Protocol Number: 0170

NCT Number: NCT03829657

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

Document Date: 05 August 2020

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure
Study Short Title:	Phase 3 Clinical Effect Durability of TD-9855 for Treating symptomatic nOH in Subjects with Primary Autonomic Failure (Redwood Study)
Sponsor Study No.:	0170
Date:	05 August 2020, Amendment 4 Replaces: Amendment 3, Date: 20 March 2020 Amendment 2, Date: 04 December 2019 Amendment 1, Date: 04 March 2019 Original Protocol Date: 05 November 2018
Test Product:	TD-9855 (ampreloxetine hydrochloride) tablets
US IND:	129797
EudraCT No.:	2018-003941-41
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
Clinical Study Director:	Michael Markowitz, MD Executive Director, Clinical Development, Neurology Theravance Biopharma Ireland Limited Telephone: +1-919-414-9948 Email: mmarkowitz@theravance.com

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

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0170: A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure

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

Estimated Number of Study Centers and Countries or Regions: Approximately 150 clinical research sites in approximately 25 countries

Background and Rationale:

In healthy individuals, changes in blood pressure (BP) are highly regulated and well controlled- with systolic blood pressure (SBP) being transiently and minimally reduced upon standing. This is reflective of the normal physiological response in which neuronally mediated pathways remain intact, thereby maintaining the appropriate cerebral perfusion. Individuals with impaired compensatory mechanisms may develop orthostatic hypotension (OH), which reduces cerebral perfusion pressure and may lead to a sensation of lightheadedness, dizziness, or syncope, amongst other symptoms. In disorders with primary or secondary autonomic impairment, OH is accompanied by the profound reduction in or failure of norepinephrine (NE) neurotransmission and is said to be neurogenic in nature[1]. Disorders with prominent autonomic impairment include neurodegenerative diseases, such as Parkinson's disease (PD), multiple system atrophy (MSA) and pure autonomic failure (PAF). Common amongst these conditions are the reported loss of peripheral sympathetic nerves containing NE in PD and PAF patients, or the central mechanism controlling NE release becoming dysfunctional in patients with MSA. When neurogenic orthostatic hypotension (nOH) becomes symptomatic, the experienced sudden drop in BP can cause dizziness, visual problems and fatigue, which greatly interfere with the daily activities of patients. This interference is highly debilitating and may cause severe injuries through frequent falling leading to potential increases in disability and morbidity[2,3].

Recent developments in the understanding of the underlying pathophysiology of various clinical forms of autonomic failure have revealed that patients with MSA are characterized by impairment of central autonomic pathways crucial for autonomic cardiovascular control but have intact peripheral postganglionic noradrenergic fibers. This is evidenced by the near normal levels of circulating plasma NE in these patients, and by the observation that cardiac uptake of labeled catecholamines is intact[4]. This latter observation implies the presence of both intact noradrenergic nerve terminals and catecholamine reuptake mechanisms. Thus, patients with MSA have peripheral residual sympathetic tone that is no longer modulated by central autonomic centers and is not under baroreflex control, which cannot be harnessed to improve orthostatic hypotension.

It is now recognized that the continual degeneration of dopaminergic neurons in the substantia nigra is preceded by the loss of non-dopaminergic neurons including NE neurons of the locus coeruleus in patients with PD. These losses ultimately result in the tremor, rigidity, akinesia and postural instability associated with PD[5,6]. In the early stages of the disease, PD and MSA follow similar pathophysiology and may be difficult to distinguish clinically.

PROTOCOL SYNOPSIS (CONTINUED)

Patients with PAF are also characterized by neurodegeneration and loss of peripheral noradrenergic fibers, as evidenced by lower levels of plasma NE and absent cardiac uptake of labeled catechols. However, the presence of residual sympathetic tone principally means that NE reuptake inhibition may serve as a useful treatment in this subset of both PAF and PD patients.

Pharmacological inhibition of NE transporters (NET) may prove beneficial toward the treatment of primary autonomic disorders by permitting patients to take advantage of their own remaining residual sympathetic tone. Norepinephrine transport inhibition increases tonically released synaptic NE by preventing its reuptake, resulting in increased BP and relief from the symptomatic effects ensuing from critical falls in BP. This mechanism of action (i.e., inhibition of NE uptake) may also offer an improved safety profile relative to other mechanisms of action, such as the addition of exogenous NE or NE prodrug. For example, published proof-of-concept studies indicate that the NET inhibitor atomoxetine is an effective pressor agent in these patients, and acutely improves standing SBP and symptoms of orthostatic intolerance[7,8].

TD-9855 (ampreloxetine hydrochloride), a new chemical entity, is a potent NE reuptake inhibitor (NRI) being developed for a range of medical treatments. It has a high affinity for binding to NE and serotonin (5-HT) transporters and is designed to demonstrate selectivity for inhibition of NE versus 5-HT uptake.

TD-9855 is orally bioavailable with pharmacokinetic (PK) properties supportive of once daily dosing. The safety and tolerability of TD-9855 have been demonstrated in a single ascending dose (SAD) study in healthy subjects at doses ranging from 2 to 50 mg and a multiple ascending dose (MAD) study in healthy subjects at daily doses of 4, 10, 20, and 40 mg for up to 14 days. In healthy subjects, a single dose up to 50 mg and multiple doses up to 20 mg daily (QD) of TD-9855 were generally well tolerated. The PK of TD-9855 was linear with near dose proportional exposure in terms of C_{max} and AUC across the anticipated therapeutic range. TD-9855 has an elimination half-life ($t_{1/2}$) of approximately 30 to 40 hours achieving steady state by 6 days. Consistent with the elimination half-life, 3- to 4-fold accumulation of TD-9855 was observed at steady state. Based on clinical PK studies in healthy subjects, TD-9855 is >90% eliminated through metabolism and CYP1A2 is the primary enzyme driving TD-9855 metabolism. Accordingly, drug-drug interactions are expected with strong inhibitors and inducers of CYP1A2 impacting TD-9855 exposure.

The safety, tolerability, and efficacy of TD-9855 were also evaluated in two Phase 2 studies including subjects with attention-deficit hyperactivity disorder (ADHD) and Fibromyalgia (FM). TD-9855 doses of 5 mg and 20 mg QD were administered for 6 weeks in both studies and was generally well tolerated with no clinically significant safety signals.

Theravance conducted a study in adult subjects with primary autonomic failure (including MSA, PD, and PAF) in which TD-9855 was investigated for the treatment of symptomatic neurogenic orthostatic hypotension (symptomatic nOH). In the 0145 Study, TD-9855 was administered to subjects once daily in doses up to 20 mg for a duration of 20 weeks to evaluate the effect on symptoms of symptomatic nOH, pressor response, safety, and tolerability.

PROTOCOL SYNOPSIS (CONTINUED)

Objectives:

The primary objectives of the study are:

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

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

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

The exploratory objectives of the study are:

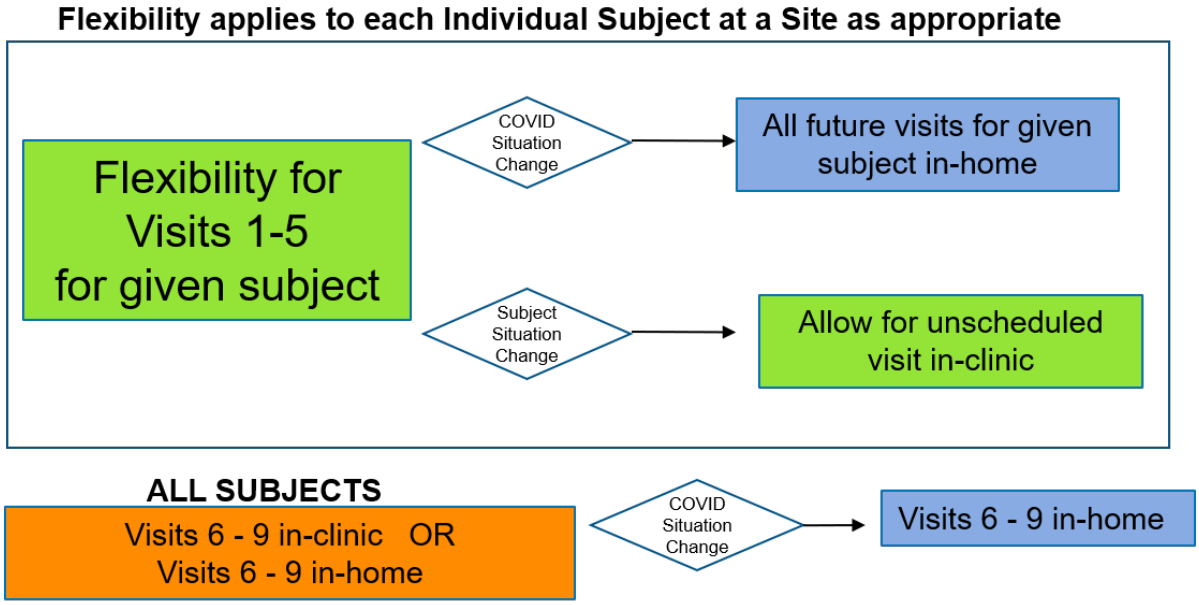
- To evaluate the effect of TD-9855 using disease-specific instruments and generic quality of life assessment
- To evaluate the effect of TD-9855 using standing blood pressure during orthostatic standing test.
- To evaluate the effect of TD-9855 using generic quality of life assessment EuroQol-5D-5L (EQ-5D-5L), Non-Motor Symptom Scale (NMSS), and Hospital Anxiety and Depression Scale (HADS)
- To evaluate pharmacodynamic markers (NE and dihydroxyphenylglycol [DHPG])
- To inform population PK modeling through collection of sparse PK samples
- To assess caregiver burden in caring for subjects with primary autonomic failure using Burden Scale for Family Caregivers - short version (BSFC-s).

