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A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure

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STATISTICAL ANALYSIS PLAN
PHASE 3

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TD-9855

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0170

STUDY TITLE:

A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure

SPONSOR:

Theravance Biopharma Ireland Limited

c/o Theravance Biopharma US, Inc.

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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 Study 0170 Statistical Analysis Plan

A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure

Plan Version: 14 December 2021

Author: [redacted]

Reviewe [redacted]

Reviewer: [redacted]

[redacted]

[redacted]

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1. LIST OF ABBREVIATIONS

Table 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AIC	Akaike's information criterion
ANCOVA	analysis of covariance
BMI	body mass index
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DHPG	dihydroxyphenylglycol
FAS	full analysis set
GCP	Good Clinical Practices
HR	heart rate
IRB	Institutional Review Board
LLN	lower limit of normal
LS	least squares
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MSA	multiple system atrophy
N	sample size
NE	norepinephrine
OL	open label
PAF	pure autonomic failure
PD	Parkinson's disease
PP	per-protocol
SBP	systolic blood pressure
SD	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
ULN	upper limit of normal

Abbreviation	Term
VAS	visual analogue scale
WBC	white blood cell count
WHO	World Health Organization

2. INTRODUCTION

This document gives the plan for the summarization and analysis of clinical data collected in Study 0170 for TD-9855.

[redacted]

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objectives are:

- To evaluate the durability of effect of TD-9855 in subjects with symptomatic neurogenic orthostatic hypotension (snOH) due to multiple system atrophy (MSA), Parkinson's disease (PD), or pure autonomic failure (PAF) compared with placebo over a double-blind, randomized withdrawal period of 6 weeks following an open-label phase of 16 weeks
- To evaluate the safety and tolerability of TD-9855 when taken for up to 22 weeks

3.1.2. Secondary and Other Objectives

The secondary objectives of the study (during the 6-week randomized withdrawal period) are as follows:

- To evaluate the durability of effect of TD-9855 by symptom and activity assessments using Orthostatic Hypotension Symptom Assessment (OHSA) and Orthostatic Hypotension Daily Activity Scale (OHDAS)
- To evaluate subjects' symptomatic improvement as measured by a wearable device

[redacted]

3.2. Study Endpoints

3.2.1. Primary Study Endpoint

The primary study efficacy endpoint is the proportion of treatment failure at Week 6 during the double-blind randomized withdrawal treatment period. Treatment failure is defined as subjects who meet the following criteria at Week 6 following randomization (V9, D155):

Change (worsening) from baseline in OHSA#1 score of at least 1.0 point and worsening of disease severity as assessed by at least 1 point change in PGI-S

The assessments done at the Week 16 (V6, D113) visit in the open-label treatment period prior to randomization are considered baseline for the double-blind randomized withdrawal treatment period of the study. Subjects who withdraw for any reason prior to V9 (D155) or subjects who fail to provide the required assessments at V9 (D155) will be considered as treatment failures.

3.2.2. Secondary Study Endpoints

The secondary endpoints include:

- Change from baseline in OHSA#1 at Week 6 post randomization (V9, D155)
- Change from baseline in OHSA composite score at Week 6 post randomization (V9, D155)
- Change from baseline in OHDAS composite score at Week 6 post randomization (V9, D155)
- Change from baseline in PGI-S at Week 6 post randomization (V9, D155)
- Change from baseline in percentage of time spent in standing position as measured by a wearable device at Week 6 post randomization (V9, D155)
- Change from baseline in average number of steps taken as measured by a wearable device at Week 6 post randomization (V9, D155)

3.2.3. [redacted]

[redacted]

[redacted]

3.2.4. Safety and Tolerability Endpoints

Safety and tolerability endpoints include:

- Physical examination
- Neurological examination
- Vital signs including ambulatory BP
- Resting ECGs
- Clinical laboratory assessments including biochemistry, hematology, urinalysis
- Concomitant medication
- Adverse events (AEs)
- Columbia Suicide Severity Rating Scale (C-SSRS)

4. STUDY DESIGN

4.1. Overview

This is a Phase 3, multi-center, randomized withdrawal study to evaluate the sustained benefit in efficacy and safety of TD-9855 in subjects with primary autonomic failures (MSA, PD, or PAF) and snOH. The following is a summary of the study design. For a full description, refer to the study protocol.

Eligible subjects are either (i) completers of Study 0169 (0169 Completers Group), or (ii) snOH subjects meeting all applicable study inclusion criteria and none of the applicable exclusion criteria (De Novo Group). The principal eligibility criteria for the 0169 Completers Group are as follows:

- Subject has completed 4 weeks of double-blind treatment in Study 0169 (V6) and, in the opinion of the investigator, could benefit from continued treatment with ampreloxetine. No minimum score of OHSA#1 is required to enter V1 of Study 0170.
- Subject had ≥ 80% study medication compliance in Study 0169

For the De Novo Group, the eligibility criteria are the same as for Study 0169. The principal criteria are as follows:

- Subject is male or female and ≥ 30 years old
- Subject meets the diagnostic criteria of symptomatic nOH, as demonstrated by a sustained reduction in BP of ≥ 20 mm Hg (systolic) or ≥ 10 mm Hg (diastolic) within 3 min of being tilted up ≥ 60° from a supine position as determined by a tilt-table test
- Subject must score ≥ 4 on the OHSA#1 at V1
- For subjects with PD only: Subject has a diagnosis of PD according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria (1992)
- For subjects with MSA only: Subject has a diagnosis of possible or probable MSA of the Parkinsonian subtype (MSA-P) or cerebellar subtype (MSA-C) according to The Gilman Criteria (2008)
- For subjects with PAF only: Subject has documented impaired autonomic reflexes, including the Valsalva maneuver performed within 24 months from the date of enrollment
- Subject has plasma norepinephrine levels ≥ 100 pg/mL after being in a seated position for 30 minutes

For the complete lists, refer to the Study 0169 and Study 0170 protocols.

The study has 3 periods: (i) 16-week open-label treatment with TD-9855, (ii) 6-week randomized treatment with blinded TD-9855 or blinded placebo, and (iii) 2-week follow-up (only for patients who do not enroll in Study 0171).

Subjects entering from Study 0169 (0169 Completers Group)

After they sign the informed consent form, subjects will enter Study 0170 Visit 1 (V1), which will be conducted on the same day as V6 of Study 0169. Study 0169 procedures conducted at V6 (Week 4, D29) will serve as the baseline assessments for V1 of Study 0170.

Subjects not participating in Study 0169 (De Novo Group)

Following signing informed consent, subjects will enter a screening period of up to 4 weeks to confirm eligibility. At the Screening visit (Visit S), subjects will provide a comprehensive medical history of their disease and treatments. The subjects' disease will be characterized and documented by the principal investigator (PI) or subinvestigator.

Subjects 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. The presence of snOH must be confirmed using a tilt table test.

Eligible subjects will undergo training of accurate scoring of their sensation of dizziness, lightheadedness, feeling faint or feeling like blacking out, as outlined by Orthostatic Hypotension Symptom Assessment Question 1 (OHSA#1).

Following the screening period, subjects will proceed to V1 to further confirm the additional eligibility criteria prior to proceeding. 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 inclusion criteria and none of the exclusion criteria and whose disease characterization is confirmed by the independent Enrollment Steering Committee (ESC) will receive TD-9855 in the open-label treatment period.

Open-Label Treatment Period (Weeks 1 to 16)

Beginning on Day 2, subjects will receive a single dose of [redacted] and continue thereafter for the 16-week duration of the open-label treatment period. After 16 weeks of treatment, eligible subjects will be randomized to either continue the active treatment or receive placebo for 6 weeks.

