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: 05 August 2020

CLINICAL STUDY PROTOCOL

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
Study Short Title:	Phase 3 Clinical Effect of TD-9855 for Treating symptomatic nOH in Subjects With Primary Autonomic Failure (Sequoia Study)
Sponsor Study No.:	0169
Date:	05 August 2020 [redacted]
Test Product:	TD-9855 (ampreloxetine hydrochloride) tablets
US IND:	129797
EudraCT No.:	2018-003289-15
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
Clinical Study Director:	[redacted] Theravance Biopharma Ireland Limited [redacted]

This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0169: 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.

Study Short Title: Phase 3 Clinical Effect of TD-9855 for Treating symptomatic nOH in Subjects with Primary Autonomic Failure (Sequoia Study).

Estimated Number of Study Centers and Countries or Regions: [redacted]

Background and Rationale:

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

PROTOCOL SYNOPSIS (CONTINUED)

Objectives:

The primary objective of the study is:

- To evaluate the efficacy of TD-9855 in subjects with multiple system atrophy (MSA), Parkinson's disease (PD), or pure autonomic failure (PAF) experiencing symptomatic neurogenic orthostatic hypotension (symptomatic 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.

The secondary objectives of the study are as follows:

- To evaluate the efficacy of TD-9855 by symptom and activity assessments using OHSA and the Orthostatic Hypotension Daily Activity Scale (OHDAS).
- To evaluate the efficacy of TD-9855 using the Patient Global Impression of Change (PGI-C).
- To evaluate the efficacy of TD-9855 in preventing incidence of falls.
- To evaluate the safety and tolerability of 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.

[redacted]

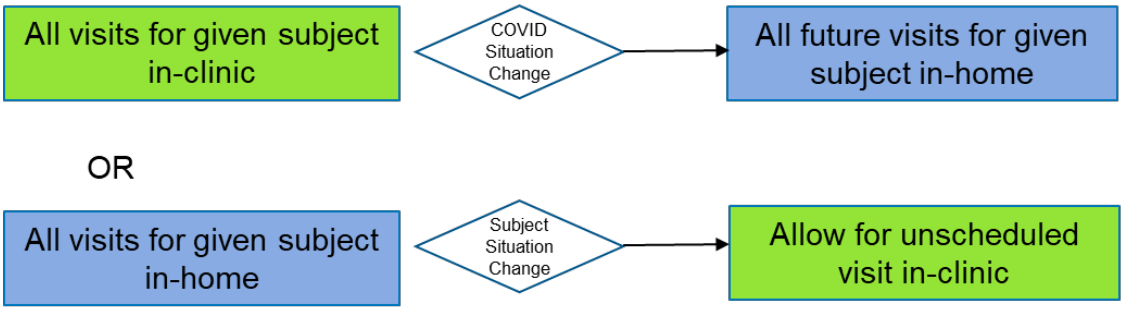
Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate efficacy, safety, and tolerability of TD-9855 in subjects with primary autonomic failures (MSA, PD, or PAF) and symptomatic nOH after 4 weeks of treatment.

PROTOCOL SYNOPSIS (CONTINUED)

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 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. 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).

These options apply to each Individual Subject at a Site as appropriate



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 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 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.

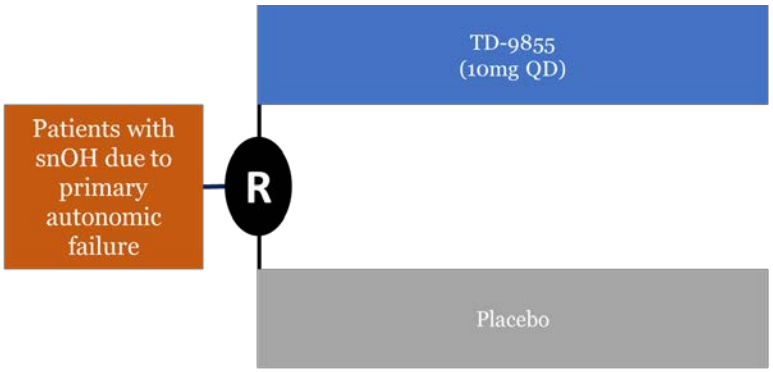
Symptomatic neurogenic orthostatic hypotension is defined as:

- A sustained reduction of BP of ≥20 mmHg (systolic) or ≥10 mmHg (diastolic) within 3 minutes of standing or tilted-up to ≥60° elevation from a supine position.

PROTOCOL SYNOPSIS (CONTINUED)

- 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 1). The presence of symptomatic 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 (DBP) 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 TD-9855 or matching placebo for the next 4 weeks.

PROTOCOL SYNOPSIS (CONTINUED)

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

Weekly assessments will be conducted as outlined in the Schedule of Study Procedures (Table 1). Refer to the footnotes in Schedule of Study Procedures (Table 1) for a description of all assessments. Refer to Appendix 9 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

Discontinuation of subjects may occur at any time. Dose stopping criteria include meeting at least 1 of the following rules:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

No dose reduction is permitted at any time.

Safety assessments will include a physical examination, neurological examination, vital signs (body temperature, HR and BP), body weight, ECGs, safety laboratory tests (hematology, chemistry, and urinalysis), C-SSRS, and AEs.

Safety will be periodically reviewed by an independent data monitoring committee, see separate charter.

Subjects will be requested to refrain from making any significant dietary changes throughout the duration of the study. Subjects should be reminded to maintain an adequate fluid intake during their scheduled visits.

Subjects completing the 4-week double-blind treatment period will be eligible to enroll and continue receiving study medication in Study 0170. The final study 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.

Enrollment Steering Committee (ESC)

The Investigator must obtain approval from the ESC prior to randomizing the subject in the study. The ESC is a committee of independent neurologists that will make a predetermination of the subject's appropriateness for study inclusion by reviewing medical information provided by the site. The ESC will review both the medical history to support the diagnosis (MSA, PD, or PAF), and confirm the presence of symptomatic

PROTOCOL SYNOPSIS (CONTINUED)

nOH based on the results of the tilt-table test. Review of the tilt-table test results may include confirmation that the subject maintains a sustained fall in blood pressure to a level that is consistent with cerebral hypoperfusion. The ESC will consult with the Investigator to address any outstanding questions. The ESC review is recommended to be completed within 48 hours and the Investigator will be informed in writing (e.g., by e-mail) of the decision. Following ESC approval of the subject, the Investigator will determine eligibility based upon the protocol Inclusion and Exclusion criteria for randomization. In cases where the ESC determines subject ineligibility based on tilt-table test findings that are not consistent with symptomatic neurogenic orthostatic hypotension, the decision will be accompanied by rationale. A dedicated charter has been implemented to address the mode of operations of the ESC to ensure the protection of the study integrity. The communication from the ESC, documenting review and approval of the subject, will serve as ESC documentation for inclusion into the study.

Duration of Study Participation:

Approximately 10 weeks

Number of Subjects:

[redacted]

Study Population:

This study will enroll adult subjects with confirmed symptomatic nOH due to MSA, PD, or PAF and who meet all of the inclusion criteria and none of the exclusion criteria defined below.

Inclusion Criteria:

A subject who meets the following criteria will be eligible for study enrollment:

1. Subject is male or female and at least 30 years old.
2. Subject is female and must be nonpregnant and nonlactating. A woman of childbearing potential must have a documented negative pregnancy test at screening.

   NOTE: A woman is considered to be of childbearing potential unless she is postmenopausal (amenorrheic for at least 2 years) or documented to be surgically sterile (bilateral tubal ligation or total hysterectomy). A female subject may be admitted to the study on the basis of a negative urine pregnancy test. If the urine bHCG (beta human chorionic gonadotropin) test is positive, a serum bHCG test must be performed. The pregnancy test must be confirmed negative for a subject to be eligible for this study.
3. During the study and for 30 days after receiving the last dose of the study drug, females of childbearing potential or males capable of fathering children must agree to use highly effective birth control measures (failure rate <1% when used

PROTOCOL SYNOPSIS (CONTINUED)

consistently and correctly) or agree to abstain from sexual intercourse (Refer to Section 4.3).

4. 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 to ≥60° from a supine position as determined by a tilt-table test.
5. Subject must score at least a 4 on the Orthostatic Hypotension Symptom Assessment Question #1 at randomization visit.
6. 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).
7. 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).
8. For subjects with PAF only: Subject has documented impaired autonomic reflexes, including the Valsalva maneuver performed within 24 months from the date of randomization.
9. Subject has plasma NE levels ≥100 pg/mL after being in seated position for 30 minutes.
10. Subject is willing and able to provide signed and dated written informed consent to participate prior to initiation of any study related procedures.
11. Subject is able to communicate well with the Investigator and clinic staff, understands the expectations of the study and is able to comply with the study procedures, requirements, and restrictions.

Exclusion Criteria:

A subject who meets any of the following criteria is not eligible for study enrollment:

1. Subject has a known systemic illness known to produce autonomic neuropathy, including but not limited to amyloidosis and autoimmune neuropathies. Subject has diabetes mellitus and diagnosis of PAF. Subject with diabetes mellitus and either MSA or PD, will be evaluated on a case by case basis by the medical monitor and considered ineligible unless they meet all of the following criteria:
   a. Well controlled type-2 DM in treatment with only oral medications and diet
   b. HgbA1C of ≤7.5% performed during screening or up to 12 weeks before screening
   c. No clinically evident peripheral neuropathy (e.g., normal sensory examination on peripheral extremities)
   d. No known retinopathy (e.g., annual ophthalmic exam is sufficient)
   e. No nephropathy (e.g., absence of albuminuria and GFR >60)
2. Subject has a known intolerance to other NRIs or serotonin norepinephrine reuptake inhibitors (SNRIs).
3. Subject currently uses concomitant antihypertensive medication for the treatment of essential hypertension.

PROTOCOL SYNOPSIS (CONTINUED)

4. Subject has used strong CYP1A2 inhibitors or inducers within 7 days or 5 half-lives, whichever is longer, prior to randomization or requires concomitant use until the follow-up visit.
5. Subject has changed dose, frequency, or type of prescribed medication for orthostatic hypotension within 7 days prior to randomization visit.
   - Midodrine and droxidopa (if applicable) must be tapered off at least 7 days prior to randomization.
6. Subject has a known or suspected alcohol or substance abuse within the past 12 months (DSM-IV-TR® definition of alcohol or substance abuse).
7. Subject has a clinically unstable coronary artery disease, or major cardiovascular or neurological event in the past 6 months.
8. Subject has used any monoamine oxidase inhibitor (MAO-I) within 14 days prior to randomization.
9. Subject has a history of untreated closed angle glaucoma, or treated closed angle glaucoma that, in the opinion of an ophthalmologist, might result in an increased risk to the subject.
10. Subject has any significant uncontrolled cardiac arrhythmia.
11. Subject has a Montreal Cognitive Assessment (MoCA) ≤23.
12. Subject is unable or unwilling to complete all protocol specified procedures including questionnaires.
13. Subject had a myocardial infarction in the past 6 months or has current unstable angina.
14. Subject has known congestive heart failure (New York Heart Association [NYHA] Class 3 or 4).
15. Subject has any malignant disease other than carcinoma in situ of the cervix or basal cell carcinoma within the past 2 years prior to screening.
16. Subject has a known gastrointestinal (GI) condition, which in the Investigator's judgment, may affect the absorption of study medication (e.g., ulcerative colitis, gastric bypass).
17. Subject has psychiatric, neurological, or behavioral disorders that may interfere with the ability of the subject to give informed consent or interfere with the conduct of the study.
18. Subject is currently receiving any investigational drug or has received an investigational drug within 30 days of dosing. An investigational drug is defined as nonregulatory agency approved drug (e.g., Food and Drug Administration).
19. Subject has a clinically significant abnormal laboratory finding(s) (e.g., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3.0 x upper limit of normal [ULN]; blood bilirubin [total] >1.5 x ULN; estimated glomerular filtration

PROTOCOL SYNOPSIS (CONTINUED)

rate (eGFR) <30 mL/min/1.73m^2, or any abnormal laboratory value that could interfere with safety of the subject).

20. Subject has demonstrated a history of lifetime suicidal ideation and/or suicidal behavior, as outlined by the C-SSRS (Baseline/Screening Version) subject should be assessed by the rater for risk of suicide and the subject's appropriateness for inclusion in the study.
21. Subject has a concurrent disease or condition that, in the opinion of the Investigator, would confound or interfere with study participation or evaluation of safety, tolerability, or pharmacokinetics of the study drug.
22. Subject has known hypersensitivity to TD-9855 (ampreloxetine hydrochloride), or any excipients in the formulation.
23. Subject has (i) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) documented with coronavirus disease 2019 [COVID-19] positive test result, OR (ii) is suspected of SARS-CoV-2 infection (clinical features without documented test results two weeks after resolution of symptoms and remains asymptomatic until Day 1), OR (iii) has been in close contact with a person with known (or suspected) SARS-CoV-2 infection and remains asymptomatic until Day 1.

Prohibitions and Restrictions:

The following are prohibited or restricted during study participation as specified:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

PROTOCOL SYNOPSIS (CONTINUED)

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

Subjects will be randomized [redacted] to receive either TD-9855 (test product) or placebo (reference product) once daily through the end of the treatment period.

The test product will be TD-9855 supplied as [redacted]

TD-9855 will be administered orally without regard to food at approximately the same time each morning and taken with approximately 8 ounces of water.

Subjects randomized to receive TD-9855 will begin taking study medication on Day 2 in the morning at a [redacted] and will continue to take this dose once daily through the end of the treatment period.

Reference Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

The reference product will be placebo tablets that are supplied to match TD-9855 in excipient content (except for TD-9855), appearance, tablet count, and in packaging (e.g., bottle label for reference product will be indistinguishable from test product except for a coded, unique bottle number).

Placebo will be administered orally without regard to food at approximately the same time each morning and taken with approximately 8 ounces of water.

Subjects randomized to receive placebo will begin taking study medication on Day 2 in the morning and will continue to take placebo once daily through the end of the treatment period.