Study Design:

This is a Phase 3, multi-center, randomized withdrawal study to evaluate the sustained benefit in efficacy and safety of TD-9855 in subjects with primary autonomic failures (MSA, PD, or PAF) and symptomatic nOH after 22 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, in discussion with each individual subject at their site, will be required to elect to conduct study visits either in the clinic or remotely. Sites must conduct the randomization withdrawal visits 6 through 9 (V6/D113 - V9/D155) for a given subject in a consistent manner to reduce the possibility of variability in data collection and reporting. Tools and systems are available to sites and subjects to support remote visits (e.g., direct to subject

PROTOCOL SYNOPSIS (CONTINUED)

shipping of study medication and other study supplies, standardized HIPAA/GDPR compliant telemedicine platform, in-home health nurses).



Due to the potential for resurgence of COVID-19 and its impact on both sites and subjects, the Sponsor will allow Investigators to request exceptions to the selected type of study visit modality for V6/D113 through V9/D155 due to COVID-19 or COVID-19 related circumstances. Approved exceptions will be recorded as COVID-19 related protocol deviations.

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

For De Novo subjects that have previously completed the Screening visit at the time regulatory and ethics approval for Amendment 4 is received, sites must reconsent the subject using the most recently approved version of the Informed Consent Form to obtain subject consent for remote study visits, if that modality is selected by the Investigator and subject. For those subjects who are already randomized into the randomized withdrawal portion of Study 0170 and active in the study at the time regulatory and ethics approval for Amendment 4 is received, the Investigator and subject should continue the remaining study visits in the same visit modality as the Randomization Visit (V6, D113).

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.

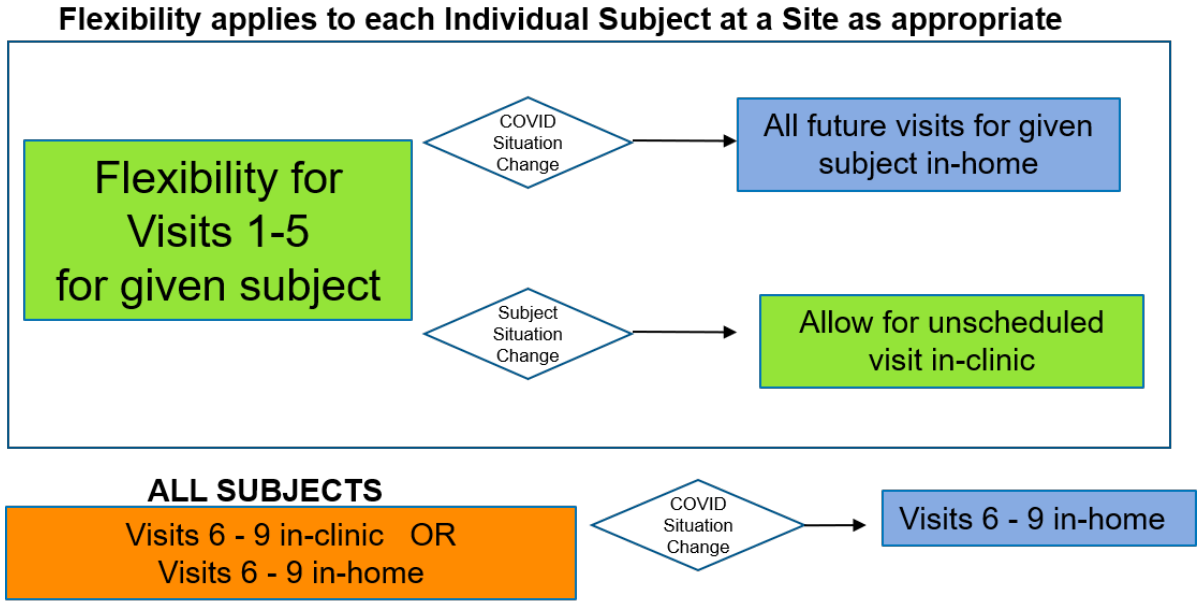
Eligible subjects are either (i) completers of Study 0169 (0169 Completers Group), or (ii) symptomatic nOH subjects meeting all applicable study inclusion criteria and none of the applicable exclusion criteria (De Novo Group).

PROTOCOL SYNOPSIS (CONTINUED)

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) 16-week open-label (OL) treatment with TD-9855, (ii) 6-week randomized placebo-controlled treatment, and (iii) 2-week follow-up (only for patients who do not enroll in Study 0171). A 4-week screening period will apply to the De Novo Group only and the Screening visit must be conducted in clinic for ALL De Novo group subjects. The schematic representation is as shown below:



Subjects entering from Study 0169 (0169 Completers Group)

Following signing of the informed consent, subjects will enter Study 0170 Visit 1 (V1), which will be conducted on the same day as V6/D29 of Study 0169. Sponsor preference is the visit modality for Study 0170, either in-clinic or remote for each subject, should be consistent with the visit modality selected by the given subject for Study 0169.

Study 0169 procedures conducted at V6/D29 will serve as the baseline assessments for V1/D1 of Study 0170.

Beginning on Day 2, subjects will receive a single dose of 10-mg TD-9855 once daily (QD) and continue thereafter for the 16-week duration of the OL treatment period. Following this 16-week OL treatment period, subjects will be randomized to either continue on the active treatment or PBO for a period of 6 weeks.

Subjects not participating in Study 0169 (De Novo Group)

Following signing informed consent, subjects will enter a screening period of up to 4 weeks to confirm eligibility. At the Screening visit (Visit S), which must be performed in the clinic, subjects will provide a comprehensive medical history of their disease and treatments. The

PROTOCOL SYNOPSIS (CONTINUED)

subjects' disease will be characterized and documented by the principal Investigator (PI) or sub-Investigator.

Subjects will receive an assessment of their physical condition, including safety and laboratory evaluations and related aspects of their disease states according to the Schedule of Study Procedures. The presence of symptomatic nOH must be confirmed using a tilt-table test.

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

Following the screening period, subjects will proceed to V1 to further confirm the additional eligibility criteria prior to proceeding. This includes the completion of the Orthostatic Hypotension Questionnaire (OHQ) in which a minimum score of 4 points in OHSA#1 is required.

Subjects meeting all inclusion criteria, none of the exclusion criteria and whose disease characterization is confirmed by the independent Enrollment Steering Committee (ESC) will receive TD-9855 in the OL period.

Beginning on Day 2, subjects will receive a single dose of 10-mg TD-9855 once daily (QD) and continue thereafter for the 16-week duration of the OL treatment period. Following this 16-week OL treatment period, subjects will be randomized to either continue on the active treatment or PBO for a period of 6 weeks.

Enrollment Steering Committee (for De Novo Group only)

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 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.

Open Label Period (Weeks 1 to 16)

Subjects enrolled into the OL period of the study will have visits scheduled for Day 15, Day 29, and every 4 weeks thereafter for assessments as outlined in the Schedule of Study Procedures. At V3 (Week 4), following the initial 4-week OL treatment, subjects must demonstrate a reduction in OHSA#1 of at least 2 points compared to the baseline value, as

PROTOCOL SYNOPSIS (CONTINUED)

determined in Study 0169 for subjects entering from Study 0169 and from V1 for De Novo Group subjects, in order to continue in Study 0170. Those subjects not meeting this continuation criterion must be discontinued and undergo an end of study visit. The end of study visit must be completed within 2 weeks from the date of the last dose.

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

Double-blind Period (Weeks 17 to 22)

Following the completion of a total of 16 weeks OL treatment with TD-9855 (V6) subjects will be assessed for randomization in a 1:1 manner. Eligible subjects will receive 6 weeks of double-blind treatment of TD-9855 or PBO once daily. Only subjects with OHSA#1 score of ≤7 will be eligible for randomization for the double-blind treatment period.

Treatment period (Weeks 1 to 22):

No dose reduction is permitted during the treatment period.

Subjects unable to tolerate 10-mg TD-9855 will be discontinued from the study.

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

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

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

Safety will be periodically reviewed by an Independent Data Monitoring Committee (IDMC).

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

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

PROTOCOL SYNOPSIS (CONTINUED)

Duration of Study Participation: Up to 24 weeks for subjects coming from Study 0169 and up to 28 weeks for de novo subjects.

Number of Subjects: The total number of subjects participating in this study will be approximately 258. After the 16-week OL phase, at least 154 subjects are expected to be randomized to either the TD-9855 or the PBO group, stratified by the subject's background disease type (MSA, PD, or PAF), assuming 60% are eligible for randomization at the end of the OL phase.

For the De Novo Group, the goal is to enroll at least 40% of MSA subjects.

All completers from study 0169 will be eligible to participate in study 0170. Assuming 10% early discontinuation, approximately 170 subjects are anticipated to be eligible for the 0169 Completers Group.

Study Population:

This study will enroll adult subjects with confirmed symptomatic nOH due to MSA, PD or PAF and who meet the inclusion and exclusion criteria defined below. Eligible subjects may be de novo or completers from Study 0169.