Subjects enrolled into the open-label treatment period of the study will return on Day 15, Day 29, and every 4 weeks thereafter for assessments as outlined in the Schedule of Study Procedures. At V3 (Week 4), following the initial 4-week open-label treatment, subjects must show a reduction in OHSA#1 of at least 2 points compared to the baseline value, as determined in Study 0169 for subjects entering from Study 0169 and from V1 for De Novo Group subjects, to continue in Study 0170. Those subjects not meeting this continuation criterion must be discontinued and undergo an end-of-study visit. The end-of-study visit must be completed within 2 weeks from the date of the last dose.

All subjects completing the initial 4-week open-label treatment period and meeting the continuation criterion will continue receiving open-label TD-9855 tablets for 12 more weeks (16 weeks total).

Double-blind Period (Weeks 17 to 22)

Following the completion of 16 weeks of open-label treatment with TD-9855 (V6) subjects will be assessed for randomization. Eligible subjects will be randomized in a 1:1 ratio to receive 6 weeks of double-blind treatment of TD-9855 or placebo once daily. Only subjects with OHSA#1 score ≤ 7 will be eligible for randomization into the double-blind treatment period.

No dose reduction is allowed during either the open-label treatment period or the randomized withdrawal treatment period.

Subjects unable to tolerate [redacted] TD-9855 will be discontinued from the study.

At any time during the study, if a subject meets at least one of the following stopping rules, they should be discontinued and undergo an end-of-study visit:

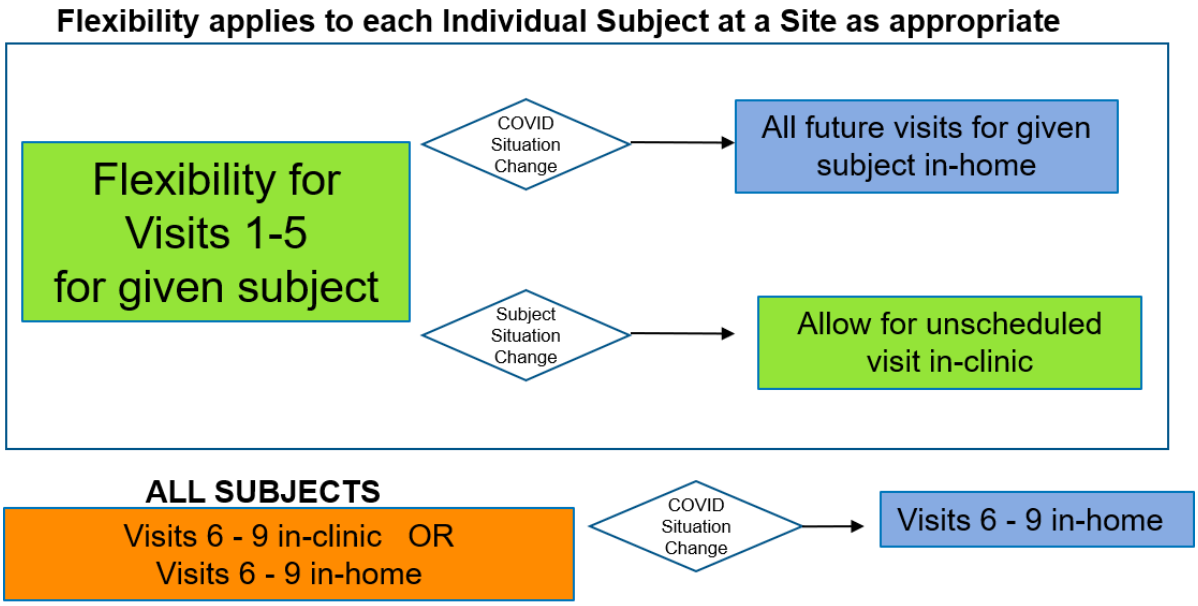
- A determination from the PI that further administration of the investigational product may pose a safety concern to the subject
- Sustained (at least 4 hours) SBP ≥ 180 mmHg or diastolic BP (DBP) ≥ 110 mmHg after 3 min of standing or after 5 min in the sitting position, or a sustained (at least 4 hours) SBP ≥ 180 mmHg or DBP ≥ 110 mmHg measured in the supine state (head/torso elevated at approximately 30° from horizontal position)
- Intolerable adverse event (AE) as determined by the PI
- Subject becomes pregnant

Safety assessments will include a physical examination, neurological examination, vital signs (body temperature, HR, respiratory rate [RR], and BP), body weight, 12-lead electrocardiograms (ECGs), laboratory tests (hematology, chemistry, and urinalysis), Columbia Suicide Severity Rating Scale (C-SSRS), and monitoring of AEs.

Subjects completing the 6-week double-blind treatment period will be eligible to continue into the open-label, long-term safety study (Study 0171). Those subjects who do not complete the 6-week double-blind treatment period or who choose not to continue into Study 0171 will complete the Early Termination Visit (V9) or follow-up visit (V10), respectively. The Early Termination Visit or Follow-Up Visit must be completed 2 weeks from the date of the last dose.

4.1.1. COVID-19 Pandemic

Given the challenges presented by the COVID-19 pandemic, the trial uses an operational design featuring the ability to conduct protocol-required visits as either in clinic or remote visits. Investigators, in discussion with each subject at their site, will be required to choose to conduct study visits either in the clinic or remotely. Sites must conduct the randomized withdrawal visits 6 through 9 (V6/D113 – V9/D155) for a given subject in a consistent manner to reduce the possibility of variability in data collection and reporting. 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 potential impact on both sites and subjects, the sponsor will allow investigators to request exceptions to the selected type of study visit modality for V6/D113 through V9/D155 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 pre-approval from the sponsor. Data collected during these visits may include any protocol-specified assessments which will be captured in the clinical database.

For De Novo subjects who 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 modality is selected by the investigator and subject. For those subjects who are already randomized into the randomized withdrawal part of Study 0170 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 (V6, D113).

4.2. Definition of Study Drugs

Open-label treatment period

All subjects will receive TD-9855 [redacted] starting on Day 2 through the end of the treatment period.

Randomized treatment period

Subjects will be randomized in a 1:1 ratio to receive either TD-9855 (test product) or placebo (reference product) once daily starting in the morning post randomization (Day 2) through the end of the treatment period.

4.3. Sample Size Considerations

[redacted]

4.4. Randomization

Central randomization for treatment allocation was implemented for the randomized withdrawal treatment period. A computer-generated randomization schedule was prepared for this study under the supervision of the sponsor.

Subjects were randomized at Day 113 (Visit 6) in a 1:1 ratio to receive TD-9855 or placebo. The randomization was stratified by disease type (MSA, PD, or PAF). It was not stratified by De Novo status (No, Yes).