Study Evaluations

Efficacy Assessments:

- OHQ
- PGI-C
- Incidence of falls

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Safety and Tolerability Assessments:

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

[redacted]

[redacted]

Statistical Methods

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Study Endpoints:

The primary study endpoint is the change from baseline in OHSA#1 (dizziness, lightheadedness, feeling faint, or feeling like blacking out) at Week 4.

The secondary endpoints are:

- 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

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Safety and tolerability endpoints include:

- 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

Analysis:

Analyses conducted based on the FAS will be based on the assigned randomized treatments.

The safety analysis set will be defined as all randomized subjects who have received at least 1 dose of study medication and subjects will be analyzed according to the actual study treatments they receive.

Unless specified otherwise, all data will be summarized by treatment group. Continuous variables will be presented using descriptive statistics. Categorical variables will be summarized using subject counts and percentage of subjects in corresponding categories.

The primary efficacy evaluation is the change from baseline of OHSA#1 at Week 4. Baseline is defined as Day 1 pre-dose measurement. Mixed model for repeated measures (MMRM) will be used to compare treatment differences. The model will include fixed effect class terms of treatment, baseline disease type (MSA, PD, PAF), week, and continuous covariate of baseline OHSA#1 score, a random subject effect, with an unstructured covariance structure using the FAS.

Least-square means and 95% confidence intervals on the differences between TD-9855 and placebo will be calculated and presented.

Missing data in the MMRM analysis is assumed as missing at random (MAR) and will not be imputed for the analysis of the primary endpoint. Sensitivity analyses on the primary endpoint will be conducted using multiple imputation. The primary analysis will be repeated on a set of pre-specified subgroups and presented in graphical format.

If the treatment effect of the primary efficacy endpoint has been demonstrated, the following secondary efficacy endpoints will be tested via statistical testing procedure, to be described in the statistical analysis plan (SAP), that will protect the family-wise Type I error rate at 2-sided significance level of 5% until a failure to reject the null hypothesis occurs. No statistical significance will be claimed after a failure to reject the null hypothesis has occurred.

PROTOCOL SYNOPSIS (CONTINUED)

- 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 at Week 4

Secondary efficacy endpoints involving assessment of change from baseline, such as OHSA composite score and OHDAS composite score, will be analyzed in a similar fashion as the primary efficacy endpoint of change from baseline in OHSA#1.

The PGI-C will be summarized as number and percentage for subjects with 'no change or better' and 'worse than no change' at Week 4. Incidence of falls will be summarized as number and percentage of subjects with at least 1 fall at Week 4. These endpoints will be tested using Cochran-Mantel Haenzel chi-square test, stratified by disease type at baseline.

For all supportive analyses including sensitivity analyses of the primary efficacy endpoint and exploratory endpoints, nominal p-values and 95% confidence intervals with no adjustment for multiplicity will be presented.

Safety data will be listed by subject and summarized using the frequency of event or descriptive statistical summaries, as appropriate. Summary tables will be provided for physical examination, neurological examination, vital signs (body temperature, HR and BP), body weight, ECGs, safety laboratory tests (hematology, chemistry, and urinalysis), C-SSRS, AEs and concomitant medications.

Table 1: Schedule of Study Procedures

Study Period:	**Screening [a] (in clinic)**	**Treatment (All visits for each subject either in clinic or remote)**					**Follow-up**
Study 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]	

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[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						

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Study 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
Safety laboratory test (chemistry, hematology, and urinalysis)	X	X[m]		X		X	
[redacted]			[redacted]	[redacted]		[redacted]	
[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	

Table 1: Schedule of Study Procedures

Study Period:	**Screening [a] (in clinic)**	**Treatment (All visits for each subject either in clinic or remote)**					**Follow-up**
Study 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
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] 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. [redacted]
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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
5-HT	Serotonin
ADHD	Attention-deficit hyperactivity disorder
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANS	Autonomic Nervous System
ASP	Autonomic Symptom Profile
AST	Aspartate aminotransferase
AUC	Area under curve
bHCG	Beta human chorionic gonadotropin
BP	Blood pressure
[redacted]	[redacted]
CFR	(United States) Code of Federal Regulations
C_{max}	Maximum concentration recorded
CNS	Central Nervous System
COA	Clinical Outcome Assessment
[redacted]	[redacted]
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DHPG	Dihydroxyphenylglycol
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessments (eCOA)
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESC	Enrollment Steering Committee
ET	Early Termed
EQ VAS	EQ Visual Analogue Scale
[redacted]	[redacted]
FAS	Full analysis set
FM	Fibromyalgia
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal

Abbreviation	Description
GLP	Good Laboratory Practice
[redacted]	[redacted]
hERG	Human ether-a-go-go-related gene
Hgba1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intra-uterine devices
MAD	Multiple ascending dose
MAO-I	Monoamine Oxidase inhibitor
MAP	Mean arterial pressure
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MMRM	Mixed Model for Repeated Measures
MoCA	Montreal Cognitive Assessment
MSA	Multiple System Atrophy
MSA-C	MSA of the cerebellar subtype
MSA-P	MSA of the Parkinsonian subtype
NE	Norepinephrine
NET	Norepinephrine transporter
[redacted]	[redacted]
nOH	Neurogenic Orthostatic Hypotension
NOAEL	No observed adverse event level
NRI	Norepinephrine reuptake inhibitor
NYHA	New York Heart Association
OH	Orthostatic Hypotension
OHQ	Orthostatic Hypotension Questionnaire
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHSA	Orthostatic Hypotension Symptom Assessment
OHSA#1	Orthostatic Hypotension Symptom Assessment Question 1
PAF	Pure Autonomic Failure
PD	Parkinson’s disease

Abbreviation	Description
[redacted]	[redacted]
PGI-C	Patient Global Impression of Change
P-gp	p-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
QD	Daily
QTcF	Corrected QT interval using the Fridericia's formula
REB	Research Ethics Board
RR	Respiratory rate
RTSM	Randomization and trial supply management
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SERT	Serotonin Reuptake Transporter
symptomatic nOH	Symptomatic Neurogenic Orthostatic Hypotension
SNRI	Serotonin norepinephrine reuptake inhibitor
SOC	System organ class
SOP	Standard Operating Procedure
SUSARS	Suspected unexpected serious adverse reaction
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TD-9855	Laboratory code for ampreloxetine hydrochloride
UKPDS	United Kingdom Parkinson's Disease Society
ULN	Upper Limit of Normal
[redacted]	[redacted]
[redacted]	[redacted]
US	United States
V1, V2, V3, etc.	Study Visits

1. INTRODUCTION

1.1. Background and Rationale

In healthy individuals, changes in blood pressure (BP) are highly regulated and well

mechanisms of action, including the addition of exogenous NE or NE prodrug. For example, [redacted]

1.2. Nonclinical Profile

A review of the nonclinical profile of TD-9855 can be found in the current version of the TD-9855 Investigator's Brochure (IB). The following is a brief summary of the pertinent findings.

1.2.1. Nonclinical Pharmacology

[redacted]

[redacted]

1.2.2. Safety Pharmacology

[redacted]

1.2.3. Nonclinical Pharmacokinetics

[redacted]

1.2.4. Toxicology

[redacted]

[redacted]

1.3. Clinical Experience

[redacted]

[redacted]

[redacted]

1.3.1. Clinical Pharmacokinetics

[redacted]

1.4. Risks and Benefits

Results from preclinical and clinical studies indicate that TD-9855 is a [redacted]

While it is not known whether TD-9855 will provide clinical efficacy, this study will provide a number of beneficial services to subjects. These include autonomic evaluations, neurohumoral evaluation, and information on new research developments in the field. Subjects will have access to routine autonomic follow up that may improve orthostatic symptoms. They will have symptom rating testing performed that may assist in educational planning.

[redacted]

[redacted]

To help ensure subject safety, subjects will be closely monitored during this study. Except for the Screening visit (V1) which must be conducted in the clinic, study visits can be conducted in the Investigator's autonomic disorders clinic or appropriately qualified research facility, or remotely using a telemedicine platform, under the supervision of qualified site personnel with help from a home health care provider.

The schedule of procedures requires subjects to be closely monitored on a regular basis during the dosing and follow-up periods. If any subject should incur any unexpected and untoward event during the testing procedure, the Investigator is instructed to provide the subject immediate and appropriate care as needed including unscheduled in clinic or remote visits.

A summary of known and potential risks to human subjects is provided in the IB in the Summary of Data and Guidance for the Investigators.

2. OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To evaluate the efficacy of TD-9855 in subjects with multiple system atrophy (MSA), Parkinson's disease (PD), or pure autonomic failure (PAF) experiencing symptomatic neurogenic orthostatic hypotension (symptomatic 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.

2.2. Secondary and Exploratory Objectives

The secondary objectives of the study are as follows:

- To evaluate the efficacy of TD-9855 by symptom and activity assessments using OHSA and the Orthostatic Hypotension Daily Activity Scale (OHDAS).
- To evaluate the efficacy of TD-9855 using the Patient Global Impression of Change (PGI-C).
- To evaluate the efficacy of TD-9855 on incidence of falls.
- To evaluate the safety and tolerability of 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.

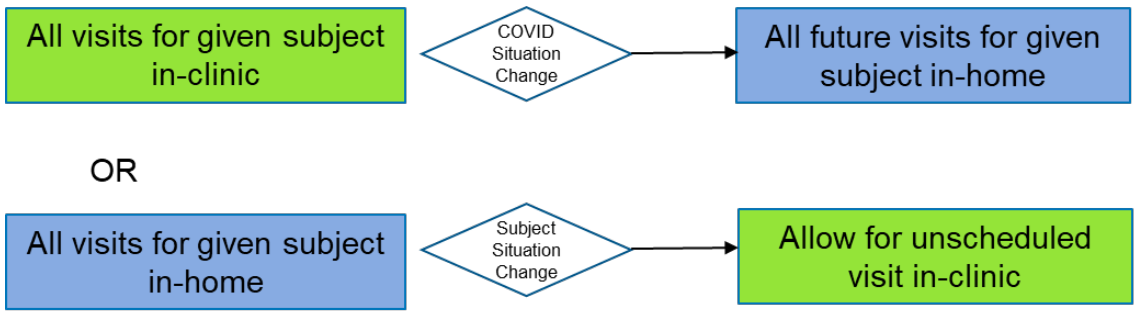
[redacted]

3. STUDY DESIGN

3.1. Overview

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate efficacy, safety, and tolerability of TD-9855 in subjects with primary autonomic failures (MSA, PD, or PAF) and symptomatic 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).

These options apply to each Individual Subject at a Site as appropriate



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.

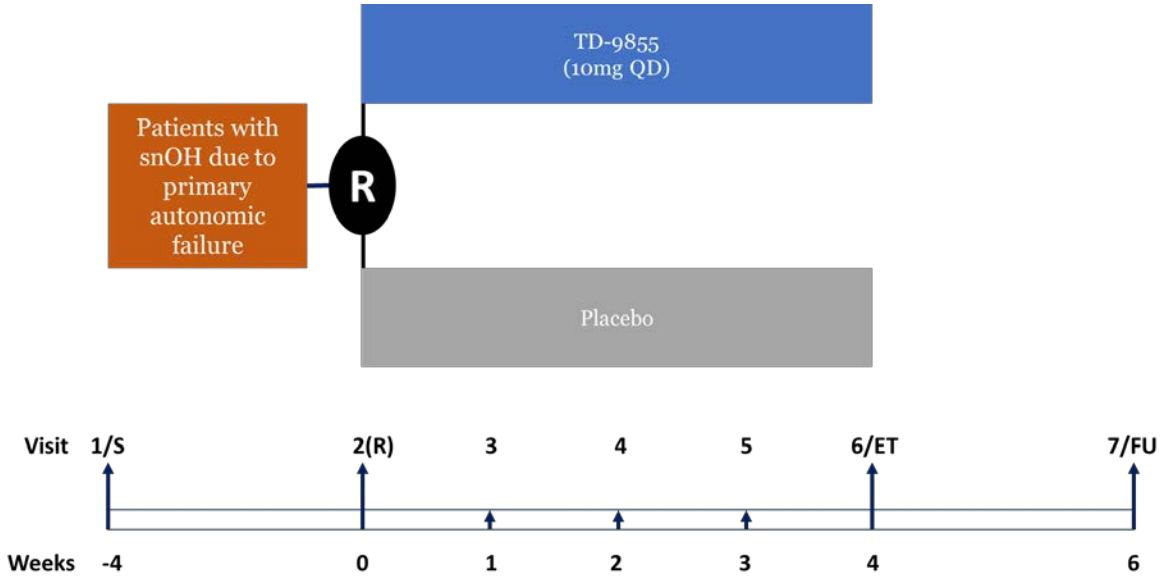
All sites are allowed at Investigator discretion to conduct either in clinic or remote unscheduled visit(s) for subject safety or unexpected subject medical needs outside of the regular visit schedule. In this case, unscheduled visits are not considered protocol deviations and the Investigator is not required to obtain 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 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 mmHg (systolic) or ≥10 mmHg (diastolic) within 3 minutes of standing or tilted-up to ≥60° 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 1). The presence of symptomatic 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 (DBP) 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 TD-9855 or matching placebo for the next 4 weeks.

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

Weekly assessments will be conducted as outlined in the Schedule of Study Procedures (Table 1). Refer to the footnotes in Schedule of Study Procedures for a description of all assessments. Refer to Appendix 9 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

Discontinuation of subjects may occur at any time. Dose stopping criteria include meeting at least 1 of the following rules:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

No dose reduction is permitted at any time.

Safety assessments will include a physical examination, neurological examination, vital signs (body temperature, HR and BP), body weight, ECGs, safety laboratory tests (hematology, chemistry, and urinalysis), C-SSRS, and AEs.

Safety will be periodically reviewed by an independent data monitoring committee, see separate charter.

Subjects will be requested to refrain from making any significant dietary changes throughout the duration of the study. Subjects should be reminded to maintain an adequate fluid intake during their scheduled visits.

Subjects completing the 4-week double-blind treatment period will be eligible to enroll and continue receiving study medication in Study 0170. The final study 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.