Inclusion Criteria (For 0169 Completers Group):

101. Completion of 4 weeks of double-blind treatment in Study 0169 (V6) and, in the opinion of the Investigator, could benefit from continued treatment with TD-9855. No minimum score of OHSA#1 is required to enter V1 of Study 0170.
102. The subject has a minimum of 80% study medication compliance in Study 0169.
103. The subject must be able to understand the nature of the study and must provide written informed consent prior to the conduct of any study procedures (including an understanding that entry to Study 0170 may result in changes occurring in the subject's current therapeutic regimen).
104. The subject must be willing to continue on treatment regardless of the possibility of randomization to either TD-9855 or PBO during the randomized withdrawal phase and must continue to meet the inclusion criteria for the preceding study (Study 0169) with the exception that tilt-table test, ESC review and approval of eligibility are not required for entry into Study 0170.

Inclusion Criteria (For De Novo Group):

1. Subject is male or female and at least 30 years old.
2. If subject is female, the subject must be non-pregnant and non-lactating. 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 beta human chorionic gonadotropin (bHCG) test is positive, a serum bHCG test must be

PROTOCOL SYNOPSIS (CONTINUED)

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 ≥60^{o} from a supine position as determined by a tilt-table test.
5. Subject must score at least a 4 on the OHSA#1 at V1.
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 understand clinic staff, understands the expectations of the study and is able to comply with the study procedures, requirements, and restrictions.

Exclusion Criteria (For 0169 Completers Group):

101. Subject may not be enrolled in another clinical trial (other than exiting Study 0169).
102. Subject has psychiatric, neurological, or behavioral disorders that may interfere with the ability of subjects to give informed consent or interfere with the conduct of the study.
103. Medical, laboratory, or surgical issues deemed by the Investigator to be clinically significant.
104. Uncooperative attitude or reasonable likelihood of non-compliance with the protocol.
105. 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.

Exclusion Criteria (For De Novo Group):

1. Subject has a known systemic illness known to produce autonomic neuropathy, including, but not limited to, amyloidosis and autoimmune neuropathies. Subject has

PROTOCOL SYNOPSIS (CONTINUED)

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.
4. Subject has used strong CYP1A2 inhibitors or inducers within 7 days or 5 half-lives, whichever is longer, prior to V1 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 V1.
   - Midodrine and droxidopa (if applicable) must be tapered off at least 7 days prior to V1.
6. Subject has known or suspected alcohol or substance abuse within the past 12 months (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR®] definition of alcohol or substance abuse).
7. Subject has a clinically unstable coronary artery disease or has had a 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 V1.
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 had any malignant disease, other than carcinoma in situ of the cervix or basal cell carcinoma, within the past 2 years prior to screening.

PROTOCOL SYNOPSIS (CONTINUED)

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 drug that is not approved by a regulatory agency (e.g., Food and Drug Administration [FDA]).
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/1.73 m^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.

Continuation Criteria

- At V3 (Week 4), following the initial 4-week OL treatment, subjects must demonstrate a reduction in OHSA#1 of at least 2 points compared to the baseline value, as determined in Study 0169 for subjects entering from Study 0169 and from V1 for de novo subjects, in order to continue in Study 0170.

Randomization Criteria for Double-Blind Period

201. Subject has OHSA#1 score of ≤7.
202. Subject's unused OL study medications (10-mg TD-9855 tablets) are returned to site.
203. The subject has a minimum of 80% study medication compliance in OL treatment period.

PROTOCOL SYNOPSIS (CONTINUED)

204. Subjects with excessive deterioration of disease or symptoms during the OL phase and in the opinion of the Investigator, would not benefit from the continual participation in the study.

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

- Subjects must stop the concomitant use of strong CYP1A2 inhibitors and inducers 7 days or 5 half-lives, whichever is longer, prior to randomization. This restriction applies to concomitant medications, herbal supplements (e.g., St John's Wort), and ordinary dietary intake. Please refer to Appendix 7 for a list of prohibited medications.
- Prescribed medications for OH other than fludrocortisone are prohibited
- Alpha blockers are prohibited (e.g., Prazosin, Terazosin, Doxazosin, Silodosin, Alfuzosin, Tamsulosin)
- Norepinephrine reuptake inhibitors (NRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are prohibited
  - NRIs (e.g., atomoxetine and reboxetine) and SNRIs (e.g., duloxetine, milnacipran, levomilnacipran, venlafaxine, desvenlafaxine)
- Psychostimulants (e.g., amphetamine, dextroamphetamine, methylphenidate, pemoline) are prohibited
- 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

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

For OL treatment period:

All subjects will receive TD-9855 and continue to take the study medication once daily starting on Day 2 through the end of the treatment period. The test product will be TD-9855 supplied as a 10-mg tablet in 35-count high-density polyethylene bottles.

For randomized treatment period:

Subjects randomized to TD-9855 will receive TD-9855 tablets and continue to take the study medication once daily starting in the morning post randomization (Day 2) through the end of the treatment period. The test product will be TD-9855 supplied as a 10-mg tablet in 35-count or 5-count high-density polyethylene bottles labeled in a blinded fashion (i.e., bottle label for test product will be indistinguishable from reference product except for a coded, unique bottle number).

For both treatment periods:

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

PROTOCOL SYNOPSIS (CONTINUED)

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

For OL treatment period

No subjects will receive the reference product.

For randomized treatment period

Subjects randomized to PBO will receive PBO tablets that match TD-9855 tablets in excipient content (except for absence of TD-9855), appearance, tablet count, and in packaging (i.e., bottle label for reference product will be indistinguishable from test product except for a coded, unique bottle number).

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

Study Evaluations

Efficacy Assessments:

- OHQ and PGI-S
- Subject's symptomatic improvement as measured by a wearable device

Exploratory Assessments:

- Orthostatic standing test
- NMSS
- EQ-5D-5L
- HADS
- BSFC-s

For subjects with PD:

- Unified Parkinson's Disease Rating Scale (UPDRS)
- Parkinson's Disease Questionaire-8 (PDQ-8)

For subjects with MSA:

- Unified Multiple System Atrophy Rating Scale (UMSARS)
- Composite Autonomic Symptom Score-31 (COMPASS-31)

Safety and Tolerability Assessments:

- Physical examination including weight
- Neurological examination
- Vital signs including ambulatory BP
- Resting ECGs

PROTOCOL SYNOPSIS (CONTINUED)

- Clinical laboratory assessments including serum chemistry, hematology, and urinalysis
- Concomitant medications
- AEs
- C-SSRS

Pharmacokinetic Assessments:

A sparse PK sampling strategy is being employed in this study where samples will be taken at select study visits as defined in the Schedule of Study Procedures. Time of ingestion of study medication will be accurately documented the day before and the day of each study visit when PK samples will be collected.

Pharmacodynamic Assessments:

Blood samples for pharmacodynamic markers ([dihydroxyphenylglycol] DHPG and NE) will be collected at select study visits as defined in the Schedule of Study Procedures after the subject has been seated for 30 minutes. This is applicable to all consenting subjects.

Statistical Methods

Sample Size:
A total sample size of 154 at randomization will provide an overall power of 90% to detect a difference of 25% (25% TD-9855 vs. 50% PBO) in the primary endpoint of the proportion of subjects that meet the criteria of treatment failure at Week 6 (V9, D155) during the double-blind randomized withdrawal phase at two-sided alpha level of 0.05.

Assuming that 60% are eligible for randomization at the end of the 16-week OL period, approximately 258 subjects will be enrolled such that 154 subjects are expected to continue into the randomized treatment period. For the De Novo Group, the goal is to enroll at least 40% of MSA subjects.

Study Endpoints:

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

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

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

The secondary endpoints include:

- Change from baseline in OHSA#1 at Week 6 post randomization (V9, D155)
- Change from baseline in OHSA composite score at Week 6 post randomization (V9, D155)

PROTOCOL SYNOPSIS (CONTINUED)

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

Exploratory endpoints include:

- Standing SBP during orthostatic standing test at Week 6 post randomization (V9, D155)
- Change from baseline in OHQ overall composite score at Week 6 post randomization (V9, D155)
- Change from baseline in EQ-5D-5L at Week 6 post randomization (V9, D155)
- NMSS at Week 6 post randomization (V9, D155)
- HADS at Week 6 post randomization (V9, D155)
- BSFC-s at Week 6 post randomization (V9, D155)

For subjects with PD

- Change from baseline in UPDRS at Week 6 post randomization (V9, D155)
- Change from baseline in PDQ-8 at Week 6 post randomization (V9, D155)

For subjects with MSA

- Change from baseline in UMSARS at Week 6 post randomization (V9, D155)

  Change from baseline in COMPASS-31 at Week 6 post randomization (V9, D155)

Safety and tolerability endpoints include:

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

Exploratory Endpoints include:

- PK and pharmacodynamic parameters

PROTOCOL SYNOPSIS (CONTINUED)

Analysis:

All efficacy analyses in the double-blind randomized withdrawal phase will be performed based on the Full Analysis Set (FAS) using the assigned randomized treatments. The FAS of the double-blind randomized withdrawal phase is defined as all randomized subjects who have received at least 1 dose of study medication post randomization.

The safety analysis set (Safety) of the double-blind randomized withdrawal phase is comprised of all randomized subjects who have receive at least 1 dose of study medication and subjects will be analyzed according to actual study treatments they receive.

The FAS and Safety for OL phase will be identical and is defined as all enrolled subjects who have received at least one dose of TD-9855.