4.5. Clinical Assessments

Study Period:	Screening [a] (De Novo Group Only – in clinic)	Open Label Treatment (Visits either in clinic or remote for each subject)					Randomized Withdrawal Period (For each subject, Visits 6 through 9, all either in clinic or remote)				Follow-up[c]
Study Day (Visit):	-28 to -7 (Visit S)	Day 1 (Visit 1)[b]	Day 15 (Visit 2) +/- 3 days	Day 29 (Visit 3) +/- 3 days	Day 57 (Visit 4) +/- 3 days	Day 85 (Visit 5) +/- 3 days	Day 113 (Visit 6) +/- 3 days	Day 127 (Visit 7) +/- 3 days	Day 141 (Visit 8) +/- 3 days	Day 155 (Visit 9) / ET +/- 3 days	Day 169 (Visit 10) +/- 3 days
Procedure											
Informed consent[d]	X	X									
Inclusion /exclusion criteria[d]	X	X[e]									
Medical history (including smoking history)[f]	X										
Concomitant medications (including smoking usage)	X[f]	X[e]	X	X	X	X	X	X	X	X	X
MoCA	X										
OHQ subject training[g]	X	X[e]		X	X	X	X	X	X	X	
OHQ (OHSA and OHDAS)		X[e]		X	X	X	X	X	X	X	
PGI-S		X[e]		X	X	X	X	X	X	X	
C-SSRS	X	X[e]		X	X	X	X	X	X	X	X
Tilt-table test[h]	X										
Randomization[i]							X				
Recommended Order of Procedures (when applicable)											
[redacted]		■			■		■			■	
[redacted]		■			■		■			■	
[redacted]		■			■		■			■	
[redacted]		■			■		■			■	
[redacted]		■			■		■			■	

Study Period:	Screening [a] (De Novo Group Only – in clinic)	Open Label Treatment (Visits either in clinic or remote for each subject)					Randomized Withdrawal Period (For each subject, Visits 6 through 9, all either in clinic or remote)				Follow-up[c]
Study Day (Visit):	-28 to -7 (Visit S)	Day 1 (Visit 1)[b]	Day 15 (Visit 2) +/- 3 days	Day 29 (Visit 3) +/- 3 days	Day 57 (Visit 4) +/- 3 days	Day 85 (Visit 5) +/- 3 days	Day 113 (Visit 6) +/- 3 days	Day 127 (Visit 7) +/- 3 days	Day 141 (Visit 8) +/- 3 days	Day 155 (Visit 9) / ET +/- 3 days	Day 169 (Visit 10) +/- 3 days
[redacted]		■			■		■			■	
[redacted]		■			■		■			■	
[redacted]		■		■	■	■	■	■	■	■	
[redacted]	■	■		■	■	■	■	■	■	■	
Vital signs (BP, HR, RR and body temperature)[l]	X	X[e]	X	X	X	X	X	X	X	X	X
Height (cm)	X										
Weight (kg)	X	X[e]					X			X	X
Physical examination[m]	X	X[e]	X				X			X	
Neurological examination	X	X[e]					X			X	
12-lead electrocardiogram[n]	X	X[e]		X			X			X	
Pregnancy test[o]	X	X[e]					X			X	
Norepinephrine (NE)	X										
Safety laboratory test (chemistry, hematology, and urinalysis)	X	X[e]	X		X		X			X	
[redacted]					■		■	■			
[redacted]		■			■						
ESC (for confirmation of diagnosis)[a]	X										
24-hour ambulatory BP device provision[r]	X	X[e]		X							

Study Period:	Screening [a] (De Novo Group Only – in clinic)	Open Label Treatment (Visits either in clinic or remote for each subject)					Randomized Withdrawal Period (For each subject, Visits 6 through 9, all either in clinic or remote)				Follow-up[c]
Study Day (Visit):	-28 to -7 (Visit S)	Day 1 (Visit 1)[b]	Day 15 (Visit 2) +/- 3 days	Day 29 (Visit 3) +/- 3 days	Day 57 (Visit 4) +/- 3 days	Day 85 (Visit 5) +/- 3 days	Day 113 (Visit 6) +/- 3 days	Day 127 (Visit 7) +/- 3 days	Day 141 (Visit 8) +/- 3 days	Day 155 (Visit 9) / ET +/- 3 days	Day 169 (Visit 10) +/- 3 days
24-hour ambulatory BP device collection[r]		X[e]	X		X						
Wearable device provision/collection[s]	X	X[e]		X	X	X	X	X	X	X	
Incidence of Falls and ABPM position Diaries	X	X[e]	X	X	X	X	X	X	X	X	
Dosing and Midodrine rescue medication Diaries		X[e]	X	X	X	X	X	X	X	X	
Adverse events	X	X[e]	X	X	X	X	X	X	X	X	X
Dispense study medication		X[e]									
Study medication dosing[t]		X									
Collect, review, and dispense study medication				X	X	X	X	X	X		
Collect and review study medication										X	
Valsalva maneuver[u]	X										

Abbreviations: [redacted]; BP: Blood Pressure; [redacted] C-SSRS: Columbia Suicide Severity Rating Scale; ESC: Enrollment Steering Committee; ET: Early Termed; [redacted]; HR: Heart Rate; MoCA: Montreal Cognitive Assessment; MSA: Multiple System Atrophy; [redacted]; OHDAS: Orthostatic Hypotension Daily Activity Scale; OHSA: Orthostatic Hypotension Symptom Assessment; OHQ: Orthostatic Hypotension Questionnaire; OL: Open Label; PAF: Pure Autonomic Failure; PD: Parkinson's Disease; [redacted] PGI-S: Patient Global Impression of Severity; RTSM: Randomization and trial supply management; RR: Respiratory Rate; UMSARS; [redacted]

a. [redacted] Subject eligibility will be assessed by the investigator during screening and primary diagnosis will be verified by the ESC prior to Day 1 (for De Novo Group subjects only); subjects meeting OHSA#1 criterion on Day 1 and who otherwise meet eligibility criteria may be enrolled via RTSM.
b. For 0169 Completers Group, Study 0169 procedures conducted at D29 will serve as the baseline assessments for D1 of Study 0170.

c. Follow-up visit is only applicable for those subjects that do not proceed to Study 0171 and will be completed two weeks from the date of the last dose. Those subjects proceeding to Study 0171 will enter from V9.
d. The De Novo Group subjects would sign the consent before screening; thus screening visit is only applicable for De Novo Group subjects, and the 0169 Completers Group would sign the consent before V1 and would start with Day 1 of Study 0170.
e. The assessments or procedures will be performed within 24 hours prior to subject taking the study medication (predose). Following completion of study assessments, the subjects will take study medication on Day 2 in the morning.
f. A complete medical and medication history evaluation will be performed during screening (for De Novo subjects only).
g. [redacted], subjects will receive thorough training on the OHQ disease instrument and will receive refresher training prior to completing the OHQ during each applicable study visit that occurs during treatment with study medication. Subjects should be rested prior to beginning the training.
h. 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.
i. Subjects will be randomized via RTSM once they meet the randomization criteria
j. [redacted]
k. 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 90 minutes prior to this assessment.
l. 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.
m. A full physical examination at the Screening visit will be performed (for De Novo subjects only). Subsequent physical examinations, per discretion of the investigator, can be abbreviated and symptomatic.
n. 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. The total time to conduct ECGs ideally would not exceed 15 minutes.
o. 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.
p. Blood samples will be collected for TD-9855 PK on the days specified. All PK sampling times will be accurately recorded by collection date, hour, and minute. Study medication dosing time on the day before each PK collection and on the day of each PK collection will be accurately recorded by dosing date, hour, and minute by the study staff using time recorded in Dosing Diary by Subjects.
q. Blood samples for pharmacodynamic markers (norepinephrine (NE) and dihydroxyphenylglycol (DHPG)), will be collected after the subject has been seated for 30 minutes. Blood sample for NE will be collected at screening (for De Novo Group subjects only) while samples for both NE and DHPG will be collected on Day 1 and Day 57. Note that all pharmacodynamic marker samples should be collected at approximately (±1 hour) the same time of day on Day 1 and Day 57 so that time-matched analysis can be performed.
r. Ambulatory blood pressure monitoring (ABPM) equipment will be provided to the De Novo Group subjects during the screening visit and on Day 1 to 0169 Completers Group. Beginning approximately 72 to 24-hours before a subject returns to the clinic for 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 will also log their posture in the ABPM Position Diary at the time of each

blood pressure measurement. Details regarding the ambulatory monitoring will be provided in a separate manual. The assessment on D1 is only for De Novo Group subjects.

s. For wearables, in countries where the wearable devices are available, 2 consecutive days of device usage will be required on the days shown. The 2 consecutive days of device usage should take place within 5 days before the subsequent visit. Site coordinators will monitor subject compliance. If the site coordinator becomes aware that a subject has not performed the required device usage, they will contact the subject and remind them to use the device.
t. Study medication will be ingested orally without regard to food at approximately the same time each morning and taken with approximately 8 ounces of water. The exact time and day of dosing will be recorded by the subject in the Dosing Diary on the mornings of study visits.
During their scheduled visits, subjects should be reminded to maintain an adequate fluid intake. For OL treatment period, subjects would start taking medications starting on Day 2.
u. 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. [redacted]

6. CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

All data from both scheduled and unscheduled visits will be presented in data listings.