3.2. Rationale for Study Design

[redacted]

[redacted]

3.3. Selection of Dose and Duration of Treatment

[redacted]

3.4. Study Endpoints

3.4.1. Primary Endpoint

The primary study endpoint is the change from baseline in OHSA#1 (dizziness, lightheadedness, feeling faint, or feeling like blacking out) at Week 4.

3.4.2. Secondary Endpoints

The secondary endpoints include:

- 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

3.4.3. [redacted]

3.4.4. Safety and Tolerability Endpoint

The safety and tolerability endpoints include:

- 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

3.5. Minimization of Bias

This is a double-blind, placebo-controlled, randomized study. Treatments will be assigned centrally using a randomization and trial supply management (RTSM) system.

All persons involved in this study, i.e., physicians, nurses, participants, and site monitors, will remain blinded at all times, except in the event of a medical emergency as outlined in Section 3.5.1.

3.5.1. Blinding

TD-9855 and placebo tablets will be of the same shape, size, and color to ensure that the blind is maintained. Also, subjects who are randomized to receive placebo will receive the equivalent number of tablets as those randomized to receive TD-9855.

A subject's treatment assignment will only be unblinded when knowledge of the treatment is essential for the further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. Any Investigator unblinding will be documented within the appropriate case report form (CRF) and will be captured in the RTSM system.

Sponsor Drug Safety personnel may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs). With these exceptions, sponsor personnel involved in the conduct of the study, data cleaning, or data analysis will remain blinded to subject treatment assignments until the database has been locked for final analysis.

3.5.2. Treatment Assignment

Once the subject has been determined to be eligible to receive study treatment, the PI or their delegate will use the RTSM system to randomize the subject and dispense study medication accordingly. Except for cases of emergency unblinding as described above, investigational site staff will remain blinded to treatment assignments until all subjects have completed the study and the database has been locked.

Further details regarding the randomization procedure and dose assignment will be outlined in the RTSM system manual.

3.5.3. Enrollment Steering Committee

The Investigator must obtain approval from the ESC prior to randomizing the subject in the study. The ESC is a committee of independent neurologists that will make a predetermination of the subject's appropriateness for study inclusion by reviewing medical information provided by the site. The ESC will review both the medical history to support the diagnosis (MSA, PD, or PAF), and confirm the presence of symptomatic nOH based on the results of the tilt-table test. Review of the tilt-table test results may include confirmation that the subject maintains a sustained drop in blood pressure to a level that is consistent with cerebral hypoperfusion. The ESC will consult with the Investigator to address any outstanding questions. The ESC review is recommended to be completed within 48 hours and the Investigator will be informed in writing (e.g., e-mail) of the decision. Following ESC approval of the subject, the Investigator will determine eligibility based upon the protocol Inclusion and Exclusion criteria for randomization.

In cases where the ESC determines subject ineligibility based on tilt-table test findings that are not consistent with symptomatic neurogenic orthostatic hypotension, the decision will be accompanied by rationale. A dedicated charter has been implemented to address the mode of operations of the ESC to ensure the protection of the study integrity. The communication from the ESC, documenting review and approval of the subject, will serve as ESC documentation for inclusion into the study.

4. STUDY POPULATION

This study will enroll adult subjects with confirmed symptomatic nOH due to MSA, PD, or PAF and who meet all of the inclusion criteria and none of the exclusion criteria defined below.

4.1. Inclusion Criteria

A subject who meets the following criteria will be eligible for study enrollment:

1. Subject is male or female and at least 30 years old.
2. Subject is female and must be nonpregnant and nonlactating. A woman of childbearing potential must have a documented negative pregnancy test at screening.

   NOTE: A woman is considered to be of childbearing potential unless she is postmenopausal (amenorrheic for at least 2 years) or documented to be surgically sterile (bilateral tubal ligation or total hysterectomy). A female subject may be admitted to the study on the basis of a negative urine pregnancy test. If the urine bHCG (beta human chorionic gonadotropin) test is positive, a serum bHCG test must be performed. The pregnancy test must be confirmed negative for a subject to be eligible for this study.
3. During the study and for 30 days after receiving the last dose of the study drug, females of childbearing potential or males capable of fathering children must agree to use highly effective birth control measures (failure rate <1% when used consistently and correctly) or agree to abstain from sexual intercourse (Refer to Section 4.3).
4. 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 to ≥60^{o} from a supine position as determined by a tilt-table test.
5. Subject must score at least a 4 on the Orthostatic Hypotension Symptom Assessment Question #1 at randomization visit.
6. 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).
7. 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).
8. For subjects with PAF only: Subject has documented impaired autonomic reflexes, including the Valsalva maneuver performed within 24 months from the date of randomization.
9. Subject has plasma NE levels ≥100 pg/mL after being in seated position for 30 minutes.
10. Subject is willing and able to provide signed and dated written informed consent to participate prior to initiation of any study related procedures.
11. Subject is able to communicate well with the Investigator and clinic staff, understands the expectations of the study and is able to comply with the study procedures, requirements, and restrictions.

4.2. Exclusion Criteria

A subject who meets any of the following criteria is not eligible for study enrollment:

1. Subject has a known systemic illness known to produce autonomic neuropathy, including but not limited to amyloidosis and autoimmune neuropathies. Subject has diabetes mellitus and diagnosis of PAF. Subject with diabetes mellitus and either MSA or PD, will be evaluated on a case by case basis by the medical monitor and considered ineligible unless they meet all of the following criteria:
   a. Well controlled type-2 DM in treatment with only oral medications and diet
   b. HgbA1C of ≤7.5% performed during screening or up to 12 weeks before screening
   c. No clinically evident peripheral neuropathy (e.g., normal sensory examination on peripheral extremities),
   d. No known retinopathy (e.g., annual ophthalmic exam is sufficient)
   e. No nephropathy (e.g., absence of albuminuria and GFR >60)
2. Subject has a known intolerance to other NRIs or SNRIs.
3. Subject currently uses concomitant antihypertensive medication for the treatment of essential hypertension.
4. Subject has used strong CYP1A2 inhibitors or inducers within 7 days or 5 half-lives, whichever is longer, prior to randomization or requires concomitant use until the follow-up visit.
5. Subject has changed dose, frequency, or type of prescribed medication for orthostatic hypotension within 7 days prior to randomization visit.
   - Midodrine and droxidopa (if applicable) must be tapered off at least 7 days prior to randomization.
6. Subject has a known or suspected alcohol or substance abuse within the past 12 months (DSM-IV-TR® definition of alcohol or substance abuse).
7. Subject has a clinically unstable coronary artery disease, or major cardiovascular or neurological event in the past 6 months.
8. Subject has used any monoamine oxidase inhibitor (MAO-I) within 14 days prior to randomization.
9. Subject has a history of untreated closed angle glaucoma, or treated closed angle glaucoma that, in the opinion of an ophthalmologist, might result in an increased risk to the subject.
10. Subject has any significant uncontrolled cardiac arrhythmia.
11. Subject has a Montreal Cognitive Assessment (MoCA) ≤23.
12. Subject is unable or unwilling to complete all protocol specified procedures including questionnaires.
13. Subject had a myocardial infarction in the past 6 months or has current unstable angina.
14. Subject has known congestive heart failure (New York Heart Association [NYHA] Class 3 or 4).

15. Subject has any malignant disease other than carcinoma in situ of the cervix or basal cell carcinoma within the past 2 years prior to screening.
16. Subject has a known gastrointestinal (GI) condition, which in the Investigator's judgment, may affect the absorption of study medication (e.g., ulcerative colitis, gastric bypass).
17. Subject has psychiatric, neurological, or behavioral disorders that may interfere with the ability of the subject to give informed consent or interfere with the conduct of the study.
18. Subject is currently receiving any investigational drug or has received an investigational drug within 30 days of dosing. An investigational drug is defined as nonregulatory agency approved drug (e.g., Food and Drug Administration).
19. Subject has a clinically significant abnormal laboratory finding(s) (e.g., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3.0 x upper limit of normal [ULN]; blood bilirubin [total] >1.5 x ULN; estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, or any abnormal laboratory value that could interfere with safety of the subject).
20. Subject has demonstrated a history of lifetime suicidal ideation and/or suicidal behavior, as outlined by the C-SSRS (Baseline/Screening Version) subject should be assessed by the rater for risk of suicide and the subject's appropriateness for inclusion in the study.
21. Subject has a concurrent disease or condition that, in the opinion of the Investigator, would confound or interfere with study participation or evaluation of safety, tolerability, or pharmacokinetics of the study drug.
22. Subject has known hypersensitivity to TD-9855 (ampreloxetine hydrochloride), or any excipients in the formulation.
23. Subject has (i) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) documented with coronavirus disease 2019 [COVID-19] positive test result, OR (ii) is suspected of SARS-CoV-2 infection (clinical features without documented test results two weeks after resolution of symptoms and remains asymptomatic until Day 1), OR (iii) has been in close contact with a person with known (or suspected) SARS-CoV-2 infection and remains asymptomatic until Day 1.

4.3. Pregnancy and Contraception

4.3.1. Females of Childbearing Potential

Females of childbearing potential must have documentation of a negative pregnancy test at screening and prior to dosing.

Females are considered to be not of childbearing potential if they have had a total hysterectomy and/or bilateral tubal ligation or hysteroscopic sterilization (documentation for surgeries must be provided before randomization) or are in a postmenopausal state (i.e., females who have had cessation of prior occurring menses for ≥24 months without alternative causes or females with premature ovarian failure).

4.3.2. Contraception for Male and Female Subjects

All female subjects of childbearing potential and males who are able to father children must agree to abstain from sexual intercourse or to use a highly effective method of birth control during the study and for at least 30 days after the completion of study drug dosing. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly.

Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner provided that partner is the sole sexual partner of the female trial participant of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success
- sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

NOTE: Birth control methods which may not be considered highly effective:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

5. STUDY MEDICATION

All study medication supplied by the sponsor must be stored in a secure location accessible only to designated study personnel.

5.1. Description of Study Medications

[redacted]

5.1.1. TD-9855 Test Product

[redacted]

5.1.2. Placebo Reference Product

[redacted]

5.2. Dosage and Administration

All study medications will be administered orally without regard to food at approximately the same time each morning and taken with approximately 8 ounces of water.

5.3. Treatment Compliance

Subjects will be instructed to provide all used and unused study medication containers at each visit. Compliance with the dosing regimen will be assessed by reconciliation of used and unused study medication.

The subjects' diary entries will also be reviewed at applicable study visits to assess compliance with study medication administration per documentation of the daily dosing times.

Subjects with poor dosing compliance (e.g., < 80% or > 120%), as assessed by reconciliation of used and unused study medication and/or missing entries on the study medication administration diary, should receive counseling, assistance, and re-training as appropriate.

5.4. Drug Accountability and Reconciliation

The Investigator or designee is responsible for maintaining accountability records for all study medication(s) received from the sponsor, in accordance with applicable government regulations and study procedures. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s). Unused and expired study medications will be disposed of in accordance with written instructions in the pharmacy manual.

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1. Refer to the footnotes in Schedule of Study Procedures (Table 1) for a description of all assessments. Refer to Appendix 9 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

6.2. Total Blood Volume

The total volume of blood to be drawn from each subject for safety, PK, and pharmacodynamic laboratory tests is approximately [redacted]. Additional safety laboratory tests may be drawn as needed to manage any emergent health needs as directed by the Investigator.

6.3. Procedures by Visit (Recommended Order)

6.3.1. Screening – Visit 1

Screening visit assessments will be performed in clinic and the following procedures must be completed first, and in the order below:

1. Written informed consent (signed and dated) after the nature of the study has been explained and before any study procedure is performed
2. Review of protocol inclusion and exclusion criteria prior to beginning subject evaluations
3. Medical history, including smoking history
4. Review concomitant medications and smoking usage
5. MoCA
6. OHQ subject training
7. C-SSRS
8. Tilt-table test

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

9. [redacted]
10. Vital signs
    a. HR, systolic BP (SBP), and diastolic BP (DBP)
    b. Respiratory rate (RR) and body temperature
11. Height (in cm) and weight (in kg)
12. Physical examination
13. Neurological examination

14. 12-lead ECG (in triplicate separated by at least 1 minute for each replicate, after the subject has been resting for at least 5 minutes)
15. Pregnancy test (in women of childbearing potential only)
16. Blood collection
    a. Hematology
    b. Chemistry
    c. NE sample collection (after being seated for approximately 30 minutes)
17. Urine collection
    a. Urinalysis
18. AE assessment (AEs, SAEs, adverse event of special interest [AESIs])
19. Incidence of falls – subject diary, dispensation and review of diary completion instructions
20. 24-hour ambulatory BP device provision (device collection prior or on Visit 2)
21. ESC (for confirmation of diagnosis)
22. Valsalva maneuver (only for subjects with PAF)

A sample screening visit with approximate duration required for subject is provided in Appendix 8.

6.3.2. Treatment Day 1 – Visit 2

Subjects meeting all applicable eligibility criteria, including ESC confirmation of diagnosis, following completion of the screening assessments will complete enrollment assessments on Day 1.

Prior to randomization, the results of the clinical and laboratory evaluations from screening (as described in Table 1) must be reviewed by the Investigator to confirm the continued eligibility of each subject to participate in the study.

The assessments will be performed within 24-hours prior to the subject taking the study medication.