In the double-blind randomized withdrawal phase, unless specified otherwise, all data will be summarized by treatment group. In the OL phase all data will be summarized for all subjects and by enrollment group (De Novo Group or 0169 Completers 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 study endpoint is the proportion of treatment failure at Week 6 during the double-blind randomized withdrawal phase. Treatment failure is defined as subjects who meet the following criteria at Week 6 following randomization (V9, D155):

> **Change (worsening) from baseline in OHSA#1 score of 1.0 point <u>and</u> worsening of disease severity as assessed by a 1-point change in PGI-S.**

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

The Logistic regression model will be used to compare treatment differences based on the FAS. The model will include fixed effect class terms of treatment, baseline disease type (MSA, PAF, PD), and continuous covariate of baseline OHSA#1 score, and baseline PGI-S score. Odds ratio with 95% confidence intervals will be calculated and presented, least-square proportion and 95% confidence intervals on the differences between TD-9855 and PBO groups will be calculated and presented. In addition, the proportion of subject with treatment failure along with proportion of subjects failing separately due to worsening of OHSA#1 and PGI-S will be reported.

Sensitivity analyses on the primary endpoint will be carried out (1) using per-protocol set which excludes subjects with major protocol deviations, (2) using multiple imputation for subject missing OHSA#1 and/or PGI-S score at Week 6 post randomization (V9, D155) and (3) by excluding subjects with missing data on primary endpoint.

The primary analysis will be repeated on a set of pre-specified subgroups (e.g., disease type) and presented in graphical format. Details will be specified in the Statistical Analysis Plan (SAP).

Secondary efficacy endpoints involving assessment of change from baseline at multiple time points such as OHSA#1, OHSA composite score, OHDAS composite score, and percent of

PROTOCOL SYNOPSIS (CONTINUED)

time spent in supine, sitting, and standing position as measured by a wearable device, will be analyzed using mixed model for repeated measures (MMRM) to compare treatment differences based on the FAS. The model will include fixed effect class terms of treatment, baseline disease type (MSA, PD, PAF), week, and continuous covariate of baseline score of the respective scale, a random subject effect, with an unstructured covariance structure. 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 PBO will be calculated and presented.

Exploratory endpoints involving assessment of change from baseline at multiple time points such as standing SBP during orthostatic standing test will be analyzed similarly.

Exploratory endpoints involving assessment of change from baseline but only at Week 6 post randomization (V9, D155) such as PDQ-8, UPDRS, UMSARS, and COMPASS-31, an analysis of covariance (ANCOVA) will be used to compare treatment differences based on the FAS. The model will include fixed effect of treatment, baseline disease type (MSA, PD and PAF) and continuous covariate of baseline score of the respective scales.

Secondary efficacy endpoints will be tested via a 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%.

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

For all supportive analyses including sensitivity analyses of the primary efficacy endpoint and other efficacy endpoints, p-values and confidence intervals will be evaluated descriptively at two-sided 5% level with no adjustment for multiplicity.

In addition, descriptive analysis of efficacy data collected during OL phase will be carried out for all subjects and by enrollment group (De Novo Group or 0169 Completers Group).

Safety data will be listed by subject and summarized using the frequency of event or descriptive statistical summaries, as appropriate. Summaries and listings will be presented separately for OL phase and double-blinded randomized withdrawal phase. Summary tables will be provided for vital signs, body weight, ECGs, safety laboratory tests, C-SSRS, AEs, and concomitant medications.

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

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

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Study Period:	**Screening [a] (De Novo Group Only – in clinic)**	**Open Label Treatment (Visits either in clinic or remote for each subject)**					**Randomized Withdrawal Period (For each subject, Visits 6 through 9, all either in clinic or remote)**				**Follow-up[c]**
Study Day (Visit):	**-28 to -7 (Visit S)**	**Day 1 (Visit 1)[b]**	**Day 15 (Visit 2) +/- 3 days**	**Day 29 (Visit 3) +/- 3 days**	**Day 57 (Visit 4) +/- 3 days**	**Day 85 (Visit 5) +/- 3 days**	**Day 113 (Visit 6) +/- 3 days**	**Day 127 (Visit 7) +/- 3 days**	**Day 141 (Visit 8) +/- 3 days**	**Day 155 (Visit 9) / ET +/- 3 days**	**Day 169 (Visit 10) +/- 3 days**
COMPASS-31 (MSA Subjects only)		X[e]			X		X			X	
EQ-5D-5L		X[e]			X		X			X	
BSFC-s		X[e]		X	X	X	X	X	X	X	
Orthostatic standing test[k]	X	X[e]		X	X	X	X	X	X	X	
Vital signs (BP, HR, RR and body temperature)[l]	X	X[e]	X	X	X	X	X	X	X	X	X
Height (cm)	X										
Weight (kg)	X	X[e]					X			X	X
Physical examination[m]	X	X[e]	X				X			X	
Neurological examination	X	X[e]					X			X	
12-lead electrocardiogram[n]	X	X[e]		X			X			X	
Pregnancy test[o]	X	X[e]					X			X	
Norepinephrine (NE)	X										
Safety laboratory test (chemistry, hematology, and urinalysis)	X	X[e]	X		X		X			X	
Pharmacokinetic sampling[p]					X		X	X			
Pharmacodynamic sampling[q]		X[e]			X						

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

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

Abbreviations: BSFC-s: Burden Scale for Family Caregivers - short version; BP: Blood Pressure; COMPASS-31: Composite Autonomic Symptoms Score-31; C-SSRS: Columbia Suicide Severity Rating Scale; ESC: Enrollment Steering Committee; ET: Early Termed; EQ-5D-5L: EuroQol-5D-5L; HADS: Hospital Anxiety and Depression Scale; HR: Heart Rate; MoCA: Montreal Cognitive Assessment; MSA: Multiple System Atrophy; NMSS: Non-motor Symptom Scale; OHDAS: Orthostatic Hypotension Daily Activity Scale; OHSA: Orthostatic Hypotension Symptom Assessment; OHQ: Orthostatic Hypotension Questionnaire; OL: Open Label; PAF: Pure Autonomic Failure; PD: Parkinson's Disease; PDQ-8: Parkinson's Disease Questionaire-8; PGI-S: Patient Global Impression of

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Severity; RTSM: Randomization and trial supply management; RR: Respiratory Rate; UMSARS: Unified Multiple System Atrophy Rating Scale; UPDRS: Unified Parkinson's Disease Rating Scale.

a. Screening Visit must be conducted in clinic for ALL De Novo group subjects. Subject eligibility will be assessed by the Investigator during screening and primary diagnosis will be verified by the ESC prior to Day 1 (for De Novo Group subjects only); subjects meeting OHSA#1 criterion on Day 1 and who otherwise meet eligibility criteria may be enrolled via RTSM.
b. For 0169 Completers Group, Study 0169 procedures conducted at D29 will serve as the baseline assessments for D1 of Study 0170 .
c. Follow-up visit is only applicable for those subjects that do not proceed to Study 0171 and will be completed two weeks from the date of the last dose. Those subjects proceeding to Study 0171 will enter from V9.
d. The De Novo Group subjects would sign the consent before screening, thus screening visit is only applicable for De Novo Group subjects, and the 0169 Completers Group would sign the consent before V1 and would start with Day 1 of Study 0170.
e. The assessments or procedures will be performed within 24-hours prior to subject taking the study medication (pre-dose). Following completion of study assessments, the subjects will take study medication on Day 2 in the morning.
f. A complete medical and medication history evaluation will be performed during screening (for de novo subjects only).
g. 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 applicable study visit that occurs during treatment with study medication. Subjects should be rested prior to beginning the training.
h. The tilt-table test should be performed following at least 12-hours of withdrawal from vasoactive medications. The tilt-table test should be performed at least 2 hours after meals and with an empty bladder.
i. Subjects will be randomized via RTSM once they meet the randomization criteria
j. The UPDRS scale should be completed in an ON state, and within 1-4 hours of taking the PD medications. All UPDRS Parts will be completed on Day 1 for De Novo Group subjects, while only Parts 2 and 3 of the questionnaire would be completed for 0169 Completers Group, and for subsequent visits for De Novo Group subjects.
k. The assessment should be performed at approximately (±2 hour) the same time of day on Day 1 (except Screening). Subjects should abstain from eating for at least 90mins prior to this assessment.
l. The vital sign measurements should be performed after the subject has rested sufficiently as determined by the appropriate site staff. The BP and HR collected at 10 minutes supine and seated from the orthostatic standing test can be used for safety vital signs assessment. Vitals can be performed as part of the mandated procedures, if needed.
m. A full physical examination at the Screening visit will be performed (for de novo subjects only). Subsequent physical examinations, per discretion of the Investigator, can be abbreviated and symptomatic.
n. ECGs are done in triplicate after the subject has been resting for at least 5 minutes in a seated or supine position before the first reading, with each replicate separated by at least 1 minute. The total time to conduct ECGs ideally would not exceed 15 minutes
o. In women of childbearing potential only. First, urine beta human chorionic gonadotropin (bHCG) test will be performed and if positive, confirmation with serum bHCG test is required. The pregnancy test must be confirmed negative for a subject to be eligible for this study.
p. Blood samples will be collected for TD-9855 PK on the days specified. All PK sampling times will be accurately recorded by collection date, hour, and minute. Study medication dosing time on the day before each PK collection and on the day of each PK collection will be accurately recorded by dosing date, hour, and minute by the study staff using time recorded in Dosing Diary by Subjects.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

q. Blood samples for pharmacodynamic markers (norepinephrine (NE) and dihydroxyphenylglycol (DHPG)), will be collected after the subject has been seated for 30 minutes. Blood sample for NE will be collected at screening (for De Novo Group subjects only) while samples for both NE and DHPG will be collected on Day 1 and Day 57. Note that all pharmacodynamic marker samples should be collected at approximately (±1 hour) the same time of day on Day 1 and Day 57 so that time-matched analysis can be performed.

