule stratified by disease type (MSA, PD, or PAF).

At least 40% of the subjects enrolled will have MSA (at least 76 subjects).

4.5. Clinical Assessments

Table 2: Schedule of Study Procedures

Study Period:	**Screening**	**Treatment**					**Follow-up**
Day (Visit):	**Day -28 to -7 (Visit 1)**	**Day 1 (Visit 2)**	**Day 8 (Visit 3) +/- 3 days**	**Day 15 (Visit 4) +/- 3 days**	**Day 22 (Visit 5) +/- 3 days**	**Day 29 (Visit 6) / ET +/- 3 days**	**Day 43[o] (Visit 7) +/- 3 days**
Mandated Order of Procedures (when applicable)							
Informed consent	X						
Inclusion /exclusion criteria	X	X					
Medical history (including smoking history)	X[b]						
Concomitant medications (and smoking usage)	X[b]	X	X	X	X	X	X
MoCA	X						
OHQ subject training[c]	X[c]	X	X	X	X	X	
OHQ (OHSA and OHDAS)		X[m]	X	X	X	X	
PGI-C						X	
C-SSRS	X	X[m,n]	X[n]	X[n]	X[n]	X[n]	X
Tilt-table test	X[d]						
Randomization		X[a]					
Recommended Order of Procedures (when applicable)							
[redacted]		[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]	

Study Period:	**Screening**	**Treatment**					**Follow-up**
Day (Visit):	**Day -28 to -7 (Visit 1)**	**Day 1 (Visit 2)**	**Day 8 (Visit 3) +/- 3 days**	**Day 15 (Visit 4) +/- 3 days**	**Day 22 (Visit 5) +/- 3 days**	**Day 29 (Visit 6) / ET +/- 3 days**	**Day 43[o] (Visit 7) +/- 3 days**
[redacted]		[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Vital Signs (Body Temperature, Heart Rate, Respiration Rate, Blood Pressure)[f]	X	X[m]	X	X	X	X	X
Height (cm)	X						
Weight (kg)	X	X[m]	X	X	X	X	X
Physical examination	X	X[m]				X	
Neurological examination	X	X[m]				X	
12-lead electrocardiogram[g]	X					X	
Pregnancy test[h]	X	X[m]				X	
Norepinephrine (NE)	X						
Safety laboratory test (chemistry, hematology, and urinalysis)	X	X[m]		X		X	
[redacted]			[redacted]	[redacted]		[redacted]	

Study Period:	**Screening**	**Treatment**					**Follow-up**
Day (Visit):	**Day -28 to -7 (Visit 1)**	**Day 1 (Visit 2)**	**Day 8 (Visit 3) +/- 3 days**	**Day 15 (Visit 4) +/- 3 days**	**Day 22 (Visit 5) +/- 3 days**	**Day 29 (Visit 6) / ET +/- 3 days**	**Day 43[o] (Visit 7) +/- 3 days**
[redacted]		[redacted]				[redacted]	
ESC (for confirmation of diagnosis)[a]	X						
24-hour ambulatory BP device provision[k]	X	X		X			
24-hour ambulatory BP device collection[k]		X	X		X		
Incidence of Falls and ABPM position Diaries	X	X[m]	X	X	X	X	
Dosing and Midodrine rescue medication Diaries		X[m]	X	X	X	X	
Adverse events	X	X	X	X	X	X	X
Dispense study medication		X[m]					
Study medication dosing[l]		X					
Collect, review, and re-dispense study medication			X	X	X		
Collect and review study medication						X	
Valsalva maneuver	X[q]						

Abbreviations: [redacted]; BP: Blood Pressure; [redacted] C-SSRS: Columbia Suicide Severity Rating Scale; ESC: Enrollment Steering Committee; ET: Early Terminated; [redacted] HR: Heart Rate; MoCA: Montreal Cognitive Assessment; [redacted]; OHDAS: Orthostatic Hypotension Daily Activity Scale; OHSA: Orthostatic Hypotension Symptom Assessment; OHQ: Orthostatic Hypotension Questionnaire; [redacted] PGI-C: Patient Global Impression of Change; Randomization and trial supply management (RTSM); RR: Respiratory Rate; [redacted]