The following procedures must be completed first, and in the order below:

1. Review of protocol inclusion and exclusion criteria prior to beginning subject evaluations
2. Review concomitant medications and smoking usage
3. OHQ subject training
4. OHQ (OHSA and OHDAS)
5. C-SSRS
6. Randomization via a RTSM system (after all pre-dose procedures have been completed and subject is confirmed to be eligible for the study)

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

[redacted]

14. Vital signs
    a. HR, SBP, and DBP
    b. RR and body temperature
15. Weight (in kg)
16. Physical examination
17. Neurological examination
18. Pregnancy test (in women of childbearing potential only)
19. Blood collection
    a. Hematology
    b. Chemistry
20. Urine collection
    a. Urinalysis

[redacted]

22. Incidence of Falls and ABPM position diaries
23. 24-hour ambulatory BP device collection and re-provision
24. Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
25. AE assessment (AEs, SAEs, AESIs)
26. Dispense study medication

6.3.3. Treatment Day 8 – Visit 3

The following procedures will be performed on the Day 8 visit (+/- 3 days) and the following procedures must be completed first, and in the order below:

1. Review concomitant medications and smoking usage
2. OHQ subject training

3. OHQ (OHSA and OHDAS)
4. C-SSRS

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

5. [redacted]

[redacted]

7. Vital signs
    a. HR, SBP, and DBP
    b. RR and body temperature
8. Weight (in kg)

[redacted]

10. Incidence of Falls and ABPM position diaries
11. 24-hour ambulatory BP device collection
12. Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
13. AE assessment (AEs, SAEs, AESIs)
14. Collect, review, then re-dispense study medication

6.3.4. Treatment Day 15 – Visit 4

The following procedures will be performed on the Day 15 visit (+/- 3 days and the following procedures must be completed first, and in the order below:

1. Review concomitant medications and smoking usage
2. OHQ subject training
3. OHQ (OHSA and OHDAS)
4. C-SSRS

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

[redacted]

[redacted]

7. Vital signs
    a. HR, SBP, and DBP
    b. RR and body temperature
8. Weight (in kg)
9. Blood collection
    a. Hematology
    b. Chemistry

10. Urine collection
    a. Urinalysis

[redacted]

12. Incidence of Falls and ABPM position diaries
13. Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
14. AE assessment (AEs, SAEs, AESIs)
15. Collect, review, then re-dispense study medication

6.3.5. Treatment Day 22 – Visit 5

The following procedures will be performed on the Day 22 visit (+/- 3 days) and the following procedures must be completed first, and in the order below:

1. Review concomitant medications and smoking usage
2. OHQ subject training
3. OHQ (OHSA and OHDAS)
4. C-SSRS

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

[redacted]

7. Vital signs
   - HR, SBP, and DBP
   - RR and body temperature
8. Weight (in kg)
9. Incidence of Falls and ABPM position diaries
10. 24-hour ambulatory BP device collection
11. Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
12. AE assessment (AEs, SAEs, AESIs)
13. Collect, review, then re-dispense study medication

6.3.6. Treatment Day 29 – Visit 6 / Early Termination

The following procedures will be performed on the Day 29 visit (+/- 3 days) and the following procedures must be completed first, and in the order below:

1. Review concomitant medications and smoking usage
2. OHQ subject training
3. OHQ (OHSA and OHDAS)

4. PGI-C
5. C-SSRS

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

[redacted]

13. Vital signs
    a. HR, SBP, and DBP
    b. RR and body temperature
14. Weight (in kg)
15. Physical examination
16. Neurological examination
17. 12-lead ECG (in triplicate separated by at least 1 minute for each replicate, after the subject has been resting for at least 5 minutes)
18. Pregnancy test (in women of childbearing potential only)
19. Blood collection
    a. Hematology
    b. Chemistry
20. Urine collection
    a. Urinalysis

[redacted]

23. Incidence of Falls and ABPM position diaries
24. Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
25. AE assessment (AEs, SAEs, AESIs)

26. Collect and review study medication

6.3.7. Follow-up Day 43 – Visit 7

The follow-up visit is applicable only for those subjects that will not proceed to Study 0170 and will be completed two weeks from the date of the last dose.

The following procedures will be performed on the Day 43 visit (+/- 3 days):

The following procedures are listed in the recommended order, however flexibility for scheduling is permitted:

1. Review concomitant medications and smoking usage
2. C-SSRS
3. Vital signs
    a. HR, SBP, and DBP
    b. RR and body temperature
4. Weight (in kg)
5. AE assessment (AEs, SAEs, AESIs)

6.4. Description of Study Procedures

Written informed consent must be obtained prior to performing any protocol specific procedures. After providing full informed consent, subjects will undergo a medical screen to determine their eligibility for participation based on the criteria outlined in this protocol.

The site should make every effort to perform procedures at the scheduled times, and information should be recorded in the source documents and on the CRFs. All subject reported outcomes for subjects with PD should be completed in an ON state, and within 1-4 hours of taking the PD medications.

Additional safety tests, such as vital signs (BP, HR, RR, and body temperature), physical examinations, ECGs, and laboratory safety assessments, may be obtained during the course of the study on the basis of newly available data to ensure appropriate safety monitoring.

6.4.1. Demographic and Baseline Assessments

Demographic information to be collected will include: year of birth, sex, race, and ethnicity.

Inclusion and exclusion criteria will be assessed at screening and on Day 1 prior to randomization. Subjects will only be eligible for enrollment into the study if they meet all the applicable inclusion and none of the applicable exclusion criteria.

Each subject will be asked to provide relevant medical history (including medication history; see Section 6.4.10.3).

6.4.2. Tilt-Table Test

A tilt-table test is used to evaluate the cause of unexplained fainting (syncope). A tilt-table attempts to trigger signs and symptoms like lightheadedness, dizziness, feeling faint, or feeling like blacking out while HR and BP are being monitored. If the subject has symptoms while in the upright position on the tilt-table, the part of the nervous system that controls BP and HR suddenly lowers for a short time, less blood flows to the brain, and could possibly

cause the subject to faint. The endpoint of tilt-table testing is the reproduction of symptoms along with the characteristic circulatory pattern of the indication mentioned above, namely the induction of reflex hypotension/bradycardia, orthostatic hypotension, postural orthostatic tachycardia syndrome, or psychogenic pseudosyncope. The tilt-table test will be applied until a sustained reduction of BP of ≥20 mmHg (systolic) or ≥10 mmHg (diastolic) is observed in ≤3 minutes of being tilted-up to ≥60º from a supine position, ideally between 60º to 65º. 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. A single tilt-table retest may be performed providing the Investigator has concluded a technical problem or operational issue during the initial test impacted the results. Under these circumstances, a follow-up tilt-table test may be performed in order to appropriately evaluate the subject's orthostasis. The follow-up tilt-table test should be performed at a minimum of one hour after the initial test, and at least 7 days prior to randomization. Assessments will be performed as specified in Schedule of Study Procedures (Table 1).

6.4.3. Montreal Cognitive Assessment

The MoCA is a global cognitive screening test with favorable psychometric properties that has been shown to be more sensitive to executive impairment than the Mini-Mental State Examination. It screens 8 domains including: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.4. Valsalva Maneuver

The Valsalva maneuver is a breathing technique that can be used to help diagnose a problem with the autonomic nervous system (ANS). Changes in intrathoracic pressure produce autonomically modulated transient changes in HR and BP. The Valsalva maneuver will be performed as specified in the Schedule of Study Procedures (Table 1) only for subjects with PAF to confirm diagnosis.

[redacted]

6.4.6. Efficacy Assessments

6.4.6.1. Orthostatic Hypotension Questionnaire

The Orthostatic Hypotension Questionnaire (OHQ) is a 2-component scale made up of a 6-item symptom assessment scale referred to as OHSA and a 4-item daily activity scale referred to as the Orthostatic Hypotension Daily Activities Scale (OHDAS). 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, and the option of selecting "cannot do for other reasons." Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.6.2. Patient Global Impression of Change

In the PGI-C scale, subject is asked to compare their current symptoms to their symptoms at study baseline (i.e., prior to randomization) on a 5-category scale ranging from 1 (much better) to 5 (much worse). Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

[redacted]

[redacted]

6.4.6.7. Incidence of Falls – Subject Diary

Falls in subjects with symptomatic neurogenic orthostatic hypotension are common and potentially catastrophic. They can lead to serious injuries including hip fractures or head trauma; furthermore, fear of falling can limit mobility and physical activity. Thus, incidence of subject-reported falls is being captured in a diary. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 3.

[redacted]

[redacted]

6.4.9. [redacted]

[redacted]

6.4.10. Safety Assessments

6.4.10.1. Columbia-Suicide Severity Rating Scale

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 for subsequent visits. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.10.2. Adverse Events

Adverse events will be reviewed and recorded from signing of the informed consent through the end of follow-up. Adverse events may be observed by the study personnel or spontaneously reported by the subject.

All AEs must be recorded in the subject's CRF and, if applicable, reported as described in Section 7.

The Investigator must take all therapeutic measures necessary for resolution of AEs. Any medications necessary for the treatment of an adverse event must be recorded in the subjects CRF. Refer to Section 7.

Except where described above, the Investigator may prescribe medications to provide adequate supportive care. However, the Investigator should use judgment to avoid medications that may confound the interpretation of this study.

6.4.10.3. Medication and Medical History

A complete medical history will be taken during the screening visit and will include evaluation visit for past and present cardiovascular, respiratory, GI, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, or any other diseases or disorders. Medical conditions will be recorded for two years prior to screening visit, along with the date of diagnosis, and any other relevant medical history that has an impact to the subject.

Medical events or conditions that arise or worsen in severity or frequency after the signing of the informed consent will be recorded as an AE.

All medications used during the 60 days prior to screening will be recorded in the source records. The only exception is drugs that were used to treat previous orthostatic hypotension; these will be recorded since the time of primary diagnosis.

6.4.10.4. Physical Examination

A full physical examination at the screening visit will be performed by an appropriately qualified individual (e.g., physician, nurse practitioner, physician's assistant, or equivalent, under the supervision of a physician) and will include examination of the following: general appearance; skin; head, ears, eyes, nose, and throat; neck; cardiovascular system; respiratory system; abdomen/gastrointestinal (GI) system; extremities; lymphatic system [lymph nodes]; and nervous system).

Subsequent physical examinations, after the screening visit on Visit 2 and Visit 6, per discretion of the Investigator, can be abbreviated and symptomatic, largely focused on evaluation of AEs, if any, and any abnormalities identified on the screening visit examination.

6.4.10.5. Height and Weight

Height (in cm) and weight (in kg) will be recorded as outlined in the Schedule of Study Procedures (Table 1). Reasonable efforts will be taken to ensure the measurements for weight occur at approximately the same time each visit using the same scale and with similar clothing.

6.4.10.6. Vital Signs

The HR, SBP and DBP, RR, and body temperature will be recorded according to the Schedule of Study Procedures (Table 1).

The vital sign measurements (BP and HR) should be performed after the subject has rested sufficiently as determined by the appropriate staff. Subject position, measurement device, and arm (left vs. right) should be kept consistent throughout the study. Blood pressure will be measured using a calibrated manual or automatic BP device.

Heart rate will be recorded by palpation of the radial pulse over at least a 30-second period or by the automated BP device.

The BP and HR collected at 10 minutes supine and seated from the [redacted] can be used for safety vital sign assessment.

Body temperature will be measured and reported in degrees Celsius. The method used to collect temperature can be either oral or tympanic but should be consistent throughout the subject's participation.

Any vital sign outside the normal range may be repeated at the discretion of the Investigator. Collection of additional vital sign measurements for routine safety monitoring at additional time points or study days may be performed at the discretion of the Investigator, or upon request by the sponsor.

6.4.10.7. Electrocardiograms

The 12-lead ECGs will be recorded in triplicate and separated by at least 1 minute for each replicate according to the Schedule of Study Procedures (Table 1) after the subject has been resting at least 5 minutes in the seated or supine position before the first reading. The total time to conduct ECGs ideally would not exceed 15 minutes. Actual time of the assessment must be recorded for each iteration. The corrected QT interval using the Fridericia's formula (QTcF) will be used. The ECGs should be reviewed on the visit day at the site to allow for any appropriate action, if required.

6.4.10.8. 24-hour Ambulatory Blood Pressure Monitoring

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 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 (Appendix 4). More details regarding the ambulatory monitoring will be provided in a separate manual.

6.4.10.9. Laboratory Tests

Laboratory tests will be performed as specified in Schedule of Study Procedures (Table 1).

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study may be performed at the discretion of the Investigator or upon request of the sponsor.

Detailed instructions and collection kits for sample collection, handling, and shipping will be provided in the laboratory manual.

6.4.10.9.1. Hematology

Hematology samples will be analyzed for the following: hematocrit and hemoglobin; red blood cell count; mean corpuscular volume; mean corpuscular hemoglobin; white blood cell count, including differential count (percent and absolute) of neutrophils, eosinophils, basophils, monocytes, lymphocytes; platelet count and HgbA1C (if applicable).

6.4.10.9.2. Chemistry

Chemistry samples will be analyzed for the following: sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, eGFR, total protein, albumin, alkaline phosphatase, ALT, AST, bilirubin, lactate dehydrogenase, and creatine phosphokinase.

6.4.10.9.3. Urinalysis

Urinalysis includes determination of specific gravity; presence of blood, protein, and leukocytes; and microscopic examination of sediment, if clinically indicated.

6.4.10.10. Neurological Examination

Any abnormalities identified at the Screening Visit will be recorded as neurological medical history. Any abnormalities or symptoms reported during treatment that arise or worsen in severity or frequency will be reported as AEs.

The PI should perform a neurological exam in clinic or via telemedicine platform for remote visits (assisted as necessary by the home health nurse) as required to assess the subject's current condition and include the following exams per the PI's medical discretion.

The examination will assess the following:

- Cranial nerves (cranial nerves II-XII, excluding funduscopic examination)
- Motor system (tone, strength, and abnormal movements)
- Sensory system (light touch, pinprick, joint position, and vibration)
- Reflexes (deep tendon reflexes and plantar responses)
- Coordination (upper and lower extremities)
- Gait (base and tandem gait)

- Station (posture and stability)

6.4.10.11. Dosing Diary Dispensation and/or Collection

On a daily basis, the subjects will record the time of study medication administration in the diary provided on Visit 2. Dosing diary with completion instructions, including study medication dosing details, will be provided to each subject. Subjects will be instructed to record daily dosing through the end of the treatment period (Appendix 5). Diary completion will be monitored for completeness at each study visit after the diary is dispensed. Subjects will be counseled on missed study medication doses and missed diary entries. Compliance with the dosing regimen will be assessed by reconciliation of used and unused study medication.

6.4.10.12. Unscheduled Visit

All sites are allowed at Investigator discretion to conduct either in clinic or remote unscheduled visits 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.

6.5. Concomitant Medications

Subjects should not have changed dose, frequency or type of prescribed medication for orthostatic hypotension within 7 days prior to the randomization visit.