r. Ambulatory blood pressure monitoring (ABPM) equipment will be provided to the De Novo Group subjects during the screening visit and on Day 1 to 0169 Completers Group. Beginning approximately 72 to 24-hours before a subject returns to the clinic for visits, subjects will put on the 24-hour blood pressure monitoring equipment and initiate the recording. Once the 24-hour session is complete, subjects will remove and return the equipment to the research center during the next visit. During each 24-hour session, the blood pressure monitoring device will be programmed to automatically measure blood pressure every 2 hours beginning at the top of the hour. During each 24-hour session, subjects will also log their posture in the ABPM Position Diary at the time of each blood pressure measurement. Details regarding the ambulatory monitoring will be provided in a separate manual. The assessment on D1 is only for De Novo Group subjects.

s. For wearables, in countries where the wearable devices are available, 2 consecutive days of device usage will be required on the days shown. The 2 consecutive days of device usage should take place within 5 days before the subsequent visit. Site coordinators will monitor subject compliance. If the site coordinator becomes aware that a subject has not performed the required device usage, they will contact the subject and remind them to use the device.

t. Study medication will be ingested orally without regard to food at approximately the same time each morning and taken with approximately 8 ounces of water. The exact time and day of dosing will be recorded by the subject in the Dosing Diary on the mornings of study visits.
During their scheduled visits, subjects should be reminded to maintain an adequate fluid intake. For OL treatment period, subjects would start taking medications starting on Day 2.

u. Valsalva maneuver is to be performed for PAF subjects only if no results are available within 24 months from the date of randomization.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
3-D	3-dimensional
5-HT	Serotonin
ABPM	Ambulatory blood pressure monitoring
ADHD	Attention-deficit hyperactivity disorder
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANS	Autonomic Nervous System
ASP	Autonomic Symptom Profile
AST	Aspartate aminotransferase
AUC	Area Under the Curve
bHCG	Beta human chorionic gonadotropin
BP	Blood pressure
BSFC-s	Burden Scale for Family Caregivers - short version
CFR	(United States) Code of Federal Regulations
C_{max}	The maximum concentration recorded
CNS	Central Nervous System
COA	Clinical Outcome Assessment
COMPASS	Composite Autonomic Symptom Score
COMPASS-31	Composite Autonomic Symptom Score-31
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

Abbreviation	Description
ET	Early Termed/ Early Termination
EQ VAS	EQ Visual Analogue Scale
EQ-5D-5L	EuroQol-5D-5L
FAS	Full analysis set
FDA	Food and Drug Administration
FM	Fibromyalgia
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
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

Abbreviation	Description
NET	Norepinephrine transporter
NMSS	Non-motor Symptom Scale
nOH	Neurogenic Orthostatic Hypotension
NOAEL	No-observed-adverse-event level
NRI	Norepinephrine reuptake inhibitor
NYHA	New York Heart Association
OATP1B3	Organic anion transporting polypeptide 1B3
OH	Orthostatic Hypotension
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHQ	Orthostatic Hypotension Questionnaire
OHSA	Orthostatic Hypotension Symptom Assessment
OHSA#1	Orthostatic Hypotension Symptom Assessment Question 1
OL	open label
PAF	Pure Autonomic Failure
PBO	placebo
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
PDQ-8	Parkinson's Disease Questionaire-8
PGI-S	Patient Global Impression of Severity
P-gp	p-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
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

Abbreviation	Description
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
UMSARS	Unified Multiple System Atrophy Rating Scale
UPDRS	Unified Parkinson’s Disease Rating Scale
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 controlled with systolic blood pressure (SBP) being transiently and minimally reduced upon standing. This is reflective of the normal physiological response in which neuronally mediated pathways remain intact, thereby maintaining the appropriate cerebral perfusion. Individuals with impaired compensatory mechanisms may develop orthostatic hypotension (OH), which reduces cerebral perfusion pressure and may lead to a sensation of lightheadedness, dizziness, or syncope, amongst other symptoms. In disorders with primary or secondary autonomic impairment, OH is accompanied by the profound reduction in or failure of norepinephrine (NE) neurotransmission and is said to be neurogenic in nature[1]. Disorders with prominent autonomic impairment include neurodegenerative diseases, such as Parkinson's disease (PD), multiple system atrophy (MSA), and pure autonomic failure (PAF). Common amongst these conditions are the reported loss of peripheral sympathetic nerves containing NE in PD and PAF patients, or the central mechanism controlling NE release becoming dysfunctional in patients with MSA. When neurogenic orthostatic hypotension (nOH) becomes symptomatic, the experienced sudden drop in BP can cause dizziness, visual problems, and fatigue, which greatly interfere with the daily activities of patients. This interference is highly debilitating and may cause severe injuries through frequent falling, leading to potential increases in disability and morbidity[2,3].

Recent developments in the understanding of the underlying pathophysiology of various clinical forms of autonomic failure have revealed that patients with MSA are characterized by impairment of central autonomic pathways crucial for autonomic cardiovascular control but have intact peripheral postganglionic noradrenergic fibers. This is evidenced by the near normal levels of circulating plasma NE in these patients, and by the observation that cardiac uptake of labeled catecholamines is intact[4]. This latter observation implies the presence of both intact noradrenergic nerve terminals and catecholamine reuptake mechanisms. Thus, patients with MSA have peripheral residual sympathetic tone that is no longer modulated by central autonomic centers and is not under baroreflex control, which cannot be harnessed to improve orthostatic hypotension.

It is now recognized that the continual degeneration of dopaminergic neurons in the substantia nigra is preceded by the loss of non-dopaminergic neurons including NE neurons of the locus coeruleus in patients with PD. These losses ultimately result in the tremor, rigidity, akinesia, and postural instability associated with PD[5,6]. In the early stages of the disease, PD and MSA follow similar pathophysiology and may be difficult to distinguish clinically.

Patients with PAF are also characterized by neurodegeneration and loss of peripheral noradrenergic fibers, as evidenced by lower levels of plasma NE and absent cardiac uptake of labeled catechols. However, the presence of residual sympathetic tone principally means that NE reuptake inhibition may serve as a useful treatment in this subset of both PAF and PD patients.

Pharmacological inhibition of NE transporters (NET) may prove beneficial toward the treatment of primary autonomic disorders by permitting patients to take advantage of their own remaining residual sympathetic tone. Norepinephrine transport inhibition increases tonically released synaptic NE by preventing its reuptake, resulting in increased BP and relief from the symptomatic effects ensuing from critical falls in BP. This mechanism of action

(i.e., inhibition of NE uptake) may also offer an improved safety profile relative to other mechanisms of action, such as the addition of exogenous NE or NE prodrug. For example, published proof-of-concept studies indicate that the NET inhibitor atomoxetine is an effective pressor agent in these patients, and acutely improves standing SBP and symptoms of orthostatic intolerance[7,8].

TD-9855 (ampreloxetine hydrochloride), a new chemical entity, is a potent NE reuptake inhibitor (NRI) being developed for a range of medical treatments. It has a high affinity for binding to NE and serotonin (5-HT) transporters and is designed to demonstrate selectivity for inhibition of NE versus 5-HT uptake.

TD-9855 is orally bioavailable with pharmacokinetic (PK) properties supportive of once daily dosing. The safety and tolerability of TD-9855 have been demonstrated in a single ascending dose (SAD) study in healthy subjects at doses ranging from 2 to 50 mg and a multiple ascending dose (MAD) study in healthy subjects at daily doses of 4, 10, 20, and 40 mg for up to 14 days. In healthy subjects, a single dose up to 50 mg and multiple doses up to 20 mg daily (QD) of TD-9855 were generally well tolerated. The PK of TD-9855 was linear with near dose proportional exposure in terms of C_{max} and AUC across the anticipated therapeutic range. TD-9855 has an elimination half-life ($t_{1/2}$) of approximately 30 to 40 hours achieving steady state by 6 days. Consistent with the elimination half-life, 3- to 4-fold accumulation of TD-9855 was observed at steady state. Based on clinical PK studies in healthy subjects, TD-9855 is >90% eliminated through metabolism and CYP1A2 is the primary enzyme driving TD-9855 metabolism. Accordingly, drug-drug interactions are expected with strong inhibitors and inducers of CYP1A2 impacting TD-9855 exposure.

The safety, tolerability, and efficacy of TD-9855 were also evaluated in two Phase 2 studies including subjects with attention-deficit hyperactivity disorder (ADHD) and Fibromyalgia (FM). TD-9855 doses of 5 mg and 20 mg QD were administered for 6 weeks in both studies and was generally well tolerated with no clinically significant safety signals.

Theravance conducted a study in adult subjects with primary autonomic failure (including MSA, PD, and PAF) in which TD-9855 was investigated for the treatment of symptomatic neurogenic orthostatic hypotension (symptomatic nOH). In the 0145 Study, TD-9855 was administered to subjects once daily in doses up to 20 mg for a duration of 20 weeks to evaluate the effect on symptoms of symptomatic nOH, pressor response, safety, and tolerability.