a. [redacted]d in clinic for ALL subjects. Subject eligibility will be assessed by the Investigator during Screening and primary diagnosis will be verified by the ESC prior to randomization; subjects meeting OHSA#1 criterion on Visit 2 (Day 1) and who otherwise meet eligibility criteria may be randomized via RTSM.
b. A complete medical and medication history evaluation will be performed during screening.
c. During the screening visit, subjects will receive thorough training on the OHQ disease instrument and will receive refresher training prior to completing the OHQ during each study visit (Visit 2 to 6). Subjects should be rested prior to beginning the training.
d. During Screening, the tilt-table test should be performed following at least 12-hours of withdrawal from vasoactive medications. The tilt-table test should be performed at least 2 hours after meals and with an empty bladder.
e. The UPDRS scale should be completed in an ON state, and within 1-4 hours of taking the PD medications. All 6 parts would be completed on Day 1, while only Parts 2 and 3 of the questionnaire would be completed on Day 29.
f. The vital sign measurements should be performed after the subject has rested sufficiently as determined by the appropriate site staff. The BP and HR collected at 10 minutes supine and seated from the orthostatic standing test can be used for safety vital signs assessment. Vitals can be performed as part of the mandated procedures, if needed.
g. ECGs are done in triplicate after the subject has been resting for at least 5 minutes in a seated or supine position before the first reading, with each replicate separated by at least 1 minute.
h. In women of childbearing potential only. First, urine beta human chorionic gonadotropin (bHCG) test will be performed and if positive, confirmation with serum bHCG test is required. The pregnancy test must be confirmed negative for a subject to be eligible for this study.
i. [redacted]
k. Ambulatory blood pressure monitoring equipment will be provided to the subject during the screening visit. Beginning approximately 72 to 24-hours before a subject conducts the Day 1 (Visit 2), and before the Day 8 and Day 22 visits, subjects will put on the 24-hour blood pressure monitoring equipment and initiate the recording. Once the 24-hour session is complete, subjects will remove and return the equipment to the research center during the next visit. During each 24-hour session, the blood pressure monitoring device will be programmed to automatically measure blood pressure every 2 hours beginning at the top of the hour. During each 24-hour session, subjects should also maintain a log of their posture at the time of each blood pressure measurement. Details regarding the ambulatory monitoring will be provided in a separate manual.
l. Study medication will be ingested in the morning at approximately the same time of day with 8 ounces of water. The exact time and day of dosing will be recorded on the mornings of study visits. Subjects should be reminded to maintain an adequate fluid intake during their scheduled visits.
m. The assessments or procedures will be performed within 24-hours prior to subject taking the study medication (pre-dose). Following randomization and completion of study assessments, the subject will begin taking study medication on Day 2 in the morning.
n. C-SSRS is to be completed following OHQ questionnaire from Visit 2 to Visit 6.
o. Follow-up visit is only applicable for those subjects that do not proceed to Study 0170 and will be completed two weeks from the date of the last dose.
p. The assessment should be performed at approximately (±2 hour) the same time of day on Day 1 (except Screening). Subjects should abstain from eating for at least 90mins prior to this assessment.
q. Valsalva maneuver is to be performed for PAF subjects only if no results are available within 24 months from the date of randomization.

5. TIMING OF PLANNED ANALYSES

The analyses will occur when all subjects have completed or terminated early from the study and the database has been cleaned and locked.

6. CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Analyses and tabulations will generally be prepared using [redacted]

Summary tables and listings will be prepared according to ICH Guideline E3 and include a "footer" providing explanatory notes.

6.1. Analysis Sets

[redacted]

6.1.1. Screen Failures

Subjects who give written informed consent but are not randomized are considered screen failures. Screen failure subjects and the reason for screen failure are captured in the EDC.

6.1.2. Randomized Analysis Set

The randomized analysis set comprises all subjects who are randomized.

6.1.3. Safety Analysis Set

The safety analysis set comprises all randomized subjects who receive at least 1 dose of study medication. The safety analysis set will be the analysis set for both general (baseline, exposure, and compliance) and safety analyses. Subjects in the safety analysis set will be grouped according to the study treatments they receive.

6.1.4. Full Analysis Set (FAS)

The Full analysis set (FAS) is defined as all randomized subjects who have received at least 1 dose of study medication and have baseline and at least 1 post baseline measurement of OHSA#1. The FAS is the primary analysis set for efficacy endpoints. FAS analyses will use the randomized treatments.

6.1.5. Per-Protocol (PP) Analysis Set

The per-protocol (PP) analysis set comprises all subjects in the FAS who have an OHSA#1 assessment at Week 4 obtained no earlier than study day 25 and no later than study day 42, did not use a prohibited medication during the treatment period, and did not meet any of the following criteria:

1. Poor study drug compliance, defined as compliance < 80% or ≥ 120% over the interval from first to last dose during the treatment period

2. Did not meet efficacy-related inclusion criteria (criterion 5, OHSA#1 score ≥ 4)
3. Took a prohibited medication prior to randomization (exclusion criterion 4, subject has used strong CYP1A2 inhibitors or inducers within 7 days or 5 half-lives before randomization or requires concomitant use until the follow-up visit; exclusion criterion 5, subject has changed dose, frequency, or type of prescribed medication for orthostatic hypotension within 7 days prior to randomization, or failed to taper off midodrine and droxidopa (if applicable) at least 7 days prior to randomization)
4. Received a treatment other than the randomized treatment

Subjects who used midodrine not per protocol will be excluded from the PP analysis set. Subjects who used midodrine as rescue therapy per the instructions in the protocol will be included in the PP analysis set, and OHSA#1 collected on the visits when rescue therapy was used (if any) will be censored.

A listing of FAS subjects excluded from the PP set will be provided, with reasons for exclusion.

6.1.6. Examination of Subgroups

To assess consistency of treatment effect across subgroups, the primary analysis of OHSA#1 will be repeated for each of the following subgroups:

1. Disease Type: MSA, PD, and PAF
2. Gender: Male and Female
3. Timing of Primary Endpoint Visit Relative to COVID-19 Pandemic Onset: Before 18MAR2020, On or After 18MAR2020

6.2. Baseline Definition

Unless stated otherwise, baseline is the last assessment (scheduled or unscheduled) obtained before the first dose of randomized study medication.

6.3. Derived and Transformed Data

6.3.1. Study Day

If the date of interest occurs on or after the date of the first dose, study day will be calculated as date of interest – date of first dose + 1.