However, unless noted otherwise, only data from visits (scheduled or unscheduled) that fall within analysis windows will be included in summaries, statistical analyses, and calculation of derived variables. [redacted] 5.

Analyses and tabulations will be prepared [redacted]

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

6.1. Columns

Separate summaries will be provided for the open-label treatment period and the randomized withdrawal treatment period. For the open-label treatment period, summary tables will include the following columns:

- Placebo Study 0169 Completers ("0169 Placebo Rollover")
- Ampreloxetine Study 0169 Completers ("0169 Amp Rollover")
- De Novo Subjects ("De Novo")
- All Subjects ("Total")

For the randomized withdrawal treatment period, summary tables will include the following columns:

- Placebo ("Placebo")
- Ampreloxetine ("TD-9855 10mg")
- All Subjects (required only for study population and compliance summaries) ("Total")

6.2. Analysis Sets

6.2.1. [redacted]

[redacted]

6.2.2. Enrolled Analysis Set

The enrolled analysis set comprises all subjects who were enrolled into the open-label treatment period.

6.2.3. Randomized Analysis Set

The randomized analysis set comprises all subjects who were randomized into the randomized withdrawal treatment period.

6.2.4. Full Analysis Set (FAS) – OL and Safety Analysis Set – OL

The FAS and safety analysis set for the open-label treatment period are identical and comprise all enrolled subjects who received at least 1 dose of TD-9855 during the period.

6.2.5. FAS – Randomized Withdrawal and Safety Analysis Set – Randomized Withdrawal

The FAS and safety analysis set for the randomized withdrawal treatment period are identical and comprise all randomized subjects who received at least 1 dose of study medication (TD-9855 or placebo) following randomization.

6.2.6. Subject Grouping for FAS vs. Safety Analysis Set Summaries

Although the FAS and safety analysis sets for each of the 2 treatment periods are identical, subject grouping for randomized withdrawal period analysis may differ. For safety analysis set analyses, subjects will be grouped according to the study treatments they received. For FAS analyses, subjects will be grouped according to the study treatments they were randomized to receive.

6.2.7. Per-Protocol (PP) Analysis Set – Randomized Withdrawal

A PP analysis set is defined for the randomized withdrawal treatment period, and comprises all subjects in the FAS – Randomized Withdrawal analysis set except those who meet any of the following criteria:

- Received wrong treatment during the randomized withdrawal treatment period
- Study medication compliance < 80% over the interval from first to last dose of the randomized withdrawal treatment period
- Did not meet certain efficacy-related inclusion criteria, specifically:
  - Inclusion criterion 4 for De Novo subjects (Subject must meet the diagnostic criteria of nOH, as demonstrated by a sustained reduction in BP of ≥ 20 mmHg (systolic) or ≥ 10 mmHg (diastolic) within 3 min of being tilted up ≥ 60^{o} from a supine position as determined by a tilt-table test.)
  - Inclusion criterion 5 for De Novo subjects (Subject must score at least a 4 on the OHSA#1 at V1.)

  - Continuation Criterion (At V3 / Week 4, following the initial 4-week open-label treatment, subjects must show a reduction in OHSA#1 of at least 2 points compared to the baseline value, as determined in Study 0169 for subjects entering from Study 0169 and from V1 for De Novo subjects, to continue in Study 0170.)
  - Randomization Criterion for randomized withdrawal treatment period (Subject has OHSA#1 score of ≤ 7.)
- Used efficacy-related prohibited concomitant medications during the randomized withdrawal treatment period

6.2.8. Subgroups

To assess consistency of treatment effect across subgroups, the following subgroups will be examined:

- Disease type: MSA, PD, and PAF
- Gender: Male and Female
- Baseline NE: < 200 pg/mL and ≥ 200 pg/mL

The disease type and gender subgroups were specified in the protocol. Smoking status subgroups were also specified in the protocol, but too few current smokers were enrolled to warrant summaries by smoking status. The dichotomized baseline NE subgroups were added because a post hoc analysis of Study 0169 indicated that for some endpoints the effect of TD-9855 on the endpoint may vary with baseline norepinephrine level. For both open-label treatment period and randomized withdrawal treatment period summaries, these subgroups will be defined using the open-label NE baseline value (Section 6.3.1). COVID-19 pandemic onset subgroups (COVID-19 pandemic onset: subjects whose week 22 visit occurred before 18MAR2020 and subjects whose week 22 visit occurred on or after 18MAR2020) were added to explore pandemic effects on data collection and subjects' daily activities and later dropped because not enough week 22 visits (only 7) occurred before 18MAR2020.

6.3. Baseline Definition

For the open-label treatment period of the study, the baseline is the Study 0169 V6 (Week 4) assessment for subjects entering from Study 0169 and the V1 assessment for De Novo subjects. If a V1 assessment was not obtained for De Novo subjects, the latest earlier assessment will be used.

The assessments obtained at the Week 16 (V6, D113) visit in the open-label treatment period prior to randomization are considered the baseline assessments for the randomized withdrawal treatment period of the study.

Two variables have special baseline definitions, norepinephrine and smoking status. Details are given in the following sections.

6.3.1. Norepinephrine (NE)

For De Novo subjects, NE was collected during screening to confirm eligibility to enroll in Study 0170. Subjects were required to have a resting seated value ≥ 100 pg/mL. For pharmacodynamic analyses, NE blood samples were to be collected for all subjects on Day 1 and Day 57. These pharmacodynamic samples were to be collected after the subject had been seated for 30 minutes and were to be collected at approximately the same time of day on Day 1 and Day 57.

Baseline NE for the open-label period was defined as follows:

- For subjects rolling over from Study 0169, the Study 0169 baseline result, which was the last NE result obtained before the first dose of study medication in Study 0169
- For De Novo subjects, the last NE result obtained before the first dose of study medication in Study 0170 (i.e., the screening result)

Baseline NE for the randomized withdrawal treatment period was defined as the last NE result obtained after the first dose of open-label study medication in Study 0170 and before the first dose of randomized study medication (i.e., as the Day 57 result).

6.3.2. Smoking Status

Baseline smoking status (never, former, and current) for the randomized withdrawal treatment period is determined from the baseline smoking status of the open-label treatment period and tobacco use during the randomized withdrawal treatment period. A ‘current’ smoker becomes a ‘former’ smoker if the subject indicates a change in tobacco use at the start of the open-label treatment period and does not consume any tobacco products during the open-label treatment period. Conversely, a ‘never’ or ‘former’ smoker becomes a ‘current’ smoker if the subject indicates a change in tobacco use and reports consuming a tobacco product at any visit of the open-label treatment period.

6.4. Variables

6.4.1. Study Day

If the date of interest occurs on or after the date of first dose (first dose of the open-label treatment period), Study Day will be calculated as (date of interest – date of first dose) + 1.