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

TD-9855 is a potent, dual inhibitor of NET and serotonin reuptake transporter (SERT) with higher in vitro potency for inhibition of NE (pIC_{50} = 8.6, IC_{50} = 2.5 nM) than 5-HT (pIC_{50} = 8.0, IC_{50} = 10.0 nM) uptake. TD-9855 exhibits selectivity for binding to NET and SERT over the dopamine transporter and various other transporter, receptor, ion channel, and enzyme targets tested.

In anesthetized rats, TD-9855 produced dose-dependent increases in mean arterial pressure (MAP) and heart rate (HR) in anesthetized rats. At doses that evoked cardiovascular effects, TD-9855 also produced dose-dependent and complete inhibition of tyramine-induced pressor responses, consistent with NET target engagement.

1.2.2. Safety Pharmacology

TD-9855 inhibits human ether-a-go-go-related gene (hERG) potassium channels with an IC_{50} of 0.95 μM. The no-effect free concentration of TD-9855 in the canine Purkinje fiber assay is 0.3 μM. Free concentrations ≥1 μM have effects consistent with multiple ion channel effects. An oral TD-9855 dose of 10 mg/kg resulted in increased BP, head tremors, and unsteady gait in dogs. The no-observed-adverse-event level (NOAEL) for these effects was 3 mg/kg.

Behavioral effects in rats, characterized by increase in home cage arousal and decreased grooming behavior, were noted but were not considered adverse up to the highest dose tested, 100 mg/kg, although adverse effects on body weight were noted in this study at 30 and 100 mg/kg, with a NOAEL of 10 mg/kg.

There were no adverse effects on respiratory function in rats at doses up to 100 mg/kg, the highest dose tested.

1.2.3. Nonclinical Pharmacokinetics

TD-9855 is orally bioavailable in rats (34.6%) and dogs (62.2%) and it penetrates the central nervous system (CNS). TD-9855 is not a p-glycoprotein (P-gp) substrate.

TD-9855 is moderately bound to plasma proteins (69.1% to 96.5%) and exhibits preferential partitioning into whole blood. No metabolites unique to humans have been identified from in vitro and in vivo studies. TD-9855 is metabolized primarily by CYP1A2 prior to conjugation by Phase 2 enzymes. Extensive metabolism of TD-9855 is observed in rats and dogs. Excretion in rats and dogs is primarily via biliary excretion.

TD-9855 exhibits weak or no inhibition of CYP450 enzymes (IC_{50} ≥6.6 μM). TD-9855 does not induce CYP450 enzymes. TD-9855 exhibits weak (IC_{50} >30 μM for organic anion transporting polypeptide 1B3 [OATP1B3]) or no inhibition of P-gp, breast cancer resistance protein, or OATP1B1. Accordingly, drug-drug interactions with TD-9855 due to inhibition of CYP450 metabolism or transporters are not anticipated in humans. Further information can be found in the TD-9855 IB.

1.2.4. Toxicology

The toxicity and toxicokinetic profile of TD-9855 has been characterized in a series of single- and repeated-dose exploratory dose-range studies. Good Laboratory Practice (GLP)-compliant studies of TD-9855 included single-dose oral and intravenous studies in rat, repeated-dose oral studies of up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs, genetic toxicology studies, and assessments of fertility, embryo-fetal toxicity, and pre- and postnatal development.

Findings of toxicological significance that were attributed to TD-9855 in toxicity studies included:

- CNS effects (tremors, agitation, convulsions) with mortality at higher doses
- Decreases in food consumption, body weight gain, and/or body weight

- Increased neonatal mortality and decreased rates of pup growth in the pre- and postnatal study in rats

Further information can be found in the TD-9855 IB.

1.3. Clinical Experience

A description of the clinical profile of TD-9855 can be found in the TD-9855 IB. The following is a brief summary of the pertinent findings.

To date, eight clinical studies have been completed with ampreloxetine. Five Phase 1 studies (0068, 0070, 0072, 0105, and 0172) were completed in healthy subjects. Three Phase 2 studies (0085, 0092, and 0145) were completed in subjects diagnosed with ADHD, FM, and symptomatic nOH, respectively. One Phase 1 study (0179) is ongoing in subjects with hepatic impairment and data are not yet available.

In the single-dose clinical study of healthy subjects (Study 0068), 40 subjects in 5 sequential cohorts were enrolled in the study, comprising a total of 10 subjects in the placebo group and 30 subjects in the TD-9855 groups (6 subjects in each of the 5 dose groups: 2, 4, 8, 20, and 50 mg). The most frequently reported TD-9855 treatment-related adverse events (AEs) were increased HR (3 subjects), dry mouth (2 subjects), and fatigue (2 subjects). Most AEs were mild, transient, and resolved spontaneously without sequelae.

Following multiple dosing (Study 0070), the overall incidence of AEs was comparable between the placebo group and the TD-9855 dose groups up to 20 mg. The most common AE was dry mouth. The majority of AEs were assessed as mild in severity. Vital signs data at the TD-9855 40-mg dose indicate the possibility of drug-related orthostatic effects, including an increased frequency of transient asymptomatic OH. Orthostatic tachycardia was observed in all treatment groups including the placebo, but no dose-response trend was apparent.

The single-dose study in healthy male subjects using positron emission tomography to assess TD-9855 NET and serotonin transporter (SERT) occupancy (Study 0072) showed greater NET occupancy than SERT binding. The NET binding varied in a dose-dependent fashion. The NET occupancy by TD-9855 increased in a plasma concentration–dependent manner over the tested dose range.

The results of the two Phase 2 clinical studies indicate that TD-9855 is generally well tolerated in subjects with ADHD (Study 0085) or with FM (Study 0092).

In Study 0085, a multicenter, randomized double-blind, parallel, placebo-controlled, proof-of-concept study, both the 5 mg and 20 mg TD-9855 doses taken for up to 6 weeks showed no clinically significant safety signals in 196 adult subjects with ADHD treated with TD-9855. Adverse events considered common and drug-related (i.e., reported in at least 5% of TD-9855 treated subjects at a rate at least twice that in the placebo group) included headache, dizziness (including postural dizziness), decreased appetite, and dry mouth.

In Study 0092, a Phase 2, placebo-controlled, parallel group, 3-group, randomized study comparing a lower dose regimen and a higher dose regimen of TD-9855 with placebo for 6 weeks in 255 adult subjects with FM treated with TD-9855, 2 serious adverse events (SAEs) were observed in the TD-9855 treatment groups: 1 SAE of neurological symptoms in the 5-mg TD-9855 treatment group was considered possibly treatment related, and 1 SAE of supraventricular tachycardia in the 20-mg TD-9855 treatment group was judged not related to study treatment. In the 20-mg TD-9855 treatment group, the most common treatment-emergent adverse events (TEAEs) were headache, nausea and constipation. These safety

findings are consistent with those observed following TD-9855 administration in Phase 1 studies.

In Study 0145, a multicenter, randomized, 3 parts, single-blind (Part A), double-blind, placebo-controlled (Part B), and open-label multiple dose extension (Part C) study of TD-9855 in subjects with symptomatic nOH is now completed with 34 subjects in Part A, 10 subjects in Part B, and 21 subjects in Part C.

Part A evaluated the dose response of single, ascending doses up to 20 mg. Although no dose response was observed, a numerical trend in increased seated and standing SBP was observed at the higher doses. An improvement in standing time of approximately 100 seconds was observed at 4 hours after dosing at 10 mg.

Part B Subjects were treated with TD-9855 (up to 15 mg) and demonstrated a sustained increase of greater than ~20 mmHg in SBP over baseline following 3 minutes of standing at 4- and 7-hours post-dose. No such increase in SBP was observed in placebo-treated subjects.

Part C evaluated durability of response, safety, and tolerability of TD-9855 in a 24-week open-label phase 2 multicenter study of subjects with nOH. Subjects were treated with oral ampreloxetine (3-20 mg) once-daily for ≤20 weeks with 4-week follow-up after treatment withdrawal (week 24). Primary efficacy endpoint OHSA#1 (improvement from baseline in the Likert scale ["dizziness, lightheadedness, feeling faint, or feeling like you might black out"]) was assessed at week 4; durability at week 20; and follow-up at week 24. A large proportion of subjects, 48% of the ITT population and 63% of Day 29 completers, met this endpoint. The mean improvement for subjects completing Day 29 was 2.4 points. Greater reductions were observed in subjects having a baseline score of > 4 at baseline (mean reduction of 3.8 points in 76.9% of responders). Similar trends in improvement were observed in OHSA and OHDAS composite scores. Twenty-one subjects enrolled in the open-label phase (mean age, 64 years; 57% multiple-system atrophy). Sixteen (76%), 11 (52%), and 10 (48%) subjects completed assessments at weeks 4, 20, and 24, respectively. Mean (SD) improvement from baseline in OHSA#1 was 2.4 (4.5), 1.9 (3.1), and -0.5 (2.7) for all subjects, and 3.8 (3.1), 3.1 (3.0), and 0.3 (1.9), for symptomatic subjects (OHSA#1 >4 at baseline) at weeks 4, 20, and 24, respectively. Similar trends in improvement were observed in OHSA and OHDAS composite scores.