If the date of interest occurs prior to the date of the first dose, study day will be calculated as date of interest – date of first dose. There is no study day 0.

In this study, subject will receive the first dose of study medication in the morning of the day following randomization and completion of baseline study assessments. Study day 1 for a subject in the analysis will be defined as the first day the subject receives study drug, which is different from the protocol definition of study day 1 as the day of randomization. To make it clear which definition is being used, in this document “Day x” (e.g., Day 1 [Visit 2]) refers to the protocol definition and “study day x” refers to study day relative to the date of the first dose.

6.3.2. Change from Baseline

Change from baseline is calculated as postbaseline result – baseline result.

If either the baseline or the postbaseline result is missing, the change from baseline is set to missing.

6.3.3. Body Mass Index (BMI)

BMI will be calculated as follows:

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

6.3.4. Analysis Visit Windows

Assessments that are summarized by visit will be assigned to analysis visits using the following analysis visit windows, without regard to the visit label associated with the assessment in the clinical database.

Table 3: Analysis Visit Windows

Analysis Visit	Analysis Visit Window	
	Start (study day)	Stop (study day)
For endpoints collected at Weeks 1, 2, 3, and 4, including C-SSRS, BSFC-s, OHSA, OHDAS, and vital signs		
Week 1 (study day 7)	2	10
Week 2 (study day 14)	11	17
Week 3 (study day 21)	18	24
Week 4 (study day 28)	25	42
For endpoints collected at Weeks 1 and 3, including ABPM position		
Week 1 (study day 7)	2	14
Week 3 (study day 21)	15	42
For endpoints collected at Weeks 2 and 4, including safety laboratory tests		
Week 2 (study day 14)	2	21
Week 4 (study day 28)	22	42
For endpoints other than PGI-C collected at Week 4, including EQ-5D, NMSS, HADS, UPDRS, PDQ-8, COMPASS-31, UMSARS, and ECG		
Week 4 (study day 28)	15	42
For PGI-C* (collected at Week 4)		
Week 4 (study day 28)	2	42

*All endpoints except PGI-C are also collected on or prior to study day -1. PGI-C, being a change assessment, is collected only at the Week 4 visit or early termination visit.

6.3.5. Multiple Assessments

In general, if multiple valid observations exist in the window of an analysis visit, the record to be included in the summary and analyses will be chosen on the following basis, unless otherwise specified:

- The record closest to the nominal visit

If records are equidistant or distance cannot be determined:

- The latest record

If records have the same date/time:

- The average

7. STUDY POPULATION

7.1. Enrollment by Investigator

Enrollment by geographic region (North America, Europe, Asia/Pacific, and Other), country, and investigator will be summarized overall and by treatment group for all randomized subjects.

7.2. Subject Disposition and Completion Status

Subject disposition will be summarized for all randomized subjects by treatment group. The summary will include the counts and percentages of subjects in each analysis set as well as of subjects who:

- Were randomized and treated with study drug
- Were randomized and not treated with study drug
- Completed the 4-week treatment period
- Didn’t complete the 4-week treatment period and the reason for not completing it (adverse event, loss of follow-up, noncompliance with study drug, physician decision, pregnancy, protocol violation, study terminated by Sponsor, and other)
- Completed the study
- Didn’t complete the study and the reason (adverse event, loss of follow-up, noncompliance with study drug, physician decision, pregnancy, protocol violation, study terminated by Sponsor, and other)
- Continued to Study 0170
- Didn’t continue to Study 0170 and the reason (did not complete study, chose not to continue, and other)

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

7.3. Protocol Deviations

FAS subjects reporting major protocol deviations will be summarized overall and by treatment group. The summary will include counts and percentages of subjects who have any major PDs and counts and percentages of subjects who have major PDs in each category. A separate summary table will be provided for COVID-19 related PDs.

A subject listing with all protocol deviations identified prior to database lock will be provided. All subject listings will be based on the randomized analysis set.

7.4. Medical History and Medical Conditions Present at Entry

Medical history will be summarized by system organ class and preferred term, overall and by treatment group, for the safety analysis set. No statistical comparisons will be performed.

Medical history will be mapped according to [redacted].

7.5. Demographic and Baseline Clinical Characteristics

A summary of demographic and baseline characteristics will include the following items: age (years), age category (<65 years, ≥65 years), sex, race, ethnicity, weight (kg), height (cm), BMI (kg/m^2), smoking status (Never, Current, Former, Missing), Diagnosis of Primary Autonomic Failure (Multiple System Atrophy, Parkinson's Disease, Pure Autonomic Failure), OHSA#1 score, OHSA composite score, OHDAS composite score, OHQ overall composite score, Supine SBP (mmHg, an average of 5 min and 10 min measurements), 3 min Standing SBP (mmHg), and norepinephrine (NE) (pg/mL).

This summary will be presented for the safety analysis set, FAS, and PP analysis set.

8. EFFICACY

8.1. General Considerations

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

Nominal p-values (i.e., unadjusted for multiple testing) will be provided as appropriate.

If a statistically significant treatment effect on the primary efficacy endpoint has been demonstrated, secondary efficacy endpoints will be tested in a hierarchical fashion using 2-sided tests at the 5% level of significance until a failure to reject the null hypothesis occurs.