If the date of interest occurs before the date of first dose, Study Day will be calculated as (date of interest – date of first dose).

The analysis dataset variable “Analysis Study Day” is defined in the Visit Windows Section (6.4.5).

6.4.2. Age

Only year of birth is captured in the clinical database. Hence, for analysis purposes, each subject’s age at enrollment into Study 0170 will be their age in integer years as reported by the site.

6.4.3. Change from Baseline

Change from baseline is calculated as postbaseline result – baseline result. If either the baseline or the postbaseline result is missing, change values are treated as missing.

6.4.4. BMI (Body Mass Index)

BMI is calculated as:

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

6.4.5. OHSA#1

For each of the 6 questions in the Orthostatic Hypotension Symptom Assessment (Section 8.8.1), respondents are asked to rate the average severity of their symptoms over the past week on an ordinal scale from 0 to 10. The text of question 1 is shown below:

OHSA#1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out												
NONE	0	1	2	3	4	5	6	7	8	9	10	WORST POSSIBLE

Subjects who complete the Week 4 visit during the open-label treatment period must have shown a Week 4 OHSA#1 decrease of at least 2 points to be eligible to continue open-label ampreloxetine treatment. For Study 0169 completers, this means a decrease from their Study 0169 baseline rating; for De Novo subjects, a decrease from their V1 rating. Subjects who complete the Week 16 visit at the end of the open-label treatment period must have a Week 16 (V6, D113) OHSA#1 rating of 7 or lower to be eligible to begin the randomized withdrawal treatment period.

Worsening in OHSA#1 During the Randomized Withdrawal Treatment Period

Worsening in OHSA#1 will be defined only for subjects with a baseline score < 10, as an increase from the baseline score. (Per protocol, all subjects should have a baseline score ≤ 7.) Worsening rates at postbaseline visits will be summarized in 2 ways: 1) including only subjects for whom a score was recorded, and 2) counting subjects for whom no score was recorded as having worsened.

6.4.6. Patient's Global Impression of Severity (PGI-S)

PGI-S is an ordinal scale which asks respondents to select the choice that best describes the current severity of symptoms of their neurogenic orthostatic hypotension. The recall period is the past week. Two versions were used in this study: a 7-point version initially and later a 5-point version. For analyses, any PGI-S scores recorded using the 7-point scale will be mapped to the 5-point scale as shown in Table 2.

Table 2: PGI-S Mapping From 7-Point to 5-Point Scale

7-Point Scale	5-Point Scale
Normal, not at all ill (1)	None (1)
Borderline ill (2)	Mild (2)
Mildly ill (3)	
Moderately ill (4)	Moderate (3)
Markedly ill (5)	Severe (4)
Severely ill (6)	
Extremely ill (7)	Very severe (5)

Listings will show the 5-point scale responses for all subjects and the 7-point scale responses for subjects who used that scale.

Worsening in PGI-S During the Randomized Withdrawal Treatment Period

Worsening in PGI-S will be defined only for subjects with a baseline score < 5, as an increase from the baseline score. Worsening rates at postbaseline visits will be summarized in 2 ways: 1) including only subjects for whom a score was recorded, and 2) counting subjects for whom no score was recorded as having worsened. Both types of summaries will exclude subjects with a baseline score of 5.

6.4.7. Treatment Failure

Treatment failure is defined as meeting the following criteria at Week 6 following randomization:

> Change (worsening) from baseline in OHSA#1 score of at least 1 point and worsening of disease severity as indicated by at least a 1-point change from baseline in PGI-S

The assessments done at the Week 16 visit in the open-label treatment period prior to randomization are considered baseline for the randomized withdrawal treatment period. Subjects who withdraw for any reason prior to Week 22 or fail to provide assessments at Week 22 will be counted as treatment failures, including subjects whose randomized withdrawal treatment period study disposition is reported as "Study Terminated by Sponsor." Subjects with a baseline score for either OHSA#1 or PGI-S which cannot worsen (e.g., a baseline PGI-S score of 5) will be counted as treatment failures if the other score is worse at Week 22 (or was not obtained).

6.4.8. Percentage of Time Spent in Standing Position and Other Wearable Device Variables

Positions while wearing the recording device were categorized as follows:

- Lying down
- Sitting
- Standing (including walking)

The percentage of time spent walking was also captured.

To obtain percentage of time spent in standing position and the other wearable device variables, subjects were asked to wear their devices for at least 2 consecutive days within the 5 days before each visit at which device data were to be obtained.

Because of rounding, sums of percentages across positions may exceed 100%.

6.5. Visit Windows

All assessments will be summarized using analysis windows. The term "out of window" will be applied to assessments that are outside an analysis window, regardless of the visit label associated with the assessments in the EDC system.

In this study, analysis windows will be defined separately for visits during the open-label treatment period and the randomized withdrawal treatment period of the study, according to the protocol-specified visit schedule. The nominal day 1 is the date of first dose of the open-label treatment, the other nominal visits during the open-label treatment period will be determined based on the days from the start of open-label dosing. The nominal day 113 is date of first dose of the randomized treatment, the other nominal visits during the randomized withdrawal treatment period will be determined based on the days from the first randomized dose date. Generally, the analysis window will be defined using the middle points between the consecutive visits (Table 3).

For De Novo subjects, both the Baseline/Screening Version and the Since Last Visit Version of the C-SSRS are collected prior to the 1st open-label dose of the study medication. The Baseline/Screening Version of the C-SSRS collected at Screening will be used as the baseline. There will be no specific analysis window for the Since Last Visit Version of the C-SSRS collected at Visit 1/Day 1; the data will be included in the summary unless the Since Last Visit Version of the C-SSRS is collected on the same day as the Baseline/Screening Version of the C-SSRS.

The following visit windows will be used in the summary of clinical data:

Table 3: Analysis Visit Windows

Nominal Period	Start (days)	Stop (days)
Vital signs (BP, HR, RR, and body temperature)		
OL Baseline	Last result prior to first dose in OL Period	
Week 2 (Day 14)	2	20
Week 4 (Day 28)	21	41
Week 8 (Day 56)	42	69
Week 12 (Day 84)	70	97
Week 16 (Day 112)	98	First Dose in RW Period [1]
RW Baseline	Last result prior to First Dose in RW Period [1]	
First Dose Day in RW Period (DD)		
Week 18 (Day 126) (DD+13)	First Dose in RW Period [1]	DD+20
Week 20 (Day 140) (DD+27)	DD+21	DD+34
Week 22 (Day 154) (DD+41)	DD+35	EOS
OHQ (OHSA and OHDAS), [redacted] C-SSRS, PGI-S, Wearable device provision/collection, Orthostatic standing test		
OL Baseline	Last result prior to first dose in OL Period	
Week 4 (Day 28)	2	41
Week 8 (Day 56)	42	69
Week 12 (Day 84)	70	97
Week 16 (Day 112)	98	First Dose in RW Period [1]
RW Baseline	Last result prior to First Dose in RW Period [1]	
First Dose Day in RW Period (DD)		
Week 18 (Day 126) (DD+13)	First Dose in RW Period [1]	DD+20
Week 20 (Day 140) (DD+27)	DD+21	DD+34

Week 22 (Day 154) (DD+41)	DD+35	EOS
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
Safety laboratory test results (chemistry, hematology, and urinalysis)		
OL Baseline	Last result prior to first dose in OL Period	
Week 2 (Day 14)	2	34
Week 8 (Day 56)	35	83
Week 16 (Day 112)	84	First Dose in RW Period [1]
RW Baseline	Last result prior to First Dose in RW Period [1]	
First Dose Day in RW Period (DD)		
Week 22 (Day 154) (DD+41)	First Dose in RW Period [1]	EOS
ECGs		
OL Baseline	Last result prior to first dose in OL Period	
Week 4 Day 28	2	71
Week 16 (Day 112)	72	First Dose in RW Period [1]
RW Baseline	Last result prior to First Dose in RW Period [1]	
First Dose Day in RW Period (DD)		
Week 22 (Day 154) (DD+41)	First Dose in RW Period [1]	EOS