[redacted]

Stable dosing regimen is defined as the same dosage and frequency on any given day.

Subjects who are smokers will be recommended to either stop smoking (cigarettes or cannabinoids in countries where cannabinoids are permissible) at least 7 days before first dose or maintain a constant smoking habit during the entire course of the study.

6.5.1. Impact of Other Medications on TD-9855

[redacted]

6.5.2. Impact of TD-9855 on Other Medications

[redacted]

6.6. Rescue Medications

[redacted]

6.7. Prohibitions and Restrictions

The following are prohibited or restricted during study participation as specified:

[redacted]

6.8. Discontinuation

6.8.1. Dose Stopping Rules

Any subject meeting 1 or more of the following stopping criteria will be required to immediately discontinue dosing with study medication and subsequently subject will be discontinued from participation in the study:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.8.2. Subject Discontinuation

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the Investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be completed. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

The sponsor will be notified of all subject withdrawals.

Reasons for which the Investigator may withdraw a subject from the study or a subject may choose to terminate participation before completion of the study include, but are not limited to, the following:

- Adverse Event
- Physician Decision
- Pregnancy
- Protocol Violation
- Withdrawal by Subject
- Other

The subject may also discontinue from the study if the study is discontinued by the Sponsor.

Subjects who discontinue study medication early because of an adverse reaction should be encouraged to continue their participation in the follow-up safety assessments. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

6.8.3. Subject Replacement

Subjects will not be replaced.

6.8.4. Study Discontinuation

The sponsor reserves the right to discontinue this study at any time for any reason.

Periodic review of unblinded safety data by an external independent data monitoring committee (Section 8.8) may lead to the board's recommendation of pausing dosing or terminating the study. In the event of premature study termination, best efforts to guarantee appropriate safety follow-up of subjects who have already been enrolled will be made and institutional review boards (IRBs) and the regulatory authorities will be informed.

6.9. Pregnancy

TD-9855 has been shown to be non-genotoxic in a standard battery of genotoxicity assays (in vitro Ames and chromosomal aberration assays and in vivo micronucleus assay in rat). TD-9855 demonstrated effects on neonatal mortality and decreased rates of pup growth in the pre- and postnatal study in rats. Based on the NOAEL in reproductive-toxicology studies in preclinical species, there exists a greater than 100x margin between exposure in preclinical species at NOAEL vs. exposure in male and female subjects at 4 weeks post stopping administration of 10mg TD-9855 dose. Thus, application of pregnancy prevention measures for 1 month post last dose of TD-9855 is sufficient to address the risk of substantial drug exposure in semen or maternal circulation.

To confirm the absence of pregnancy in female subjects of childbearing potential, urine beta human chorionic gonadotropin (bHCG) testing will be performed during specified visits, as listed in the Schedule of Study Procedures (Table 1). If the urine bHCG test is positive, a serum bHCG test must be performed. The pregnancy test must be confirmed negative for a subject to be eligible for this study unless the PI deems the test is falsely positive.

If a subject becomes pregnant while taking TD-9855, or during the 1 month after the last dose of treatment, the pregnancy must be reported to the sponsor's medical monitor (or designee) immediately (within 24-hours) by following the procedures for SAE reporting as outlined in Section 7.4.3. Study drug must be discontinued for any pregnant subject still on study drug treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7. ADVERSE EVENTS

7.1. Definitions

The definitions below are based on International Council for Harmonization (ICH) guideline E2A, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting."

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical trial subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events.
- AEs may be preexisting events that increase in frequency, severity, or change in nature or seriousness during or as a consequence of participation in clinical studies.
- AEs may be pre- or posttreatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).
- AEs may result from an overdose of the study medication.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study medication or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the sponsor will be notified according to the procedures for SAE reporting as outlined in Section 7.4.3. Follow-up information regarding the outcome of the pregnancy and any fetal or neonatal sequelae will be obtained and documented.

7.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation. "Life threatening" refers to a situation in which the subject was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department. A scheduled hospitalization for a preexisting condition that has not worsened during participation in the study does not meet this criterion. Preplanned hospitalizations for an elective medical/surgical procedure, scheduled treatments, or routine check-ups do not meet this criterion. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- Disability- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect in the offspring of a subject who received study medication
- Important medical events that may not result in death, be immediately life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in hospitalization
  - Development of drug dependency or drug abuse

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an AE and not an AE in itself. Deaths of unknown cause for which the Investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- "Occurring at any dose" does not imply that the subject is receiving study medication at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE but may have contributed to the event.

7.1.4. Adverse Event of Special Interest

- At each study visit, the Investigator (or designee) will specifically query for any AESIs. The following events are considered AESIs for this study:
  - Supine hypertension
  - Cardiovascular events (myocardial infarction, cerebrovascular accident, cardiac arrhythmia, congestive heart failure)
  - Convulsion
- All AESIs must be reported to Sponsor Clinical Safety and Pharmacovigilance within 24-hours of awareness by the Investigator or his/her designee.

The AESI Report Form must be completed in accordance with the AESI Report Form Completion Guidelines. If all information on the AESI Report Form is not available at the time of the initial report, follow-up AESI reports will be completed and submitted.

To report an AESI, complete and send the AESI Report Form to the following:

Theravance Biopharma Clinical Safety

[redacted]

For medical questions regarding an AESI, contact the medical monitor by telephone as follows:

Medical Monitor Contact Information:

[redacted]

7.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as chemistry, hematology, or urinalysis) or other abnormal assessments (such as ECGs, x-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the Investigator must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE), as described in Section 7.1.1 (Adverse Event) and Section 7.1.2 (Serious Adverse Event).

If there are any AE questions, the Investigator is encouraged to contact the sponsor to discuss.

7.3. Assessment of Adverse Events

All AEs will be assessed by the Investigator and recorded in the CRF, including the dates of onset and resolution, severity, relationship to study medication, outcome, and action taken with study medication.

7.3.1. Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of AEs will be assessed according to the following definitions:

- **Mild:** The AE is noticeable to the subject and/or the Investigator but does not interfere with routine activity.
- **Moderate:** The AE interferes with routine activity but responds to symptomatic therapy or rest.
- **Severe:** The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy.

7.3.2. Causal Relationship to Study Medication

The Investigator's assessment of causality is based on clinical judgment regarding the reasonable possibility that the study medication caused the event and may include consideration of some or all of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, comorbid conditions, other medications, and environmental factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study medication.
- Whether the AE resolved or improved with decreasing the dose or stopping the study medication ("de-challenge") or recurred or worsened upon re-exposure to the study medication ("re-challenge").

The causal relationship between the study medication and the AE will be described using one of the following categories:

- **Not Related:** Evidence exists that the AE has an etiology other than the study medication (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Related:** A temporal relationship exists between the event onset and administration of the study medication. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon re-challenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

7.4. Adverse Event Reporting and Recording

7.4.1. Adverse Event Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of subjects and is mandated by regulatory agencies. The sponsor has established standard operating procedures (SOPs) in compliance with regulatory requirements worldwide to ensure appropriate reporting of safety information. All clinical trials sponsored by Theravance Biopharma will be conducted in accordance with these procedures.

7.4.2. Adverse Event and Serious Adverse Event Recording

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded from signing informed consent through the last study visit (or last subject contact in the case of a follow-up telephone call). The AEs will be recorded on the AE page of the CRF. The SAEs, regardless of relationship to study medication will be recorded from signing informed consent through the last study visit (or last subject contact in the case of a follow-up telephone call). Additionally, Investigators may report SAEs assessed as related to study medication through 30 days following the last study visit (or last subject contact in the case of a follow-up telephone call). All SAEs will be recorded on both the SAE/AESI Report Form and the AE page of the CRF and should include the following:

Description of event:

- Signs and symptoms due to a common etiology should be reported as a single diagnosis; for example, cough, runny nose, sneezing, sore throat, and head congestion would be reported as “upper respiratory infection.”
- A diagnosis or description must be as specific and as complete as possible (e.g., “lower extremity edema” instead of “edema”).
- Hospitalization or surgical procedures should not be used as AE terms (e.g., if a subject was hospitalized for cholecystectomy due to cholecystitis, the AE term should be recorded as cholecystitis, and not as the procedure, cholecystectomy).
- “Death” should not be used as an AE term unless the cause of death is unknown. For events with a fatal outcome, the cause of death should be the AE term (e.g., if a subject died of an acute myocardial infarction, the AE term should be recorded as “Myocardial Infarction” and the event outcome as fatal).

Relationship to study medication: The Investigator will make an assessment of the causal relationship of the study medication to the AE using the guidelines in Section 7.3.2.

Severity: The severity of the AE will be assessed using the guidelines in Section 7.3.1.

Outcome: The outcome of AEs will be recorded.

Therapeutic measures: Measures taken for the treatment or management of the AEs will be recorded.

7.4.3. Serious Adverse Event and Adverse Event of Special Interest Reporting Timeline

All SAEs and AESIs must be reported to Clinical Safety and Pharmacovigilance within 24-hours of the time the Investigator or his/her designee becomes aware that an SAE or AESI has occurred, whether or not the event is considered to be related to study medication. If the initial SAE or AESI is reported by telephone, a written report signed by the Investigator must be submitted within 24-hours.

The SAE/AESI Report Form must be completed in accordance with the SAE/AESI Report Form Completion Guidelines. If all information on the SAE/AESI Report Form is not available at the time of the initial report, follow-up SAE or AESI questionnaires will be completed and submitted.

To report an SAE or AESI, complete and send the SAE/AESI Report Form to the following:

Theravance Biopharma Clinical Safety

[redacted]

For medical questions regarding an SAE or AESI, contact the medical monitor by telephone as follows:

Medical Monitor Contact Information:

[redacted]

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the Investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study medication and is unexpected/unlisted based on the current TD-9855 IB. In this case, all Investigators will receive notification of the event. The Investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.5. Adverse Event Follow-up

A subject experiencing an AE, AESI, or SAE will be followed by the Investigator or his/her trained delegate(s) through the follow-up visit or until the Investigator and/or the sponsor has determined that the AE, AESI, or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The sponsor may request follow-up of certain AEs until resolution and documentation of assessments made during this period.

The Investigator must take all therapeutic measures necessary for resolution of an AE. Any medications necessary for treatment of the AE must be recorded in the concomitant medication section of the CRF.

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

All data for each subject will be listed as collected. All statistical summaries and analyses will be performed using [redacted]

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range [25% quartile, 75% quartile], minimum, and maximum) unless otherwise specified in the statistical analysis plan (SAP) or table shell. Categorical data will be summarized using counts and percentages.

For analysis, Day 1 is defined as the day of the first study medication dose. The preceding day is Day –1.

Baseline is the last assessment (scheduled or unscheduled) obtained before start of study medication dosing, unless otherwise specified in the SAP. Baseline for endpoints that have more than one component is calculated from the individual component baselines, whether or not they were assessed during the same visit.

Any changes to the data summaries and analyses outlined in this section will be described in the applicable SAP. Any changes to the definition of the endpoints will also be included in a protocol amendment.

8.2. Sample Size and Power

A total of approximately [redacted] will be randomized in a [redacted]

The primary analysis will occur when all subjects in the Full analysis set (FAS) have completed the primary endpoint assessment (OHSA#1 at Week 4) and the database has been cleaned and locked. A total sample size of [redacted] will have an overall power of 90% to detect a treatment difference of 1.5 in the primary endpoint of change from baseline in OHSA#1, assuming a common standard deviation of 3.0 for both treatment groups at a 2-sided alpha level of 0.05.

Assuming a 10% dropout rate by Week 4, it is anticipated that the study will randomize approximately [redacted] in order to achieve [redacted] in the FAS.

8.3. Analysis Sets

[redacted]

[redacted]

8.3.1. Examination of Subgroups

Predefined subgroups will include, stratification stratum (i.e., disease type), gender, and smoking status. Additional subgroups may be predefined in the SAP.

8.3.2. Major Protocol Analysis Deviations

The following protocol deviations are defined as major and would be considered to have an impact on the analysis of efficacy data:

- [redacted]
- [redacted]
- [redacted]

Additional criteria may be specified in the SAP.

8.4. General Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

8.4.1. Demographics and Other Baseline Characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index, and other medical history will be summarized.

8.4.2. Medical History

Summary of medical history will be provided.