8.2. Statement of the Null and Alternative Hypotheses for the Primary Endpoint

The primary endpoint, the change from baseline in OHSA#1 (dizziness, lightheadedness, feeling faint or feeling like blacking out) at Week 4, is used to evaluate the effectiveness of TD-9855 (ampreloxetine) therapy relative to the placebo.

The null hypothesis for the treatment comparison is that there is no difference between ampreloxetine (TD-9855) (active) group and the placebo group in the mean change in OHSA#1 from baseline at Week 4. The alternative hypothesis is that there is a difference. The hypothesis testing schema is expressed as follows:

$$H_0 : \mu_{Active} = \mu_{\text{placebo}}$$
$$H_1 : \mu_{Active} \neq \mu_{\text{placebo}}$$

where μ stands for the mean change from baseline at Week 4.

8.3. Analysis of the Primary Efficacy Endpoint

8.3.1. Primary Efficacy Analysis

A mixed effects model for repeated measures (MMRM) incorporating the change from baseline in OHSA#1 as the dependent variable will be used to assess the primary endpoint hypothesis.

The model will include fixed class terms for treatment group and baseline disease type (MSA, PD, PAF), a covariate for baseline OHSA#1 score, and a time effect (week) and its interaction terms with treatment and baseline OHSA#1 score. An unstructured covariance structure (type=UN) to account for the repeated measures within a subject will be fitted. If the model doesn't converge, the data will be reanalyzed fitting a compound symmetric covariance structure (type=CS) and a compound symmetric with heterogenous variance covariance structure (type=CSH) and the structure with a lower AIC value will be selected.

Least squares (LS) mean change in OHSA#1 in each treatment group and the difference in LS mean change between treatment groups will be estimated. Point estimates, 95% confidence intervals (CIs), and p-values will be provided.

Figures

A plot will present the LS mean change from baseline in OHSA#1 at each postbaseline time point by treatment group with 95% CIs.

8.3.2. Sensitivity and Supplementary Analyses for Primary Efficacy Endpoint

A sensitivity analysis is planned to evaluate the sensitivity of the primary efficacy analysis results to the assumption that missing data are missing at random (MAR). A supplementary per protocol analysis will be performed.

8.3.2.1. Per Protocol Analysis

The per protocol analysis follows the same MMRM method described in Section 8.3.1 and is restricted to subjects in the PP analysis set.

8.3.2.2. Tipping Point Analysis

The tipping-point analysis will be conducted for the primary efficacy endpoint, change in OHSA#1 at Week 4, to evaluate the robustness against deviation from the missing at random (MAR) assumption using MMRM. The tipping-point analysis refers to imputing the missing data with a range of scenarios to identify the tipping point at which the imputation overturns the significance of the treatment effect under MAR assumption. The tipping point is determined as the minimum shift value to overturn the significant results of the multiple imputation (MI) when the shift value is added to the Week 4 imputed values for active group subjects. If the tipping point is implausibly large, it is concluded that the study results are not sensitive to the MAR assumption.

For the tipping point analysis, the MMRM model as specified for the primary efficacy analysis will be fitted. The initial results obtained when no shift is applied to active group Week 4 imputed values will be provided, along with the minimum shift that overturns the significant result.

8.3.2.3. Analysis Accounting for Visit Modality Change

There could be systematic differences between OHSA#1 scores collected during remote visits and OHSA#1 scores collected during in-clinic visits. Hence, a sensitivity analysis to assess the effect of visit modality on the primary efficacy analysis will be performed by adding a post baseline visit modality class variable with values “In-clinic” and “Remote” to the primary analysis model. The analysis will include all subjects in FAS. Week 4 LS mean and LS mean difference estimates and p-values will be provided.

8.3.2.4. Subgroup Analyses

To characterize the consistency of the treatment effect for the primary endpoint, the primary endpoint analysis will be repeated for the subgroups specified in Section 6.1.6.

The subgroup analyses will use the same analysis model and reporting structure as in Section 8.3.1. For the disease type subgroup analyses, the disease type stratum terms are redundant and will be omitted from the model. Subgroup analysis will not be performed when $n < 10$ or $n > N - 10$, where n is the number of FAS subjects in the subgroup and N is the number in the FAS.

For each subgroup, a plot of LS mean change from baseline in OHSA#1 at each postbaseline time point will be presented by treatment group with 95% CIs.

In addition, a forest plot of the difference between the treatment groups in LS mean change from baseline in OHSA#1 at Week 4 with 95% CI will be plotted. The x-axis will be difference in LS mean change from baseline and the y-axis will be the subgroups.

8.3.2.5. [redacted]

8.4. Analysis of Secondary Efficacy Endpoints

8.4.1. Analysis of Change From Baseline in OHSA and OHDAS Composite Score

The following two secondary efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint, as described in Section 8.3.1, using the baseline value of the endpoint as the covariate:

- Change from baseline in OHSA composite score in Weeks 1 to 4
- Change from baseline in OHDAS composite score in Weeks 1 to 4

The hypothesis testing schema is similar to the primary efficacy endpoint for the treatment comparison, i.e., no difference between ampreloxetine (TD-9855) (active) group and the placebo.

Figures

Plots will present the LS mean change from baseline at each postbaseline time point by treatment group with 95% CIs for OHSA and OHDAS composite scores.