ABPM (collected in OL period only)		
Open-Label Baseline	Last results collected prior to first dose in OL Period	
Week 2 (Day 14)	2	23
Week 8 (Day 56)	24	OL Disposition Date

[1] First dose in RW period: When both a date and time are available for the first dose in the RW period and the assessment of interest, dates and times are used to determine the end of Analysis Week 16 (Day 112) and the beginning of the first applicable analysis week in the RW period, e.g. Analysis Week 18 (Day 126): An assessment is assigned to Analysis Week 16 (Day 112) if its date and time are prior to the date and time of the first dose in the RW period, and it is assigned to the first applicable analysis week in the RW period, e.g. Analysis Week 18 (Day 126) if it is on/after the date and time of the first dose in the RW period.
If only the date of the first dose in the RW period and/or the assessment of interest is available, dates are used to determine the end of Analysis Week 16 (Day 112) and the beginning of the first applicable analysis week in the RW period, e.g., Analysis Week 18 (Day 26): In this case, an assessment with a date prior to or on the date of first dose in the RW period is assigned to Analysis Week 12 (Day 112), and it is assigned to Week 18 (Day 126) if it is after the date of first dose in the RW period. In other words, if a subject took their first RW dose on the same day as their Visit 6 Day 113 visit, it is assumed that all assessments were done prior to the subject taking that first RW dose.

Nominal Period	Start (days)	Stop (days)
Vital signs (BP, HR, RR, and body temperature), incidence of Falls and ABPM position Diaries		
Open-Label Baseline		
Week 2 (Day 14)	2	20
Week 4 (Day 28)	21	41
Week 8 (Day 56)	42	69
Week 12 (Day 84)	70	97
Week 16 (Day 112)	**98**	**Last day prior to randomization**
RW Baseline **First dose date in RW (DD)**		
Week 18 (DD+13)	DD	DD+20
Week 20 (RD+27)	DD+21	DD+34
Week 22 (RD+41)	DD+35	EOT
OHQ (OHSA and OHDAS), [redacted], C-SSRS, PGI-S, Wearable device provision/collection, Orthostatic standing test		
Open-Label Baseline		
Week 4 (Day 28)	2	41
Week 8 (Day 56)	42	69
Week 12 (Day 84)	70	97
Week 16 (Day 112)	98	Last day prior to randomization
Randomized Withdrawal Baseline First dose date in RW (DD)		
Week 18 (DD+13)	DD	DD+20
Week 20 (RD+27)	DD+21	DD+34
Week 22 (RD+41)	DD+35	EOT
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
Safety laboratory test (chemistry, hematology, and urinalysis)		

Nominal Period	Start (days)	Stop (days)
Vital signs (BP, HR, RR, and body temperature), incidence of Falls and ABPM position Diaries		
Open-Label Baseline		
Week 2 (Day 14)	2	20
Week 4 (Day 28)	21	41
Week 8 (Day 56)	42	69
Week 12 (Day 84)	70	97
Week 16 (Day 112)	**98**	**Last day prior to randomization**
RW Baseline **First dose date in RW (DD)**		
Week 18 (DD+13)	DD	DD+20
Week 20 (RD+27)	DD+21	DD+34
Week 22 (RD+41)	DD+35	EOT
OHQ (OHSA and OHDAS), [redacted]s, C-SSRS, PGI-S, Wearable device provision/collection, Orthostatic standing test		
Open-Label Baseline		
Week 4 (Day 28)	2	41
Week 8 (Day 56)	42	69
Week 12 (Day 84)	70	97
Week 16 (Day 112)	98	Last day prior to randomization
Randomized Withdrawal Baseline First dose date in RW (DD)		
Week 18 (DD+13)	DD	DD+20
Week 20 (RD+27)	DD+21	DD+34
Week 22 (RD+41)	DD+35	EOT
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

6.5.1. Multiple Assessments

In general, if multiple valid observations exist at a visit or collection time point, the record to be included in the summary and analyses will be chosen based on the following:

- The record closest to the nominal time

If 2 records are equidistant or distance cannot be determined:

- The later record

If 2 or more records with same date/time:

- Average (generally applies to assessments done in triplicate)

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.

7.2. Subject Disposition

For the open-label treatment period, the subject disposition summary will be based on the enrolled analysis set and will include counts and percentages of subjects who:

- Enrolled
- Enrolled and were treated with study treatment
- Completed the open-label treatment period
- Did not complete the open-label treatment period, overall and by the reason for not completing it: adverse event, lost to follow-up, physician decision, pregnancy, protocol violation, study terminated by sponsor, withdrawal by subject, failure to meet open-label continuation requirement at Visit 3 (Day 29), or other
- Continued to the randomized withdrawal treatment period
- Did not continue to the randomized withdrawal treatment period

For the randomized withdrawal treatment period, the subject disposition summary will be based on the randomized analysis set and will include counts and percentages of subjects who:

- Were randomized
- Were randomized and treated with study treatment
- Completed the randomized withdrawal treatment period
- Did not complete the randomized withdrawal treatment period, overall and by the reason for not completing it: adverse event, lost to follow-up, physician decision, pregnancy, protocol violation, study terminated by sponsor, withdrawal by subject, or other
- Completed the study
- Did not complete the study
- Continued to Study 0171
- Did not continue to Study 0171

Listings of subject disposition (one for the open-label treatment period and one for the randomized withdrawal treatment period) will include the date the informed consent form was signed, dates of first dose and last dose of study drug, primary reason for discontinuation of study treatment, study completion status, and primary reason for study termination.

7.3. Protocol Deviations

Summaries of major protocol deviations will include counts and percentages of subjects who have any major protocol deviations and counts and percentages of subjects who have major protocol deviations in each category. A by-subject listing of all protocol deviations will be provided.

7.4. Medical History and Medical Conditions Present at Entry

Medical history will be mapped according to [redacted] and summarized by system organ class and preferred term.

7.5. Demographic and Baseline Characteristics

Summaries of demographic and baseline characteristics will include the following: 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 Composite Score, 10 min Supine SBP (mmHg), 10 min Seated SBP (mmHg), 3 min Standing SBP (mmHg), and NE (pg/mL).

For the open-label treatment period, this summary will be presented for the open-label safety analysis set. For the randomized withdrawal treatment period, this summary will be presented for the randomized withdrawal FAS.

8. EFFICACY

8.1. General Considerations

The efficacy data collected in the open-label treatment period will be summarized descriptively.

Nominal p-values will be provided as appropriate for randomized withdrawal treatment period efficacy data analyses.

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

The primary efficacy endpoint is the proportion of treatment failure at Week 6, the end of the randomized withdrawal treatment period.

The null hypothesis is that there is no difference between the proportion of treatment failure in subjects receiving TD-9855 (P_{active}) and the proportion of treatment failure in subjects receiving placebo ($P_{placebo}$) at Week 6 during the randomized withdrawal treatment period. The alternative hypothesis is that they differ:

$$H_0 : P_{Active} = P_{placebo}$$
$$H_1 : P_{Active} \neq P_{placebo}$$

8.3. Subgroup Analyses

Subgroup analyses will characterize the consistency of the treatment effect across the specified subgroups (Section 6.2.8).