8.5. Analysis of Efficacy

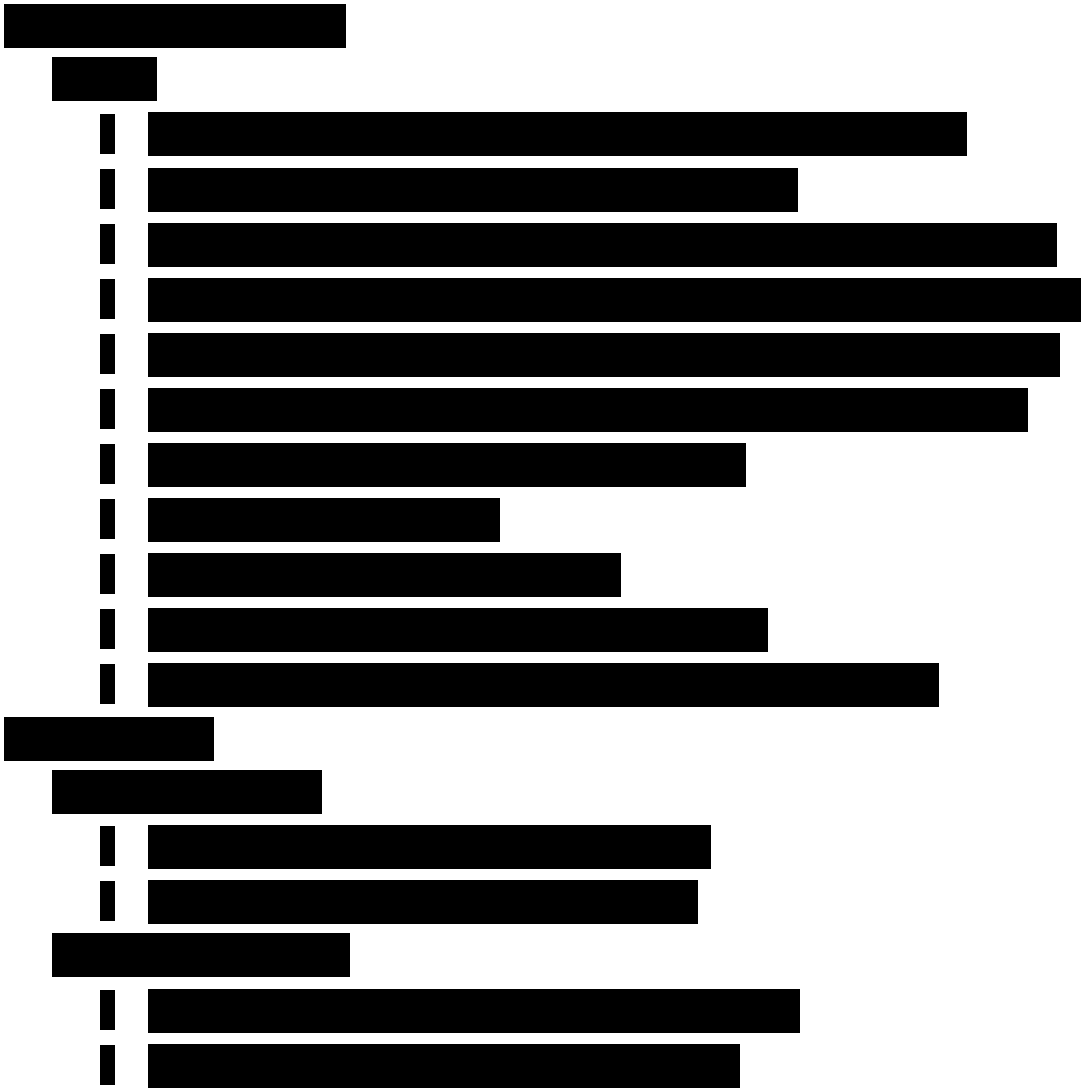
8.5.1. Efficacy Endpoints

The primary study endpoint is:

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

The secondary endpoints are:

- 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



8.5.1.1. Primary Efficacy Evaluation

The primary efficacy evaluation is the change from baseline of OHSA#1 at Week 4. Baseline is defined as Day 1 pre-dose measurement. Mixed model for repeated measures (MMRM) will be used to compare treatment differences. The model will include fixed effect class terms of treatment, baseline disease type (MSA, PD, PAF), week, and continuous covariate of baseline OHSA#1 score, a random subject effect, with an unstructured covariance structure using the FAS. If the model doesn't converge, compound symmetry or other covariance structures will be used as alternative covariance structure.

Least-square means and 95% confidence intervals on the differences between TD-9855 and placebo will be calculated and presented.

Missing data in the MMRM analysis is assumed as missing at random (MAR) and will not be imputed for the analysis of the primary endpoint. Sensitivity analyses of the primary endpoint will be conducted using multiple imputation.

The primary analysis will be repeated on a set of prespecified subgroups and presented in graphical format.

8.5.1.2. Secondary and Exploratory Efficacy Evaluations

The secondary efficacy endpoints involving assessment of change from baseline, such as OHSA composite score and OHDAS composite score, will be analyzed in a similar fashion as the primary efficacy endpoint of change from baseline in OHSA#1.

The PGI-C will be summarized as number and percentage for subjects with 'no change or better' and 'worse than no change' at Week 4. Incidence of falls will be summarized as number and percentage of subjects with at least 1 fall in Week 4. The PGI-C and incidence of falls will be tested using Cochran-Mantel Haenzel chi-square test stratified by disease type at baseline.

8.5.2. Multiplicity Adjustment

If the treatment effect of the primary efficacy endpoint has been demonstrated at a 2-sided statistical significance level of 5%, secondary efficacy endpoints (Section 8.5.1) will be tested using the same statistical significance level. The secondary endpoints will be tested sequentially via a prospectively defined order to be described in the SAP, until a failure to reject the null hypothesis occurs. No statistical significance will be claimed after a failure to reject the null hypothesis has occurred.

For all supportive analyses including sensitivity analyses of the primary efficacy endpoint and exploratory endpoints, nominal p-values and 95% confidence intervals with no adjustment for multiplicity will be presented.

8.5.3. [redacted]

[redacted]

8.5.4. [redacted]

[redacted]

8.6. Safety Analyses

Safety data, including C-SSRS, will be summarized by treatment received. Summaries will be provided by nominal visit and time point or for the entire treatment period, as appropriate for the type of data. Quantitative data collected at unscheduled times will be listed but will not be included in summaries. Categorical data collected at unscheduled times (e.g., ECG finding categories) will not be included in summaries by time point but will be included in summaries of findings during the entire treatment period.

Safety analyses will be performed using the safety analysis set. Unless specified otherwise there will be no imputation of missing data in safety summaries. Subjects without post baseline measurement (e.g. ECG or vital signs) for a given time point will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

8.6.1. Extent of Exposure

[redacted]

8.6.2. Adverse Event Data

The AEs will be coded to the preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will present by system organ class (SOC), preferred term, and severity (mild, moderate, severe), the number and percentage of subjects for whom events were reported.

In general, a treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date and time of the first dose of study medication and up to the date of last dose of study medication plus the number of days in the follow-up period.

The number and percentage of subjects who experience TEAEs will be summarized. Summaries of TEAEs will include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

All AEs reported will be listed by subject. A listing will be provided for all subjects who experience an SAE. Listings will also be provided for subjects who discontinued study treatment prematurely because of AEs and subjects who temporarily interrupted study treatment because of AEs. The AESIs, as described in Section 7.1.4, will be listed and summarized.

8.6.3. Concomitant Medications

All medications used during the 60 days prior to screening will be recorded in the source records. The only exception is drugs that were used to treat previous orthostatic hypotension; these will be recorded since the time of primary diagnosis.
Medication names will be mapped according to the World Health Organization Drug Dictionary. Both prior and concomitant medications summaries will be provided, by drug class and preferred name.

8.6.4. Laboratory Data

Laboratory values, changes from baseline, values relative to normal ranges, and values and changes meeting specified criteria, will be summarized.

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

8.6.5. Vital Signs Data

The HR, systolic and diastolic BP, RR, and body temperature values at each visit and time point and changes from baseline at each visit and time point after the first dose will be summarized and counts and percentages will be shown for the categories.

Table 2: Vital Sign Assessment Outlier Thresholds

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

8.6.6. Electrocardiogram Data

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

Table 3: Electrocardiogram Test 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	

In addition, QTcF (msec) 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).

All recorded ECG interval values and ECG assessments will be presented in a by-subject listing. A separate listing of subjects with extreme values or changes, as specified in the SAP (e.g., values of QTcF ≥450 msec if male or ≥470 msec if female, QTcF increases from baseline >60 msec) will be provided.

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

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

Cumulative distribution plots will be provided for maximum change in QTcF by day.

8.7. Missing Data Handling

[redacted]

8.7.1. Mitigation and Analysis Strategies in Response to COVID-19

[redacted]

8.8. Independent Data Monitoring Committee

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

9. STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1. Principal Investigator Responsibilities

Before beginning the study, the PI at each site must provide to the sponsor or its designee either a fully executed and signed Form FDA 1572 (for US sites) or the equivalent information on the study-specific form. If applicable, a "Disclosure: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455; Financial Disclosure Form) should also be provided. For applicable studies, Financial Disclosure Forms must also be completed for all sub-investigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A sub-investigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows, research staff designed as Clinical Outcome Assessment (COA) raters].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study, including oversight of the home health provider.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the applicable local and international regulatory requirements relating to obtaining informed consent at that site are met, for example in the US, compliance with Chapter 21 Code of Federal Regulations (CFR) Part 50 and IRB review and approval in 21 CFR 56 is required and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with applicable local and international harmonized regulatory requirements, for example in the US, 21 CFR 312.64 is required and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required.
- He or she has read and understands the information in the TD-9855 IB, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments.
- He or she will ensure that adequate and accurate records in accordance with local and international regulatory requirements, and to make those records available for inspection, for example in the US, in accordance with 21 CFR 312.62 and 21 CFR 312.68 and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required.

- He or she will ensure that the IRB/ Independent Ethics Committee (IEC) complies with the local and international regulatory requirements (for example in the US, compliance with 21 CFR 56 is required and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required), and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other local and international regulatory requirements regarding the obligations of clinical Investigators and all other pertinent requirements, for example, in the US, 21 CFR 312, and outside of the US, ICH E6 and/or local regulatory requirements.

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the Investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and Good Clinical Practice (GCP) requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until the Investigator has been notified by the sponsor that regulatory agency approval of the clinical trial (or acknowledgement of the notification if applicable) has been received and appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the Investigator and copies are received by the sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the sponsor study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The Investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3. Informed Consent

A properly written and executed ICF, in compliance with-ICH E6 (GCP Guideline, Section 4.8), 21 CFR 50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. The Investigator will prepare the ICF or revise the template ICF and provide the documents to the sponsor (or designee) for approval before submission to the IRB/IEC/REB. The sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

The Investigator will provide copies of the signed ICF to each subject (or the subject's legally authorized representative) and will maintain the original in the subject's record file.

9.4. Data Recording and Quality Assurance

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

A CRF (approved by the sponsor) is required and should be completed (in English) for each randomized subject. The Investigator has ultimate responsibility for the accuracy, authenticity, completeness, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms. The Investigator must review and sign the CRFs to attest that the data contained on the CRFs are correct.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic CRFs approved by the sponsor, or via other data collection methods, e.g., electronic clinical outcome assessments (eCOA), electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each subject that is screened. Training on systems used by site personnel (e.g. EDC, eCOA) or study subjects (e.g. eCOA) will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The Investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The Investigator is designated as the signatory coordinating Investigator.

An electronic copy of the CRF casebooks and eCOAs will be sent to the site for retention with other study documents after full completion of the study, i.e., after database lock.

The Investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The Investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the Investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5. Document Retention

Until otherwise notified by the sponsor, an investigative site must retain in a controlled manner all study documents required by the sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The Investigator must consult the sponsor representative before disposal of any study records and must notify the sponsor of any change in the location or disposition of the study files. If an Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6. Confidentiality

The Investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, the study sponsor's affiliated companies, the study sponsor's designated service providers, regulatory agencies, and the IRB or IEC. The Investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the US) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the Investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the Investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7. Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the sponsor, representatives of the sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The Investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8. Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the sponsor will monitor all aspects of the study according to GCP and SOPs for compliance with applicable government regulations. The Investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the sponsor or its designees.

Members of the sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs, and applicable laws, rules, and regulations.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify the sponsor immediately. The Investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation), and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an Investigator, institution, institution staff, or representatives of the sponsor will lead to prompt action by the sponsor to secure compliance. Continued noncompliance may result in termination of the Investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9. Publication

The sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The sponsor will retain the ownership of the data collected in this study. The Investigator will provide any proposed manuscript or abstract to the sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between the sponsor and the Investigator.

10. REFERENCES

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11. APPENDICES

APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0169
Protocol 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
Version:	1.0 [redacted]
Version Date:	05 August 2020

I have read the protocol described above and agree to conduct this study in accordance with the procedures described therein. I also agree to conduct the study in compliance with all applicable regulations.

Investigator's Name (print)

Investigator's Signature

Date

APPENDIX 2. EXAMPLES OF DISEASE INSTRUMENTS

Appendix 2-1

Theravance Biopharma	Protocol: 0169		[redacted]
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	
Visit	Subject ID Number		
	1 6 9 -	-	

Orthostatic Hypotension Symptom Assessment (OHSA)

Please circle the number on the scale that best rates how severe your symptoms from low blood pressure have been ***on the average*** over the past week. Please respond to every symptom. If you do not experience the symptom, circle zero (0). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM

1. Dizziness, lightheadedness, feeling faint, or feeling like you might blackout

NONE 0 1 2 3 4 5 6 7 8 9 10 WORST POSSIBLE

2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)

NONE 0 1 2 3 4 5 6 7 8 9 10 WORST POSSIBLE

3. Weakness

NONE 0 1 2 3 4 5 6 7 8 9 10 WORST POSSIBLE

4. Fatigue

NONE 0 1 2 3 4 5 6 7 8 9 10 WORST POSSIBLE

5. Trouble concentrating

NONE 0 1 2 3 4 5 6 7 8 9 10 WORST POSSIBLE

6. Head/neck discomfort

NONE 0 1 2 3 4 5 6 7 8 9 10 WORST POSSIBLE

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Protocol: 0169																
Visit	Subject ID Number													Rater Initials		
	1	6	9	-						-						

Orthostatic Hypotension Daily Activities Scale (OHDAS)

We are interested in how the low blood pressure symptoms you experience affect your daily life. Please rate each item by circling the number that best represents how much the activity has been interfered with ***on the average*** over the past week by the low blood pressure symptoms you experienced.

If you cannot do the activity for reasons other than low blood pressure, please check the box at the right.