8.4.2. Analysis of PGI-C and Incidence of Falls

There are two binary secondary efficacy endpoints and their analyses are described below.

Patient Global Impression of Change (PGI-C)

PGI-C is a 5-point scale depicting the overall change in a patient's neurogenic orthostatic hypotension symptoms since the initiation of study medication. Patients rate their change as "Much better," "A little better," "No change," "A little worse," or "Much worse." Early versions of the protocol (original and Amendment 1) used the PGI-C on a 7-point scale. For analysis purposes, the 7-point scale will be mapped to the 5-point scale (Table 4). However, the data will be listed as collected.

The PGI-C will be summarized as number and percentage of subjects with "better" and "no change or worse" at Week 4 (see Appendix 1).

The proportion of subjects with PGI-C responses indicating improvement and the proportion with at least one fall will be compared between treatment groups using a Cochran-Mantel-Haenszel chi-squared test stratified by disease type at baseline.

Table 4: Mapping of PGI-C From 7-Point Scale to 5-Point Scale

7-Point Scale	5-Point Scale
Very Much Improved	Much Better
Much Improved	
Minimally Improved	A Little Better
No Change	No Change
Minimally Worse	A Little Worse
Much Worse	Much Worse
Very Much Worse	

In case the treatment groups differ substantially with respect to timing of assessment, the PGI-C analysis will be supplemented by a sensitivity analysis restricted to subjects with PGI-C collected within the narrowed window study day 25 to 42.

A plot will be presented to show the CMH-weighted average proportion of subjects with PGI-C responses indicating improvement by treatment group at Week 4.

Incidence of falls

Incidence of falls will be summarized as number and percentage of subjects with at least one fall during the interval from the date of the first dose to the date of the last dose.

The falls analysis will be supplemented by corresponding analyses of the incidence of at least one near-fall and of the incidence of at least one fall or near-fall, and by generalized linear model-based analyses of the reported number of falls, near-falls, and falls or near-falls during the treatment period. For these count analyses, the null and alternative hypotheses will be

$$H_0: \theta = 1$$

$$H_1: \theta \neq 1$$

where θ is the TD-9855:placebo weekly incidence density ratio of falls (or near-falls, or either) during the evaluation period. The analyses will be performed by fitting a generalized linear model with a negative binomial error distribution, log link, and log time at risk in weeks as the offset, including disease type stratum and the pre-treatment weekly incidence rate of falls (or near-falls, or either) as covariates. For purposes of this analysis, the pretreatment period will be defined as beginning on the date of the screening visit and ending on the day before the first dose date.

Analysis results provided will include the model-based estimates of weekly incidence rate for each treatment group and point and interval estimates of their ratio, and descriptive statistics for the number of events per patient week during the pretreatment period and during the evaluation period. For falls, this will be calculated as:

$$7 \times (\text{total number of falls reported})/(\text{evaluation end date - first dose date + 1})$$

The incidence rate will be calculated likewise for near-falls and for falls and near-falls combined.

A plot will be presented to show the CMH-weighted average proportion of subjects with at least one fall during the treatment period by treatment group.

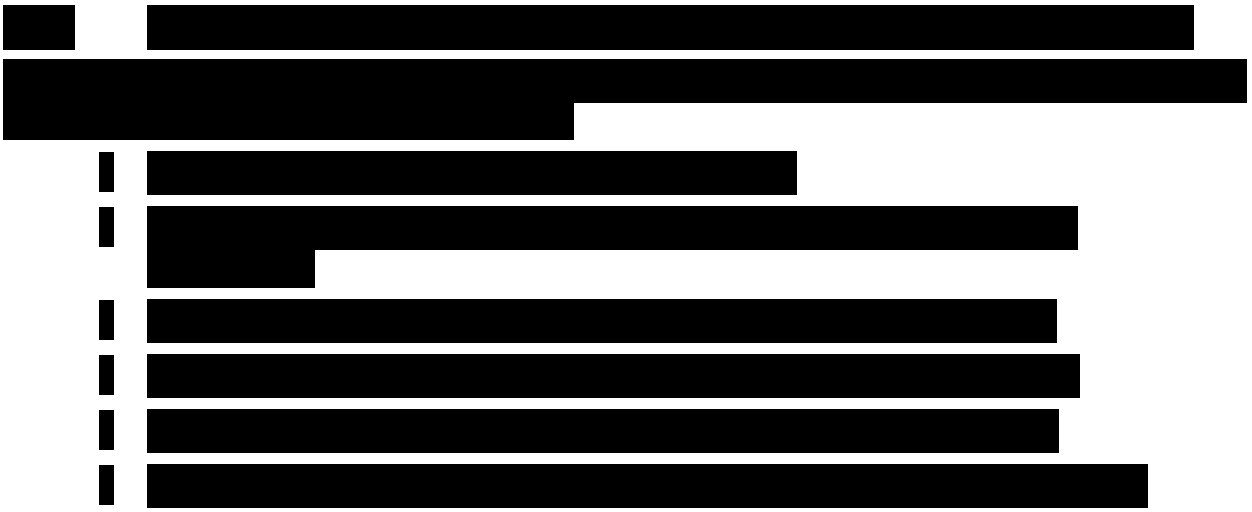
8.4.3. Multiplicity Adjustment

If a statistically significant treatment effect has been demonstrated for the primary efficacy endpoint, the following secondary efficacy endpoints will be tested in a hierarchical fashion in the order below using 2-sided tests at the 5% level of significance until a failure to reject the null hypothesis occurs:

- Change from baseline in OHSA composite score at Week 4
- Change from baseline in OHDAS composite score at Week 4
- PGI-C at Week 4
- Incidence of falls during treatment

For all other analyses, including additional analyses of the primary efficacy endpoint, analyses of the other secondary efficacy endpoints change from baseline in OHSA composite score in Weeks 1 to 3 and change from baseline in OHDAS composite score in Weeks 1 to 3, and analyses of exploratory endpoints, unadjusted p-values and nominal 95% CI intervals will be provided.