Ampreloxetine resulted in a mean increase in standing SBP at all visits and all time points including post treatment. On Day 29, at 3 minutes standing, the mean increase from baseline was ≥7 mm Hg; the mean increase was ≥20 mm Hg at visits after Day 29. At Day 29, a large proportion of subjects (64% to 77%) maintained an SBP of ≥ 80 mmHg after standing for 3 minutes. Consistent responses in both seated and standing SBP increases were observed.

Ampreloxetine was administered at up to 20-mg doses to 21 subjects with symptomatic nOH for up to 20 weeks in Part C of the study. Ampreloxetine was well tolerated in this study with no deaths. A total of 6 SAEs (4 preferred terms), unrelated to treatment (23.8%), were observed in 5 subjects (all in Part C). These SAEs were urinary tract infection in 3 subjects; and jaw fracture, pain in extremity, and meniscus injury in 1 subject each.

Overall, of the 34 subjects dosed in the study, 3 subjects discontinued study drug due to TEAEs: 1 in Part A (TEAE of visual hallucination of moderate severity considered possibly/probably related to study drug); and 2 in Part C (SAE of jaw fracture considered unrelated to study drug and TEAE of headache of moderate severity considered possibly/probably related to study drug).

The most frequently reported drug-related TEAEs were headache in 4 subjects (2 each in Part A and Part C) and hypertension in 2 subjects (Part C).

The most frequently reported TEAEs in the study were urinary tract infection (2 subjects who received TD-9855 vs. 1 subject who received placebo in Part A, 1 subject who received TD-9855 in Part B, and 5 subjects in Part C); and headache (4 subjects who received TD-9855 vs. 2 subjects who received placebo in Part A, and 3 subjects in Part C).

The study did not reveal any new safety signals of potential concern.

Overall, ampreloxetine has exhibited an acceptable safety and tolerability profile in the Phase 1 and Phase 2 clinical programs to date. Common AEs were typically associated with the drug's noradrenergic mechanism of action and occurred at rates comparable to those of other marketed SNRI drugs.

1.3.1. Clinical Pharmacokinetics

TD-9855 is orally bioavailable with PK properties supportive of once daily dosing. The PK profile of TD-9855 has been measured in a SAD study in healthy subjects at doses ranging from 2 to 50 mg and a MAD study in healthy subjects at daily doses of 4, 10, 20, and 40 mg for up to 14 days. The PK of TD-9855 was linear with near dose proportional exposure in terms of C_{max} and AUC across the anticipated therapeutic range. TD-9855 has a $t_{1/2}$ of approximately 30 to 40 hours, achieving steady state by 6 days. Consistent with the $t_{1/2}$, 3- to 4-fold accumulation of TD-9855 was observed at steady state. Based on clinical PK studies in healthy subjects, TD-9855 is >90% eliminated through metabolism, and CYP1A2 is the primary enzyme driving TD-9855 metabolism. Accordingly, drug-drug interactions are expected with strong inhibitors and inducers of CYP1A2 impacting TD-9855 exposure.

Further information can be found in the TD-9855 IB.

1.4. Risks and Benefits

Results from preclinical and clinical studies indicate that TD-9855 is a potent inhibitor of NET with modest selectivity for NET over SERT. These studies demonstrated a moderate increase in HR and BP, suggesting that TD-9855 has the potential to provide a novel treatment option for symptomatic nOH.

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.

During the conduct of the TD-9855 clinical development program, the following have been recognized as important potential risks, with none characterized as identified risks associated with the administration of TD-9855:

- Increase in HR
- Increase in BP
- Syncope

Possible risks to subjects participating in this study include AEs associated with other serotonin norepinephrine reuptake inhibitors (SNRIs), such as nausea, dry mouth, headache, dizziness, somnolence, fatigue, diarrhea, insomnia, vomiting, syncope, seizures, constipation, hyponatremia, hyperhidrosis, urinary retention, and decrease appetite.

Furthermore, subjects may experience adverse effects as a result of study procedures, such as repeated blood sampling and associated procedures.

To help ensure subject safety, subjects will be closely monitored during this study. Study visits except for the Screening visit (S) for De Novo group subjects 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 durability of effect of TD-9855 in subjects with symptomatic neurogenic orthostatic hypotension (symptomatic nOH) due to multiple system atrophy (MSA), Parkinson's disease (PD), or pure autonomic failure (PAF) compared with placebo (PBO) over a double-blind, randomized withdrawal period of 6 weeks following an open label (OL) treatment of 16 weeks.
- To evaluate the safety and tolerability of TD-9855 when taken for up to 22 weeks.

2.2. Secondary and Other Objectives

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

Key secondary objectives:

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

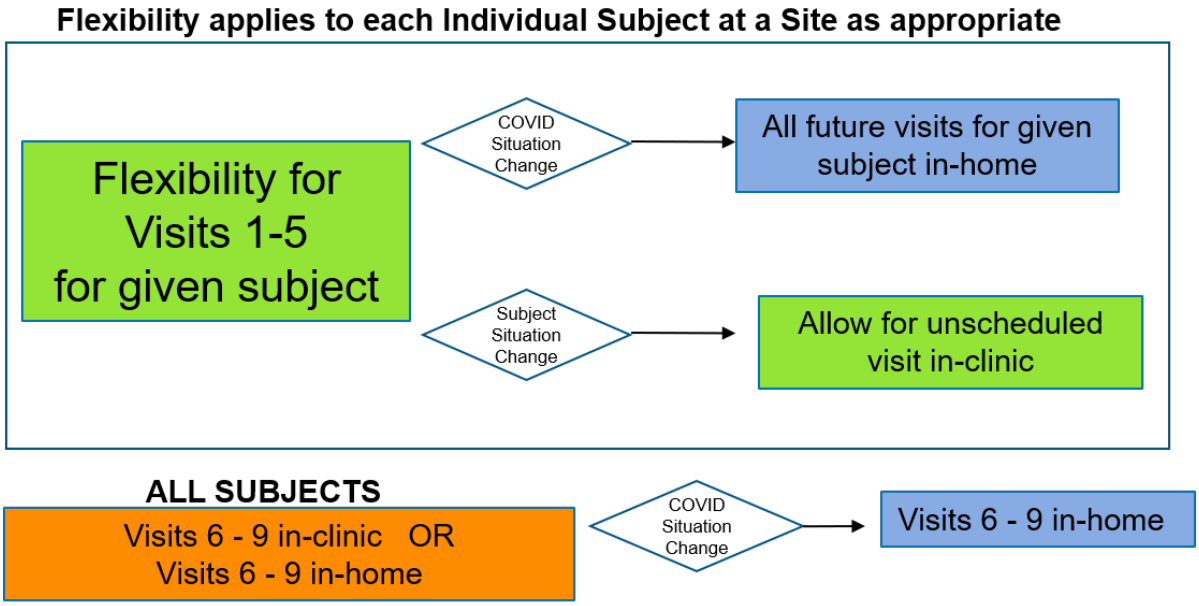
The exploratory objectives of the study are:

- To evaluate the effect of TD-9855 using disease-specific instruments and generic quality of life assessment.
- To evaluate the effect of TD-9855 using standing blood pressure during orthostatic standing test.
- To evaluate the effect of TD-9855 using generic quality of life assessment EuroQol-5D-5L (EQ-5D-5L), Non-Motor Symptom Scale (NMSS), and Hospital Anxiety and Depression Scale (HADS).
- To evaluate pharmacodynamic markers (NE and dihydroxyphenylglycol [DHPG]).
- To inform population PK modeling through collection of sparse PK samples.
- To assess caregiver burden in caring for subjects with primary autonomic failure using Burden Scale for Family Caregivers - short version (BSFC-s).

3. STUDY DESIGN

3.1. Overview

This is a Phase 3, multi-center, randomized withdrawal study to evaluate the sustained benefit in efficacy and safety of TD-9855 in subjects with primary autonomic failures (MSA, PD, or PAF) and symptomatic nOH after 22 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, in discussion with each individual subject at their site, will be required to elect to conduct visits either in the clinic or remotely. Sites must conduct the randomization withdrawal visits 6 through 9 (V6/D113 - V9/D155) for a given subject in a consistent manner to reduce the possibility of variability in data collection and reporting. Tools and systems are available to sites and subjects to support remote visits (e.g., direct to subject shipping of study medication and other study supplies, standardized HIPAA/GDPR compliant telemedicine platform, in-home health nurses).



Due to the potential for resurgence of COVID-19 and its impact on both sites and subjects, the Sponsor will allow Investigators to request exceptions to the selected type of study visit modality for V6/D113 through V9/D155 due to COVID-19 or COVID-19 related circumstances. Approved exceptions will be recorded as COVID-19 related protocol deviations.

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

For De Novo subjects that have previously completed the Screening visit at the time regulatory and ethics approval for Amendment 4 is received, sites must reconsent the subject using the most recently approved version of the Informed Consent Form to obtain subject consent for remote study visits, if that modality is selected by the Investigator and

subject. For those subjects who are already randomized into the randomized withdrawal portion of Study 0170 and active in the study at the time regulatory and ethics approval for Amendment 4 is received, the Investigator and subject should continue the remaining study visits in the same visit modality as the Randomization Visit (V6/D113).