1. Activities that require standing for a short time

No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference

CANNOT DO FOR OTHER REASONS ☐

2. Activities that require standing for a long time

No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference

CANNOT DO FOR OTHER REASONS ☐

3. Activities that require walking for a short time

No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference

CANNOT DO FOR OTHER REASONS ☐

4. Activities that require walking for a long time

No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference

CANNOT DO FOR OTHER REASONS ☐

THR173023_0169_OHQ_English(US)_v1.0_2018_Aug_01.doc

Appendix 2-2

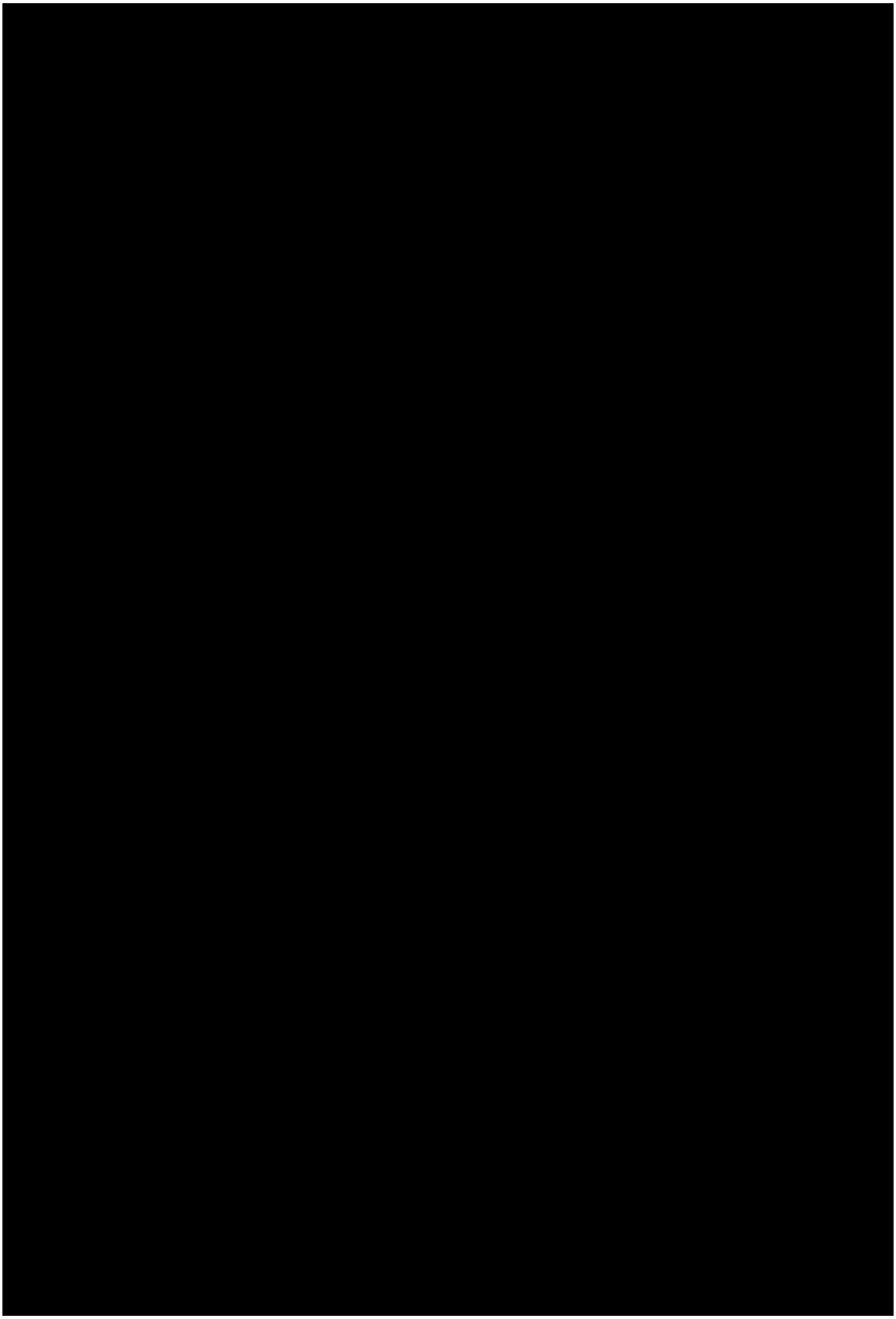
Theravance Biopharma	Protocol: 0169													[redacted]
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)				
												:		
Visit	Subject ID Number													
	1	6	9	-						-				

Patient Global Impression of Change (PGI-C)

Please choose the response below that best describes the overall change in your neurogenic orthostatic hypotension symptoms **since you started taking the study medication**.

- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse

Appendix 2-3



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Appendix 2-4

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Appendix 2-5

[redacted]

[redacted]

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Appendix 2-6

[redacted]

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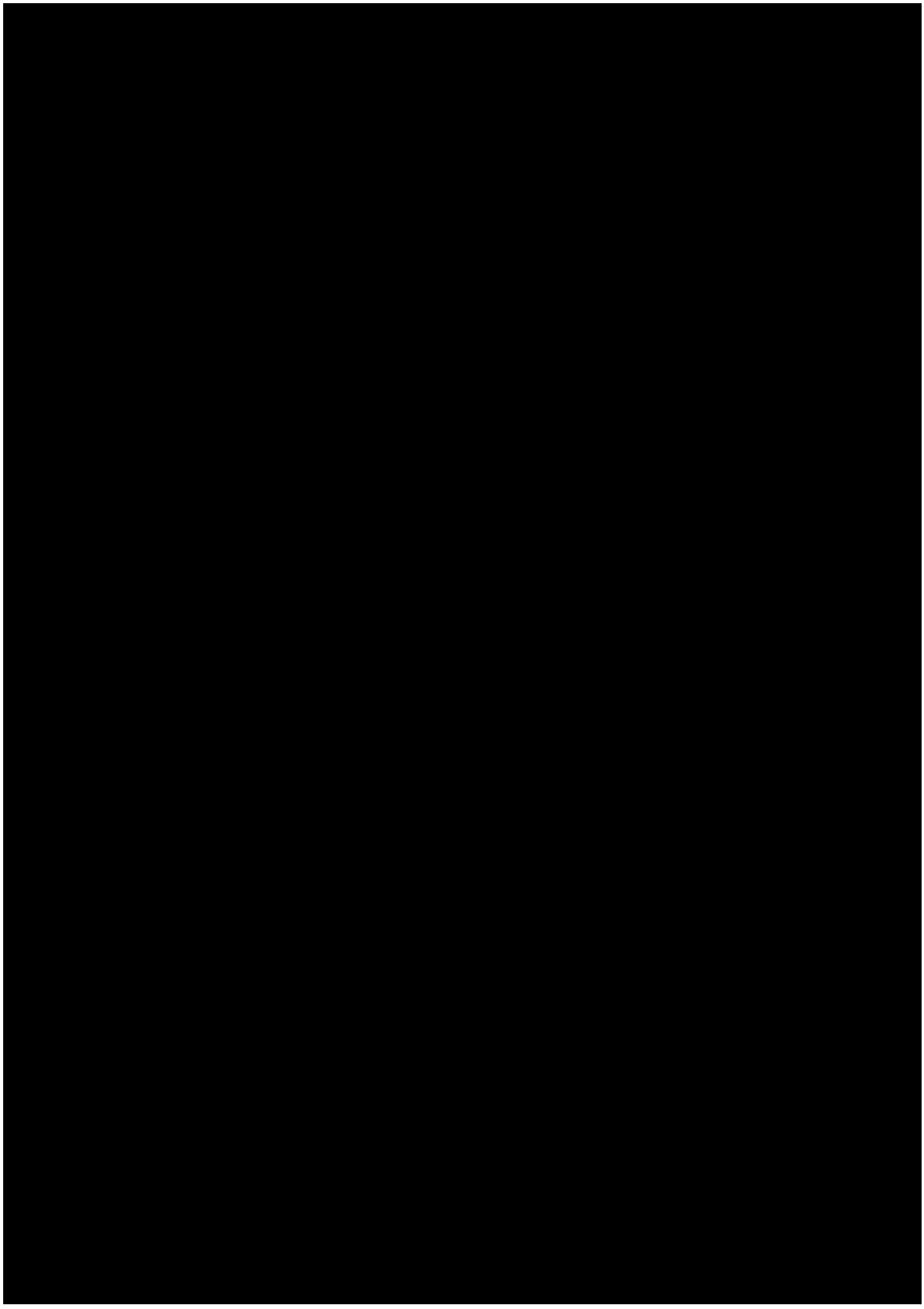
[redacted]



Appendix 2-7

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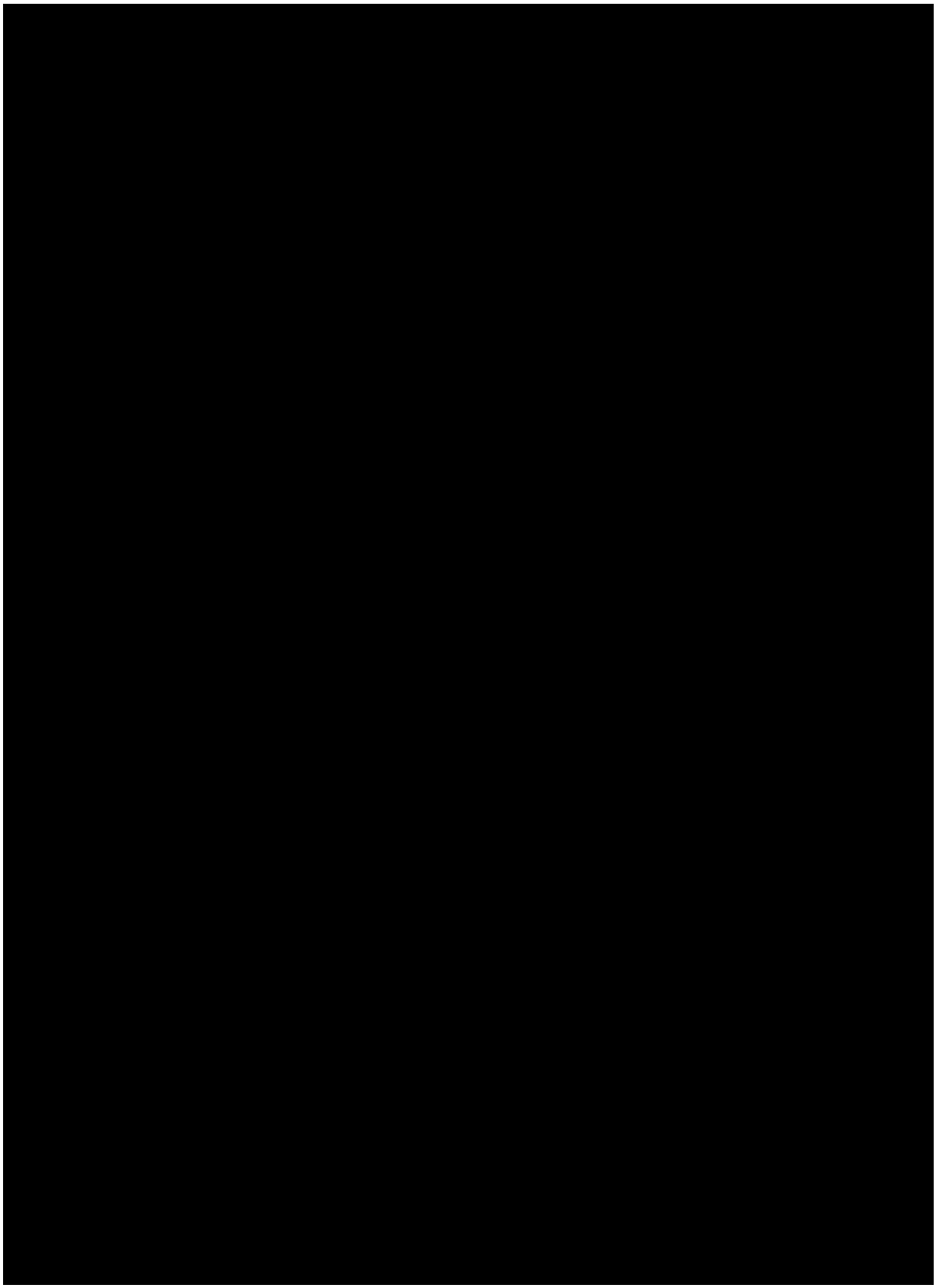
Appendix 2-8

[redacted]

[redacted]

[redacted]



Appendix 2-9

[redacted]

[redacted]

Appendix 2-10

[redacted]

Appendix 2-11

Theravance Biopharma	Protocol: 0169		[redacted]
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	
Visit	Subject ID Number		Rater Initials
	169- -		

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

Appendix 2-12

Protocol: 0169																			
Visit	Subject ID Number															Rater Initials			
	1	6	9	-						-									

SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**		**Past 12 Months**	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
INTENSITY OF IDEATION				
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation*** <u>Past 12 Months</u> - ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation***	Most Severe		Most Severe	
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___		___	
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	___		___	
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	___		___	
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply	___		___	
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply	___		___	

 C-SSRS—Baseline/Screening (Version 1/14/09)

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Protocol: 0169																		
Visit	Subject ID Number															Rater Initials		
	1	6	9	-						-								

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 12 Months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Baseline/Screening (Version 1/14/09)

Appendix 2-13

Theravance Biopharma	Protocol: 0169													[redacted]
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:		
Visit	Subject ID Number													Rater Initials
	1	6	9	-						-				

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

Protocol: 0169																	
Visit	Subject ID Number														Rater Initials		
	1	6	9	-						-							

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
___

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
___

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
___

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
___

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
___

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Protocol: 0169																			
Visit	Subject ID Number															Rater Initials			
	1	6	9	-						-									

SUICIDAL BEHAVIOR
(Check all that apply, so long as these are separate events; must ask about all types)

Since Last Visit

Actual Attempt:
A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.
Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.
Have you made a suicide attempt?
Have you done anything to harm yourself?
Have you done anything dangerous where you could have died?
What did you do?
Did you_____as a way to end your life?
Did you want to die (even a little) when you_____?
Were you trying to end your life when you_____?
Or Did you think it was possible you could have died from_____?
Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)
If yes, describe:

Yes ☐ No ☐

Total # of Attempts _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes ☐ No ☐

Interrupted Attempt:
When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.
Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?
If yes, describe:

Yes ☐ No ☐

Total # of interrupted _____

Aborted Attempt:
When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?
If yes, describe:

Yes ☐ No ☐

Total # of aborted _____

Preparatory Acts or Behavior:
Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?
If yes, describe:

Yes ☐ No ☐

Suicidal Behavior:
Suicidal behavior was present during the assessment period?

Yes ☐ No ☐

Suicide:

Yes ☐ No ☐

Answer for Actual Attempts Only

Most Lethal Attempt Date:

Actual Lethality/Medical Damage:
0. No physical damage or very minor physical damage (e.g., surface scratches).
1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).
2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).
3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).
4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).
5. Death

Enter Code _____

Potential Lethality: Only Answer if Actual Lethality=0
Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).