8.5. Analysis of Exploratory Efficacy Endpoints



[redacted]

8.5.2. [redacted]

[redacted]

8.6. Scoring and Analysis of Clinical Outcome Assessments

This section discusses the scoring of clinical outcome assessments and provides additional details on their analyses.

8.6.1. OHQ

The Orthostatic Hypotension Questionnaire (OHQ) includes two parts, the Orthostatic Hypotension Symptom Assessment (OHSA) to measure the presence and severity of symptoms and the Orthostatic Hypotension Daily Activity Scale (OHDAS) to measure the impact of orthostatic symptoms on daily activities. Recall period is "over the past week."

OHSA consists of six questions, each rating the intensity of one characteristic symptom of NOH:

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)
3. Generalized weakness
4. Fatigue
5. Trouble concentrating
6. Head/neck discomfort

OHDAS consists of four questions that assess the impact of NOH symptoms on daily activities.

The items are scored on an 11-point scale from 0 to 10, with 0 indicating no symptoms/no interference and 10 indicating the worst possible symptoms/complete interference. OHDAS has an option of selecting "cannot be done for other reasons," which will not be included in scoring.

OHSA and OHDAS composite scores are an unweighted average of the scores of their nonmissing constituent items. The OHQ overall composite score will be calculated as

(Sum of nonmissing OHSA item scores / Number of nonmissing OHSA items + Sum of nonmissing OHDAS item scores / Number of nonmissing OHDAS items)/2

The calculated OHSA and OHDAS composite scores and the OHQ overall composite score will will be rounded to the nearest 0.1.

OHSA#1 is assessed as the primary efficacy endpoint and its analysis is described in Section 8.4.1. Additionally, composite scores of OHSA and OHDAS, OHQ overall composite score, and individual item scores for OHSA items 2-6 and OHDAS items 1-4 will be analyzed similarly.

8.6.2. [redacted]

[redacted]

8.6.5. [redacted]

[redacted]

Table 5: [redacted]

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

Table 6: [redacted]

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

[redacted]

8.6.7. [redacted]

[redacted]

8.6.8. [redacted]

Table 7: [redacted]

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

[redacted]

9. Safety and Tolerability

The analysis of safety and tolerability data includes an overall summary of adverse events, drug exposure (duration of treatment), dosing information/compliance, concomitant medications, clinical laboratory results, vital signs, ECGs, and C-SSRS.

In general, inferential statistical tests are not performed for the analyses of safety and tolerability data.

For all safety analyses, the safety analysis set will be used. The listing of TEAE and vitals signs will be provided using the randomized analysis set to include the subjects from site 27045.

9.1. Adverse Events

Adverse events are collected from signing of the informed consent through the end of follow-up. Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®, version 24.0).

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to 14 days after the date of last dose of study drug. However, for patients who continued into Study 0170, any AE occurs after Study 0170 Visit 1 (Study 0169 Visit 6) will be considered as a TEAE for Study 0170 and will not be included in the AE summary for Study 0169 to avoid double counting.

AEs observed during the period from obtaining informed consent to the start of administration of study drug will not be considered as TEAEs and will be listed only.

AEs and TEAEs will be listed by subject. In addition, subjects with AEs leading to permanent or temporary discontinuation of treatment will be listed separately.

TEAEs will be summarized overall with counts and percentages of subjects with the events, by treatment group, system organ class, and preferred term. TEAEs leading to permanent or temporary discontinuation of treatment, related to study treatment (i.e., any reported as related), serious TEAEs, frequent TEAEs (defined as >3% in the study population), TEAEs by severity, TEAEs of special interest, deaths, and TEAEs by maximum severity and causality will be summarized.

If no adverse events meeting a specific table criterion are observed, the summary table will indicate that there were no occurrences.

9.1.1. [redacted]

[redacted]

[redacted]

9.2. Extent of Exposure and Treatment Compliance

Duration of study drug exposure (days) will be summarized. Duration of exposure to study drug is calculated as (date of last dose – date of first dose + 1).

Subjects will receive their assigned dose (10-mg dose of ampreloxetine (TD-9855) or matching placebo) once daily. Treatment compliance as a percentage of the expected total dose will be calculated as follows, using the information captured on the CRF page for "Study Drug Dispensing / Return":

- 100 × (number of tablets dispensed – number of tablets returned)/ (date of last dose – date of first dose + 1)

Treatment compliance as a percentage of expected total dose will be summarized by treatment group for the safety analysis set as a continuous variable and using the following categories, after rounding to the nearest 0.1%:

- ≥120%
- ≥80% - <120%
- <80%

Study drug administration (date/time and study day) and drug accountability data will be listed.