8.4. Analysis of the Primary Efficacy Endpoint

8.4.1. Primary Efficacy Analysis

A logistic regression model will be fitted to estimate the effect of treatment on the primary endpoint. The model will include terms for treatment and baseline disease type (MSA, PAF, PD) and will include baseline OHSA#1 score and baseline PGI-S as continuous covariates. (Including baseline OHSA#1 and baseline PGI-S as continuous covariates models the effect of a 1-point increase in baseline score as multiplying the odds of failure by the same constant, regardless of the score.) Point estimates and 95% CIs for odds ratios will be presented. Also presented will be "least squares" treatment failure proportions (point estimates and standard errors) for each treatment and disease type.

In addition, the proportions of subjects with at least a 1-point worsening in OHSA#1 and at least a 1-point worsening in PGI-S will be summarized separately by postbaseline visit, and stratified (by baseline score) Cochran-Mantel-Haenszel test p-values for testing equality of TD-9855 and placebo worsening rates and mean scores at each postbaseline visit will be included. A 2 × 2 table showing concordance (OHSA#1 worsening status (Yes/No) by PGI-S worsening status (Yes/No)) at Week 6, with Cohen's kappa measure of agreement statistics, will also be provided.

A listing by treatment group for all FAS subjects will be provided, to include subject ID, baseline disease type (MSA, PAF, PD), baseline OHSA#1 score, baseline PGI-S score, change from baseline OHSA#1 score at Week 22, change from baseline PGI-S score at Week 22, and treatment failure status (Yes/No).

Additional Analyses of the Primary Efficacy Endpoint

PP Analysis

The primary efficacy analysis will be repeated for the PP analysis set.

Missing Data Handling

For the primary efficacy analysis, subjects who did not complete the Week 6 visit because the study was terminated early by the sponsor are counted as treatment failures, like all other subjects who failed to complete the randomized withdrawal period. The primary efficacy analysis will be repeated excluding these subjects.

Subgroup Analyses

To assess consistency of treatment failure TD-9855:placebo odds ratios across subgroups, the analysis of the primary endpoint will be repeated for each of the subgroups specified in Section 6.2.8.

A forest plot will be provided showing the TD-9855:placebo odds ratio point estimates and 95% CIs for each subgroup.

8.5. Analysis of Secondary Efficacy Endpoints

The assessments associated with the secondary efficacy endpoints for this study are conducted at multiple time points during the randomized withdrawal period: Visit 6 (Day 113, baseline), Visit 7 (Day 127), Visit 8 (Day 141), and Visit 9 (Day 155). Hence, a mixed effects model for repeated measures (MMRM) will be fitted to analyze the secondary efficacy endpoints that have data available:

- OHSA#1
- OHSA composite score
- OHDAS composite score
- PGI-S
- Percentage of time spent in standing position (including walking) while wearing the device
- Average number of steps taken per hour while wearing the device

The change from baseline (or equivalently the postbaseline value) will be used as the dependent variable in the model. The model will include terms for treatment, disease type (MSA, PD, PAF), visit, and treatment by visit interactions, and the baseline value of the endpoint as a continuous covariate. Within-subject correlation will be modelled using an unstructured variance-covariance matrix. The Kenward and Roger method for approximating the denominator degrees of freedom will be used. Missing endpoint values will be assumed to be missing at random (MAR). If the

model does not 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.

LS mean change for each treatment group and the difference in the LS mean change between treatment groups with respect to the secondary endpoint analyzed will be estimated by fitting the MMRM model. Standard errors, 95% confidence intervals, and p-values will be provided.

Subgroup Analyses

To assess consistency of treatment differences across subgroups, the analysis of the secondary endpoints will be repeated for each of the subgroups specified in Section 6.2.8.

8.6. Multiple Testing Plan

If the primary endpoint is met, i.e., the TD-9855 vs. placebo odds of treatment failure at Week 6 post randomization (V9, D155) point estimate is < 1 and the 2-sided p-value is < 0.05, secondary efficacy endpoints will be tested in the sequence shown below until the first failure to reject a null hypothesis occurs.

1. Change from baseline in OHSA#1 at Week 6 post randomization (V9, D155)
2. Change from baseline in OHSA composite score at Week 6 post randomization (V9, D155)
3. Change from baseline in OHDAS composite score at Week 6 post randomization (V9, D155)
4. Change from baseline in PGI-S at Week 6 post randomization (V9, D155)
5. Change from baseline in percentage of time spent in standing position (including walking) as measured by a wearable device at Week 6 post randomization (V9, D155)
6. Change from baseline in average number of steps taken as measured by a wearable device at Week 6 post randomization (V9, D155)

This controls the familywise type 1 error rate at 0.05.

For all other analyses, there will be no adjustments for multiplicity.

8.7. [redacted]

8.7.1. Falls

Falls and near-falls are the only count-data exploratory endpoints. They will be summarized descriptively, by showing counts and percentages of subjects with at least 1 fall during each treatment period and by showing counts and percentages of subjects with at least 1 fall or near-fall during each treatment period. In addition, for falls and for falls + near-falls, the following categorical summaries with counts and percentages will be provided:

- None
- 1
- 2
- 3 or more

For the randomized withdrawal treatment period, these summaries will also be provided for the 3 disease type subgroups, and the MSA subgroup summary will adjust for a measure of motor function, UMSARS Part II score, by presenting counts and percentages both overall and by dichotomized score subgroup: ≤ 22 (the median baseline score) and ≥ 23. The PD subgroup summary was also to be adjusted for a measure of motor function, Modified Hoehn and Yahr Stage (Table 4). This was not necessary, however, since the reported stage was 1 for almost all of the PD subjects who entered the randomized withdrawal treatment period.

Table 4. Modified Hoehn and Yahr Staging

Stage	Modified Hoehn and Yahr Scale
1	Unilateral involvement only
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

8.8. Scoring of Clinical Outcome Assessments

8.8.1. Orthostatic Hypotension Questionnaire (OHQ))

The OHQ has 2 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. The recall period is "over the past week."

The OHSA has 6 questions, each rating the intensity of one characteristic symptom of NOH:

7. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
8. Problems with vision (blurring, seeing spots, tunnel vision, etc.)
9. Generalized weakness
10. Fatigue
11. Trouble concentrating
12. Head/neck discomfort

The OHDAS has 4 questions that assess the impact of NOH symptoms on daily activities. The responses are scored from 0 to 10, with 0 indicating no symptoms/no interference and 10 indicating the worst possible symptoms/complete interference. Respondents may select "cannot be done for other reasons," which will be treated as a missing response when scores are calculated.

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

½ × (Sum of non-missing OHSA item scores / Number of non-missing OHSA items + Sum of non-missing OHDAS item scores / Number of non-missing OHDAS items)

The calculated OHSA and OHDAS composite scores and OHQ overall composite score will be rounded to 1 decimal place.

[redacted]

Table 5. Schwab and England ADL Scale

100% = Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty. 90% = Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty. 80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness. 70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores. 60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible. 50% = More dependent. Help with half, slower, etc. Difficulty with everything. 40% = Very dependent. Can assist with all chores, but do few alone. 30% = With effort, now and then does a few chores alone or begins alone. Much help needed. 20% = Nothing alone. Can be a slight help with some chores. Severe invalid. 10% = Totally dependent, helpless. Complete invalid. 0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

A medical professional who specializes in Parkinson's disease assesses each item of the UPDRS. The items in Parts 1–4 yield a possible maximum of 199 points, representing maximal disability, with a score of zero representing no disability. Scores for Parts 1–4 are calculated as the sum of the item scores, excluding items that could not be rated. The total score for Parts 1–4 is calculated as the sum of the scores for the parts.