0 = Behavior not likely to result in injury
1 = Behavior likely to result in injury but not likely to cause death
2 = Behavior likely to result in death despite available medical care

Enter Code _____

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Appendix 2-14

Theravance Biopharma	Protocol: 0169		[redacted]
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	
Visit	Subject ID Number		Rater Initials
	169- -		

Montreal Cognitive Assessment
(MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from 1 then to A then to 2 and so on. End here* [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 −A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: "*Copy this drawing as accurately as you can, in the space below*".

Scoring: One point is allocated for a correctly executed drawing.
- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a **clock**. Put in all the numbers and set the time to 10 past 11".*

Scoring: One point is allocated for each of the following three criteria:
- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

THR173023_0169_MoCA_English(US)_Version 7.1_2018-Jul-30

4. Naming:

Administration: Beginning on the left, point to each figure and say: *"Tell me the name of this animal".*

Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions*: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them".* Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *"I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.
At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, *"I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them*". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.*" Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.*: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*".

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: *"Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. **Sentence repetition**:

Administration: The examiner gives the following instructions: *"I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]: ***I only know that John is the one to help today."*** Following the response, say: *"Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]: ***The cat always hid under the couch when dogs were in the room."***

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today," substituting "hides" for "hid", altering plurals, etc.).

8. **Verbal fluency**:

Administration: The examiner gives the following instruction: *"Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready?* [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop."*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

9. **Abstraction**:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: *"Tell me how an orange and a banana are alike"*. If the subject answers in a concrete manner, then say only one additional time: *"Tell me another way in which those items are alike"*. If the subject does not give the appropriate response *(fruit)*, say, *"Yes, and they are also both fruit."* Do not give any additional instructions or clarification. After the practice trial, say: *"Now, tell me how a train and a bicycle are alike"*. Following the response, administer the second trial, saying: *"Now tell me how a ruler and a watch are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:
Train-bicycle = means of transportation, means of travelling, you take trips in both;
Ruler-watch = measuring instruments, used to measure.
The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark (√) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues.**

Optional:
Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (√) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *"Which of the following words do you think it was, NOSE, FACE, or HAND?"*
Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE:	category cue: part of the body	multiple choice: nose, face, hand
VELVET:	category cue: type of fabric	multiple choice: denim, cotton, velvet
CHURCH:	category cue: type of building	multiple choice: church, school, hospital
DAISY:	category cue: type of flower	multiple choice: rose, daisy, tulip
RED:	category cue: a colour	multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

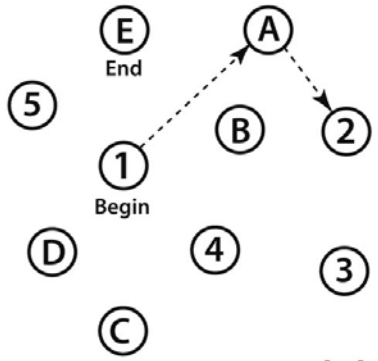
TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

Appendix 2-15

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



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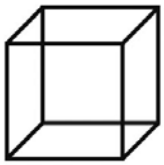


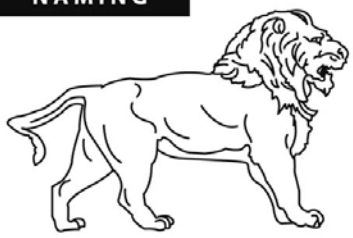
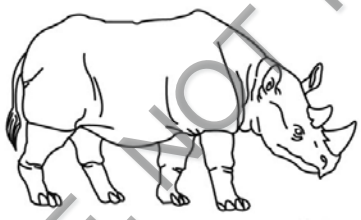
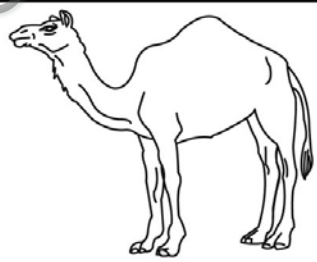
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX 3. INCIDENCE OF FALLS

Subject ID: ______________________

Visit Dispensed: ________________ **Date Returned:** ____________________

Instructions:

1) For each **Time of Day**, entry should be made at the end of that time period.

2) If you did not fall or have a near-fall, put a check mark in the **No Falls** or **No Near-Falls** box for that time of day.

3) If you had a fall or near-fall, record the number of **Falls** or **Near-Falls** in the appropriate box for that time of day.

Definitions:

A fall is defined as: **an unexpected event in which you come to rest on the ground, floor, or lower level.**

A near-fall is defined as: **losing your balance but managing to stay upright, for example by holding on to something or someone.**

Day of the Week/ Date	Time of Day	No Falls	No Near-Falls	Falls	Near-Falls
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______
Day of the Week:	Morning: Awakening to 12PM			Number = ______	Number = ______
	Afternoon: 12 PM to Bedtime			Number = ______	Number = ______
Date:	Night: Bedtime to Awakening			Number = ______	Number = ______

If you recorded a **Fall** or **Near Fall** above, were you injured as a result?

Please check one: No___ or Yes___

APPENDIX 4. AMBULATORY BLOOD PRESSURE MONITORING - POSITION DIARY

Marin 0169 Ambulatory Blood Pressure Monitoring - Position Diary

Subject ID: ____________________

Date Diary Dispensed: ________________ **Date Diary Returned:** __________________

Instructions: YOU MUST BRING THIS DIARY TO EVERY STUDY VISIT

1) Please indicate the Day of the Week, Date, Time, Your Body Position, and any comments.
2) Each "**Time and Subject's Body position**" entry should be completed immediately after the inflation and deflation cycle. The date and day of the week should be the **start** of the 24 hour monitoring.
3) You will hear a warning beep a few seconds before each inflation.
4) You should remain still, in position you are in (standing, sitting or lying down) at the time the automatic inflation starts.
5) You should relax your arm and allow the device to go through the inflation and deflation cycle.

Start Date: _________________ **Day of the Week:** _________________

Time		Body position
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:
_____:_____	☐ am ☐ pm	☐ Standing ☐ Sitting ☐ Lying down ☐ Other ____________________ Comments:

TO BE COMPLETED BY SITE PERSONNEL ONLY:
I confirm that I have carefully reviewed all entries in this diary.
Signature of Reviewer: ________________ Date of Review: ________________
Reviewer Print Name: ________________ Reviewer Title: ________________

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APPENDIX 5. DOSING DIARY

Subject ID:_____

Date Diary Dispensed:_____ **Date Diary Returned:**_____

Instructions: YOU MUST BRING THIS DIARY AND YOUR STUDY MEDICATIONS TO EVERY STUDY VISIT

1) Please indicate the Day of the week, date, time, and any comments.
2) For each "**Time**", immediately after taking the medication the entry for time should be
3) Dosing should occur every day at approximately the same time
4) Do not use any recreational drugs or drink excessive alcohol during the study period.
5) Do not participate in another investigational study.
6) Refrain from making any significant dietary changes throughout the duration of the study.
7) Ensure adequate fluid intake during the scheduled visits
8) Subjects who are smokers will be recommended to either stop smoking >7 days before first dose or maintai a constant smoking habit during the entire course of the study.

Day of the Week/ Date	Time	Comments (Eg: -Reason for missed or partial dose -Significant Dietary Changes)
Day of the Week: Date:	_____:_____	
Day of the Week: Date:	_____:_____	
Day of the Week: Date:	_____:_____	
Day of the Week: Date:	_____:_____	
Day of the Week: Date:	_____:_____	
Day of the Week: Date:	_____:_____	
Day of the Week: Date:	_____:_____	

TO BE COMPLETED BY SITE PERSONNEL ONLY:

I confirm that I have carefully reviewed all entries in this diary.

Signature of reviewer: _____ Date of Review: _____

Reviewer Print Name: _____ Reviewer Title: _____

[redacted]

[redacted]

[redacted]

APPENDIX 9. OVERVIEW OF DECENTRALIZATION PLAN

This appendix provides information for those sites who choose to conduct remote study visits for at least one of their subjects. Detailed instructions for the conduct of both in clinic and remote study visits can be found in the Study Procedures Manual, which must be used in conjunction with the protocol.

The Principal Investigator retains accountability for all data collected and processed for each study subject either via in clinic or remote visits. Procedures to protect subject safety, subject privacy, and data integrity will be followed by all personnel (clinic and home health personnel) involved in study conduct.

Rationale for Decentralized Platform:

Considering the frailty of the symptomatic nOH subject population, the risk of future exposure to COVID-19 via in clinic visits, the unpredictable duration of the pandemic, and the potential for additional waves of the COVID-19 pandemic, the study will utilize an operational design featuring the ability for sites to conduct protocol required visits as either in clinic or remote visits.

Selection of Visit Modality:

The Screening visit for all subjects must be conducted in clinic, regardless of which visit modality selection an Investigator and subject make.

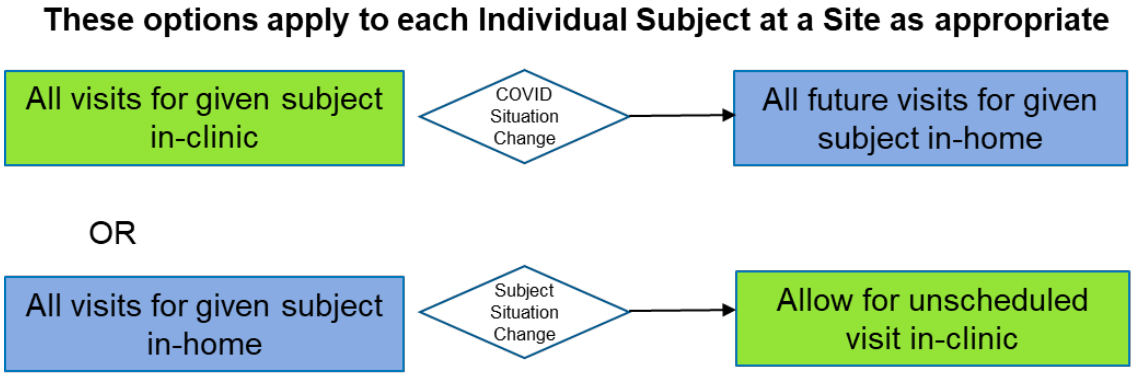
All sites must conduct all study visits for Study 0169 for a given subject in a consistent manner to reduce the possibility of variability in data collection and reporting. Therefore, Investigators, in discussion with each individual subject at their site, will be required to elect to conduct all visits either in the clinic, or remotely.

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).

For those sites who opt to use remote visits (the decentralized platform) for study conduct, all required regulatory and ethics committee or IRB approvals will be obtained before utilization of remote study visits under the decentralized platform.

Sites will use the most recent approved version of the Informed Consent Form to obtain subject consent for remote study visits.

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 typed of study visit modality due to COVID-19 or COVID-19 related circumstances. Approved exceptions will be recorded as COVID-19 related protocol deviations.



Before a change in visit type from in clinic to remote is made, the Investigator will submit an exemption request to the Sponsor via the established process. Theravance (or their designee) will review and respond to these exemption requests as per established processes and timelines. Requests for and approval of exemptions in visit modality will be documented and retained in study records at the Investigator site.

Once an Investigator and subject have elected a visit type (in clinic or remote) the expectation is for all post-Screening visits for that subject to be conducted via the same modality, except as described above.

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.

Conduct of the Study and the Decentralized Platform:

All sites will follow the protocol Schedule of Procedures (see Table 1 of the protocol) for study visit scheduling and protocol required procedures (either in clinic or remote). Refer to the Study Procedures Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

Training and mechanisms will be available to sites and subjects to support remote visits.

Sites will continue to follow their established processes and procedures for the conduct of in-clinic study visits.

Study operations support for remote visits:

Tools and systems are provided by the Sponsor and are available to sites and subjects to support remote visits:

- A courier service has been engaged to ship investigational study drug and other study supplies to the subject (or designee).

- A standardized HIPAA/GDPR compliant telemedicine platform will be provided so that site personnel can participate in remote visits that are conducted in the subject's home (or designated location), utilizing Home Health Providers.
- A Home Health Provider (HHP) service has been employed.
- Medically qualified and trained HHP staff employed will visit the subject's home (or designated location) and will work with Site Staff (SS) to conduct each remote study visit from the privacy of the subject's home or designated location (such as a caregiver's home).
- During these remote visits, in coordination with Site Staff, the HHPs will use the Rater Station to facilitate collection of patient reported outcomes, will collect blood samples for safety labs and PK testing, will collect ECGs, and will measure the subject's vital signs.
- All data collected during the remote visits will be transferred to the Investigator and the study site via established processes (either electronically or on paper).

Data signifying where the visit was conducted (in clinic or remote), how the data were collected, and who collected data remotely will be recorded in subject source documents and in the clinical study database.

A Home Health Provider Delegation Log will be used to record the names of HHP professionals who assist Site Staff with the conduct of the remote visits. This separate delegation log will distinguish between those individuals who are part of the site staff (recorded on Site Delegation Log) and those who are employed by the HH Provider.

Logistics Arrangements for Remote Visits:

For remote study visits, the home health personnel conducting the visit will be notified by the clinic-based study staff of each upcoming scheduled visit for the study subject(s). The clinic-based staff will coordinate with the home health personnel to ensure access to all necessary subject source documents, required equipment, and procedural instructions to complete the remote assessment.

Clinic-based staff will participate in the remote study visit(s) via the established telemedicine platform available for the study.

Home health personnel will transfer the source documents completed during the remote visit to the Investigator's site via established processes. Home health personnel will transfer via established secure means the data collected in electronic format to the appropriate data repository for inclusion in the clinical database.

Data collected in paper format (subject diaries and any handwritten source notes) will be retrieved by HHP during the remote visit and will be returned to the Investigator's site.

Appropriate technical support and training will be provided to facilitate remote conduct of required study assessments.

Laboratory samples collected by home health personnel during the remote visit will be prepared for shipment to designated laboratories following established collection and shipping procedures.

Summary:

In closing, the tools, mechanisms, and processes put into place as part of the Decentralized Platform support sites and subjects who choose remote visits. Further, they protect subject safety, privacy, and consistency in data collection and reporting. In the event of future resurgences of the COVID-19 pandemic, these tools, mechanisms, and processes will be available to sites and subjects who have selected the in clinic visit modality.