9.3. Concomitant and Other Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODD, 3Q 2020 C3). Medications entered on the case report form will be mapped to Anatomic Therapeutic Chemical (ATC) drug class and generic drug name. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and preferred name (ATC level 5, chemical substance).

Prior medications are medications used before initiation of study drug. Concomitant medications are medications used after initiation of study drug, including ongoing prior medications and medications beginning up to 14 days after the last dose of study drug.

The number and percentage of subjects receiving prior and concomitant medications will be summarized by treatment group, medication class and standardized medication name (preferred name) for the safety analysis set. ATC level 4 is generally used to determine the medication class for a medication. If ATC level 4 is not available, the next available level of ATC code (i.e., level 3, level 2, or level 1) will be used. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and preferred name) will be counted only once.

Summaries of prohibited prior medications will be provided.

On-treatment midodrine usage will be summarized for days of midodrine usage and daily dosage (mg) of midodrine. For days of midodrine usage, counts and percentages will be provided for the following categories:

- 0
- 1
- 2
- 3
- 4
- ≥ 5

Numbers and percentages of subjects who took midodrine on assessment days will be provided.

Listings of prior medications, concomitant medications, and midodrine usage will be provided.

9.4. Laboratory Data

Quantitative hematology, serum chemistry and urinalysis test results will be summarized in terms of observed values and changes from baseline for each visit. In addition, changes from baseline for each visit relative to normal ranges (e.g., shifts from normal to abnormal high/low) will be summarized in shift tables for hematology and serum chemistry.

Listings will flag laboratory values that are outside the normal range, and listings of all abnormal laboratory values will be provided.

9.5. Vital Signs and Weight

The weight and vital sign (HR, systolic and diastolic BP, RR, and body temperature) values and their changes from baseline at each visit will be summarized. At visits when both vital signs and orthostatic standing test are performed, the vital signs (BP and HR) collected after 10 minutes supine and seated from the orthostatic standing test will be used for safety vital signs assessment. Therefore, the summaries will also include body position (supine and seated) as appropriate. The counts and percentages of subjects with vital signs in the following categories will be presented in a vital sign outlier summary. The outliers will be flagged in the listing.

Table 8: Vital Signs Outlier Thresholds

Heart Rate (bpm)	**Systolic Blood Pressure (mmHg)**	**Diastolic Blood Pressure (mmHg)**
<40 >110 >120	<85 >160	<45 >100

9.5.1. Ambulatory Blood Pressure

Ambulatory blood pressure monitoring equipment will be provided to the subjects during the screening visit. Beginning approximately 72 to 24 hours before subjects return to the clinic on Visit 2, and before the Week 1 and Week 3 visits, subjects will put on the 24-hour blood pressure monitoring equipment and initiate the recording. Once the 24-hour session is complete, subjects will remove and return the equipment to the research center during the next visit. During each 24-hour session, the BP monitoring device will be programmed to automatically measure BP every 2 hours beginning at the top of the hour. During each 24-hour session, subjects should also maintain a log of their posture at the time of each BP measurement.

The ABPM time point and body position time point will be matched using a +/- 10 minutes window. Values outside the window will be excluded from analysis by position. If there are multiple position time points within the ABPM time point window, the position closest to the ABPM time will be used. If more than one entry is closest, the earlier entry will be used.

The SBP, DBP, and HR in the supine position from ABPM will be summarized for 24 hour, daytime (8am-4pm), and nighttime (11pm-5am) average by treatment and visit. Assessments in other positions will be listed.

9.6. ECGs

A summary of ECG parameters, including QTcF, PR interval, QT interval, QRS duration, RR, and HR, will be summarized in terms of observed values and change from baseline. The ECG are planned to be collected as triplicates and the average of the measures will be used for the summary.

Outlier Analysis

The number of subjects with absolute ECG values and change from baseline in the ranges shown in Table 9 will be presented in electrocardiogram outlier summary by visit.

In addition, in the same summary, QTcF will also be summarized by the following categories, Normal (males <430, females <450), Borderline (males (≥430, <450); females (≥450, <470)) and Prolonged (males ≥450, females ≥470).

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF ≥ 450 msec if male or ≥ 470 msec if female or an increase > 60 msec will be provided, as necessary.

Investigator Assessment of ECG Readings

The investigator's assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Table 9: ECG Outlier Thresholds

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

9.7. C-SSRS

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation). The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The C-SSRS Baseline/Screening Version will be used at Visit 1 and the C-SSRS Since Last Visit Version will be used at subsequent visits.

Although the Since Last Visit Version of C-SSRS is collected at Visit 2 prior to the 1st dose of the study medication on the following day, it cannot be used as the baseline for C-SSRS assessment. The Baseline/Screening Version of C-SSRS collected at Visit 1 will be used as the baseline. If the Since Last Visit Version of C-SSRS is collected on the same day as the Baseline/Screening Version of C-SSRS, the Since Last Visit Version of C-SSRS doesn't have a valid reference and hence will be excluded from summaries and analyses. But it will be presented in the listing.

The following eleven C-SSRS categories, accepted by FDA as their standard, include five subtypes of suicidal ideation (1-5), five subtypes of suicidal behavior (6-10), and self-injurious behavior without suicidal intent (11). They all have binary responses (yes/no).