All UPDRS parts will be completed on Day 1 for De Novo subjects, while only Parts 2 and 3 of the questionnaire will be completed for subjects rolling over from Study 0169. At later visits, only Parts 2 and 3 will be administered.

8.8.3. [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]
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Table 7: Weight

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9. SAFETY AND TOLERABILITY

Analyses of safety and tolerability data include summaries of adverse events and summaries of drug exposure (duration of treatment), dosing information/compliance, concomitant medications, clinical laboratory test results, vital signs, ECGs, and C-SSRS responses.

All safety summaries will be presented separately for the open-label treatment period and the randomized withdrawal treatment period. Columns will be as specified in Section 6.1.

9.1. Adverse Events

Adverse events are collected from signing of the informed consent form through the end of follow-up. Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®, version 24.1).

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 through 14 days after the date of last dose of study drug. AEs that begin more than 14 days after the date of last dose of study drug and AEs that begin during the period from obtaining informed consent to the start of administration of study drug will not be considered treatment-emergent and will be listed only.

The following AE summaries will be provided for each treatment period:

- TEAE overall summary
- TEAEs by preferred term
- TEAEs by system organ class and preferred term
- Moderate or severe TEAEs by system organ class and preferred term
- TEAEs by preferred term with frequency > 3% of safety analysis set subjects
- TEAEs by system organ class, preferred term, and severity
- Drug-related TEAEs by system organ class and preferred term
- Drug-related TEAEs by system organ class, preferred term, and severity
- Drug-related moderate or severe TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Drug-related serious TEAEs by system organ class and preferred term
- TEAEs resulting in on-study deaths
- TEAEs leading to premature study drug discontinuation
- TEAEs leading to temporary interruption of study drug
- TEAEs of special interest by system organ class and preferred term (Section 9.1.1)

If no adverse events meeting a specific table definition were reported, the body of the table will contain only a statement that no events met the table definition.

The following AE listings will be provided:

- TEAEs
- AEs leading to premature study drug discontinuation
- AEs resulting in temporary interruption of study drug
- Serious adverse events
- Deaths
- Non-treatment-emergent adverse events
- Adverse events of special interest (Section 9.1.1)
- Adverse events for excluded site 27045 (Section 6.2.1)

9.1.1. [redacted]

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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 take their assigned study medication 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 returned)/
(date of last dose – date of first dose + 1)

Treatment compliance as a percentage of expected total dose will be summarized 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, version 1Q 2021 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 taken before the first dose of study drug. Concomitant medications are medications taken after the first dose up through 14 days after the last dose, and include ongoing prior medications.

The number and percentage of subjects receiving prior medications, the number and percentage receiving concomitant medications, and the number and percentage receiving prohibited concomitant medications will be summarized by medication class and standardized medication name (preferred name). If available, ATC level 4 will be used to determine the medication class. 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.

All medications will be listed.

On-treatment midodrine usage will be summarized by providing a categorical summary of number of uses and descriptive summaries (n, mean, SD, etc.) of usage rate (uses/month), calculated as (number of uses)/(treatment period duration in days, divided by 28) and total dose (mg). For number of uses, counts and percentages will be provided for the following categories:

- 0
- 1
- 2
- 3
- 4
- 5
- 6 – 10

- 11 – 20
- > 20

A use is defined as taking 1 or more 2.5-mg midodrine tablets on a single occasion, e.g., 2 tablets taken at 0900 and 2 tablets taken at 1200 = 2 uses, for a total daily dose of 10 mg.

9.4. Laboratory Data

Laboratory data hematology and serum chemistry summaries will include summary statistics for observed values and for changes from baseline at each postdose 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 test results. Urinalysis data will be listed only.

Listings will flag laboratory values that are outside the normal range.

9.5. Vital Signs and Weight

Weight and vital signs (HR and systolic and diastolic BP) and their changes from baseline at postbaseline visits will be summarized. (Following the start of the open-label treatment period, weight is collected at the beginning and end of the randomized withdrawal treatment period and at the 10-day follow-up visit.) At visits when orthostatic standing test results are collected, the vital signs (BP and HR) collected after 10 minutes supine and 10 minutes seated from the orthostatic standing test will be used for these summaries. Therefore, the BP and HR summaries for these visits will include body position (supine and seated). At Visit 2 (Day 15), which does not include an orthostatic standing test, the position in which BP and HR were collected is not recorded. Visit 2 measurements will be assumed to have been collected while the subjects were seated.

The counts and percentages of subjects with vital signs in the ranges shown in Table 9 will be presented in an extreme values summary. Extreme values will be flagged in the listing.

Table 9: Vital Signs Extreme Value Thresholds

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

9.5.1. Ambulatory Blood Pressure

Ambulatory blood pressure monitoring equipment will be provided to subjects during the screening visit. Beginning approximately 72 to 24 hours before subjects return to the clinic on 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 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.

ABPM position and body position time points will be matched using a ± 10 minutes window. If there is more than 1 body position time point within the window, the position time point closest to the ABPM time point will be used. If there is a tie, the earlier position time point will be used.

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. 12-Lead Safety ECGs

ECG summaries will include summary statistics for observed values and changes from baseline. Heart rate and the following intervals will be included: PR, QRS, QT, and QTcF. A listing of 12-lead safety ECG data collected will be provided. A separate listing of data for subjects with postbaseline values of QTcF ≥ 500 msec or a QTcF increase from baseline > 60 msec will also be provided.

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 by visit.

Categorical ECG Summary

QTcF (msec) will be summarized by the following categories: Normal (males < 430, females < 450), Borderline (males [≥ 430, < 450], females [≥ 450, < 470]), and Prolonged (males ≥ 450, females ≥ 470).

The number of subjects with absolute ECG values and changes from baseline in the ranges shown in Table 10 will be presented by visit.

Table 10: ECG Thresholds and Ranges

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percent 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. Columbia-Suicide Severity Rating Scale (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 overidentification of suicidal behavior. The C-SSRS Baseline/Screening Version is available at screening visit for De Novo subjects; the C-SSRS Since Last Visit Version is available for both rollover and De Novo subjects at subsequent visits. If the Since Last Visit Version of the C-SSRS is collected on the same day as the Baseline/Screening Version of the C-SSRS, the Since Last Visit Version of the C-SSRS does not have a valid reference and hence will be excluded from summarization and analysis. It will be included in the listing.

The following 11 C-SSRS categories include 5 subtypes of suicidal ideation (1–5), 5 subtypes of suicidal behavior (6–10), and self-injurious behavior without suicidal intent. 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

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), at each visit where the CSSRS was collected. The summary of the Baseline/Screening Version of the C-SSRS will present separately the assessment over the subject's lifetime and during the last 12 months. Only responses for De Novo subjects will be summarized, as the Baseline/Screening Version was administered in study 0169 for the rollover subjects.

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11. APPENDICES

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11.1.4. Laboratory Data

For laboratory data, a missing baseline value will be replaced with the last available assessment, 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 "$< x$" (where x is the LOD). More specifically, $x-1$ is used for data summarization if the data are reported in the form "$< x$" 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/quantitation limit will be used for calculation of descriptive statistics if the data are reported in the form "$\leq x$" or "$\geq x$".

11.2. Changes to Protocol-Specified Analyses

- Removal of smoking status subgroups
- Addition of baseline norepinephrine subgroups
- To the planned analyses of standing SBP at 3 minutes and at 10 minutes during the orthostatic standing test, addition of similar analyses of standing heart rate at 3 minutes and at 10 minutes

11.3. Sample Code

Sample code for logistic regression, MMRM, and ANCOVA analyses is provided in Study_0170_Statistical Analysis Plan – A3 Sample Code.docx.