1. Wish to be Dead
2. Non-specific Active Suicidal Thoughts

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5. Active Suicidal Ideation with Specific Plan and Intent
6. Preparatory Acts or Behavior
7. Aborted Attempt
8. Interrupted Attempt
9. Actual Attempt (non-fatal)
10. Completed Suicide
11. Self-injurious behavior without suicidal intent

Frequency counts and percentages will be presented for subjects in each C-SSRS category, as well as subjects with any suicidal ideation (1-5), subjects with any suicidal behavior (6-10), and subjects with any suicidal ideation or behavior (1-10), by treatment group at each visit where the items were collected. The summary of the Baseline/Screening Version of C-SSRS will present separately the assessment over the subject's lifetime and during the last 12 months.

10. POTENTIAL IMPACT OF COVID-19

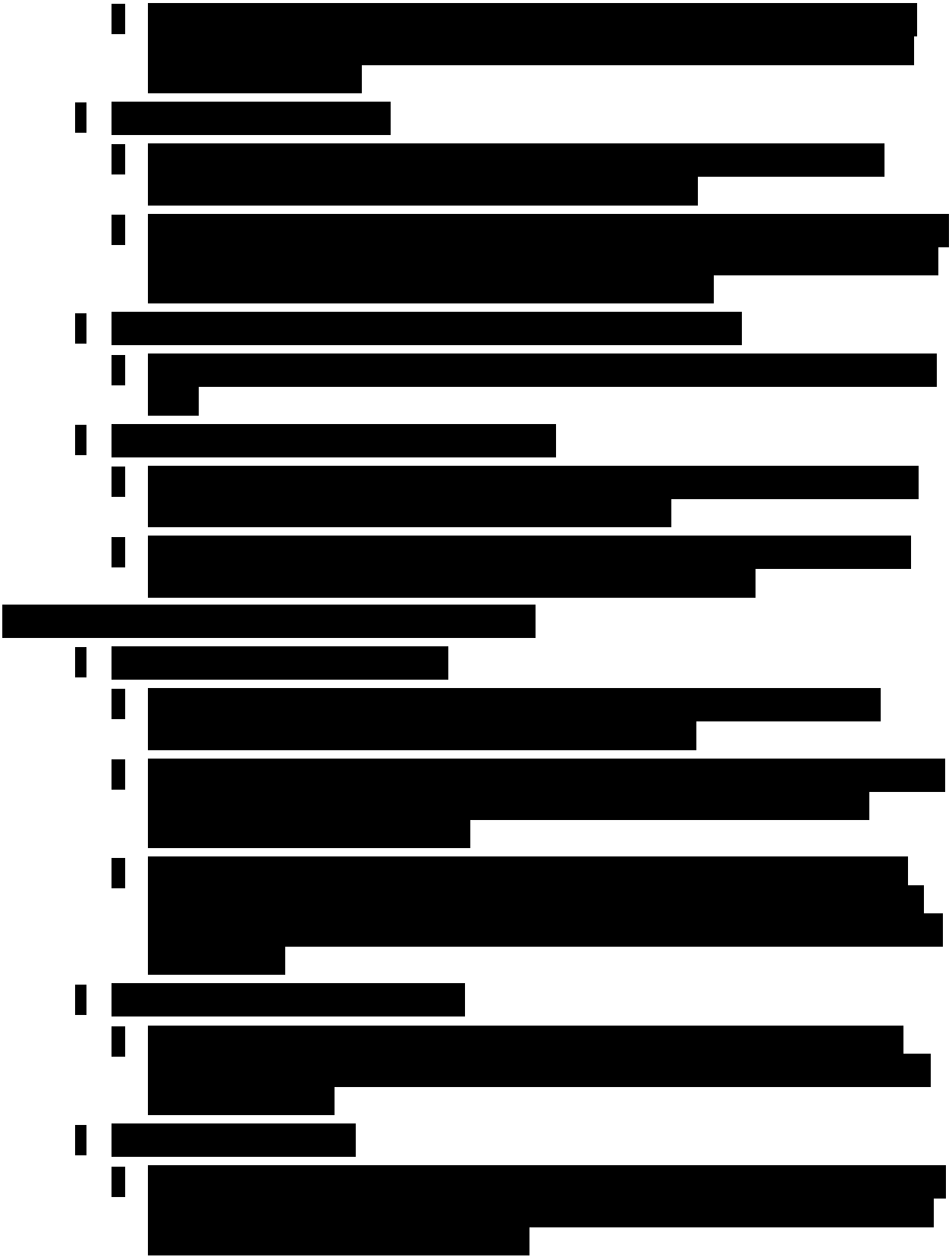
The following additional analyses will be performed to assess the potential impact of COVID-19 on the data collection, extent of missing data, patient population, treatment and/or study discontinuation:

- Subject visits before or after COVID-19 pandemic onset by visit modality
- Separate summaries of demographic and baseline characteristics for subjects randomized before and after COVID-19 pandemic onset
- Separate subject disposition tables for subjects who completed or discontinued treatment before and after COVID-19 pandemic onset
- Subgroup analyses of OHSA#1 using MMRM for subgroups defined by timing of primary endpoint visit relative to COVID-19 pandemic onset (before, on or after)

11. REFERENCES

12. SUPPORTING DOCUMENTATION

12.1.



[redacted]

Laboratory data that are continuous in nature but are less than the lower limit of [redacted]

- [redacted]
- [redacted]