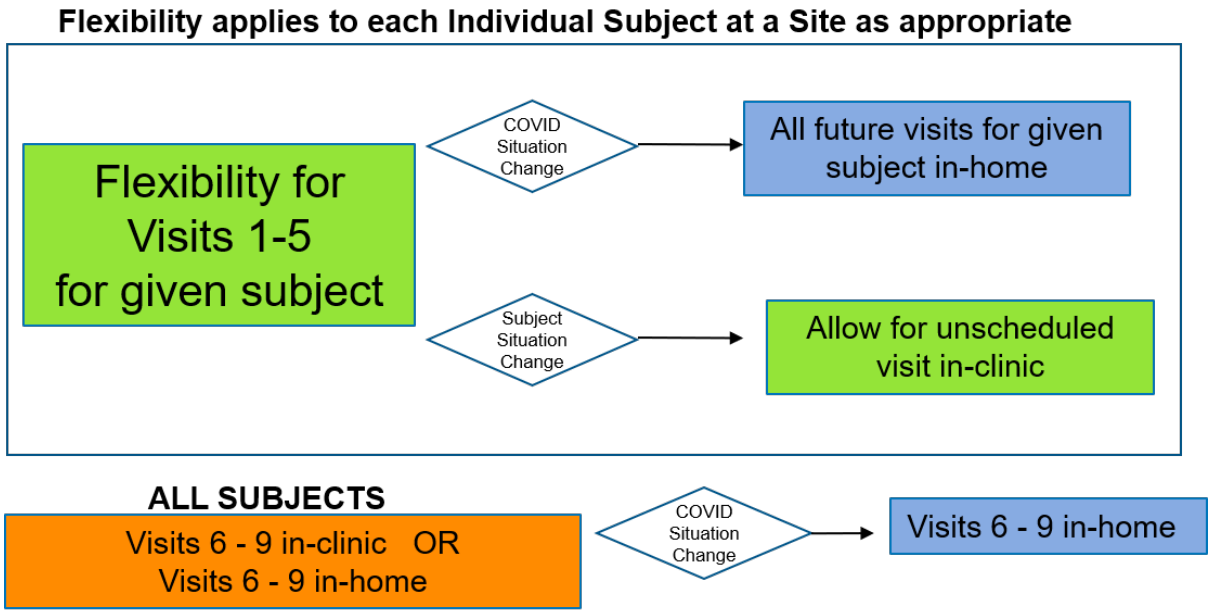
Refer to Appendix 9 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

Eligible subjects are either (i) completers of Study 0169 (0169 Completers Group), or (ii) symptomatic nOH subjects meeting all applicable study inclusion criteria and none of the applicable exclusion criteria (De Novo Group).

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^{o} elevation from a supine position.
- A score of at least a 4 on the Orthostatic Hypotension Symptom Assessment Question #1

The study consists of 3 periods: (i) 16-week open-label (OL) treatment with TD-9855, (ii) 6-week randomized placebo-controlled treatment, and (iii) 2-week follow-up (only for patients who do not enroll in Study 0171). A 4-week screening period will apply to the De Novo Group only and the Screening visit must be conducted in clinic for ALL De Novo group subjects. The schematic representation is as shown below:



Subjects entering from Study 0169 (0169 Completers Group)

Following signing of the informed consent, subjects will enter Study 0170 Visit 1 (V1), which will be conducted on the same day as V6 / D29 of Study 0169 of Study 0169. The visit modality for 0170, either in-clinic or remote for each subject, for a given subject should be consistent with the modality selected by the subject for study 0169.

Study 0169 procedures conducted at V6 will serve as the baseline assessments for V1 of Study 0170.

Beginning on Day 2, subjects will receive a single dose of 10-mg TD-9855 once daily (QD) and continue thereafter for the 16-week duration of the OL treatment period. Following this 16-week OL treatment period, subjects will be randomized to either continue on the active treatment or PBO for a period of 6 weeks.

Subjects not participating in Study 0169 (De Novo Group)

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

Subjects will receive an assessment of their physical condition, including safety and laboratory evaluations and related aspects of their disease states according to the Schedule of Study Procedures. The presence of symptomatic nOH must be confirmed using a tilt-table test.

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

Following the screening period, subjects will proceed to V1 to further confirm the additional eligibility criteria prior to proceeding. This includes the completion of the Orthostatic Hypotension Questionnaire (OHQ) in which a minimum score of 4 points in OHSA#1 is required.

Subjects meeting all inclusion criteria, none of the exclusion criteria, and whose disease characterization is confirmed by the independent Enrollment Steering Committee (ESC) (see Section 3.5.3, also separate charter will be available), will receive TD-9855 in the OL period.

Beginning on Day 2, subjects will receive a single dose of 10-mg TD-9855 once daily (QD) and continue thereafter for the 16-week duration of the OL treatment period. Following this 16-week OL treatment period, subjects will be randomized to either continue on the active treatment or PBO for a period of 6 weeks.

Open Label Period (Weeks 1 to 16)

Subjects enrolled into the OL period of the study will have visits scheduled for Day 15, Day 29, and every 4 weeks thereafter for assessments as outlined in the Schedule of Study Procedures. At V3 (Week 4), following the initial 4-week OL treatment, subjects must demonstrate a reduction in OHSA#1 of at least 2 points compared to the baseline value, as determined in Study 0169 for subjects entering from Study 0169 and from V1 for de novo subjects, in order to continue in Study 0170. Those subjects not meeting this continuation

criterion must be discontinued and undergo an end of study visit. The end of study visit must be completed within 2 weeks from the date of the last dose.

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

Double-blind Period (Weeks 17 to 22)

Following the completion of a total of 16 weeks OL treatment with TD-9855 (V6) subjects will be assessed for randomization in a 1:1 manner. Eligible subjects will receive 6 weeks of double-blind treatment of TD-9855 or PBO once daily. Only subjects with OHSA#1 score of ≤7 will be eligible for randomization for the double-blind treatment period.

Treatment period (Weeks 1 to 22):

No dose reduction is permitted during the treatment period.

Subjects unable to tolerate 10-mg TD-9855 will be discontinued from the study.

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

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

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

Safety will be periodically reviewed by an Independent Data Monitoring Committee (IDMC); see separate charter.

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

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

3.2. Rationale for Study Design

Utilizing a randomized withdrawal following a predefined open label period, this study is designed to evaluate worsening from baseline in the OHSA#1 score of 1.0 point and a worsening of disease severity as assessed by a 1-point change in Patient Global Impression of Severity (PGI-S), in subjects with symptomatic nOH with a primary diagnosis of MSA, PD, or PAF following 6 weeks of daily treatment with TD-9855 at a dose of 10-mg compared to placebo. OHSA#1 is the validated primary efficacy endpoint in this patient population. The inclusion of PGI-S with OHSA#1 further exemplifies the patient-centric assessments thereby refining the treatment failure criteria. Prior to the randomized withdrawal phase of the study, all eligible subjects will receive OL TD-9855 for a period of 16 weeks. The OL period is designed to capture durability of effect following long-term TD-9855 administration. This durability of effect is confirmed through the subsequent randomized withdrawal period. The eligibility criteria are designed to adequately characterize these subjects and will include confirmation from an ESC (committee of independent neurologists) to determine the appropriateness of each subject for study inclusion. Prespecified population and PK and pharmacodynamic sampling will be used to further profile TD-9855 and the relationship between plasma exposure and TD-9855 efficacy. A dedicated charter outlining the procedure will include the details needed on the ESC form, a timeline for review, and the decision conveyed. In addition, an IDMC comprised of independent key opinion leaders, potentially from the field of neurology, cardiology, dysautonomia, and biostatistics, will evaluate the safety of TD-9855, with a dedicated charter outlining Study 0170 assessments at planned time points. Prespecified safety endpoints and measurements have been selected based upon their known relevance to a patient population that has been diagnosed with MSA, PD or PAF. Subjects that complete Study 0170 will be eligible to participate in Study 0171, which is designed to evaluate the long-term safety of TD-9855 in a 6-month OL design.

3.3. Selection of Dose and Duration of Treatment

TD-9855 has been previously investigated in FM and ADHD at doses up to 20 mg QD. TD-9855 was also investigated in a study in patients with nOH. Study 0145 was conducted in three parts including Part A (exploratory), Part B (proof-of-concept), and Part C (ongoing OL extension) to determine if TD-9855 improves the acute pressor response and OHSA#1, respectively. OHSA#1 is a measure of dizziness, lightheadedness, feeling faint, or the sensation of being about to black out.

Part A evaluated the dose response of single, ascending doses up to 20 mg. Although no dose response was observed, a numerical trend in increased seated and standing SBP was observed at the higher doses. An improvement in standing time of approximately 100 seconds was observed at 4 hours after dosing at 10 mg.

In Part B, subjects treated with TD-9855 (single dose up to 15 mg) demonstrated a sustained increase of approximately 20 mmHg in SBP over baseline following 3 minutes of standing at 4, 7, and 9 hours post-dose. No such increase in SBP was observed in placebo-treated subjects.

Part C evaluated durability of response, safety, and tolerability of TD-9855 over 20 weeks in an open label extension design. Top line results of interim data available for the first 4 weeks of the study (through Day 29) demonstrate durable improvements in subjects' disease symptom severity after treatment with TD-9855, as measured by OHSA #1.

Subjects demonstrated a mean symptom improvement of 2.4 points from baseline at four weeks. Importantly, mean symptom improvement from baseline was greatest (3.8 points) in nOH subjects who reported dizziness symptoms (OHSA#1 $\geq$ 4) at baseline. Additionally, TD-9855 consistently increased systolic blood pressure (SBP), including clinically meaningful increases in standing SBP at the 3-minute assessment at all time points up to Day 29. There were no drug-related SAEs reported, and TD-9855 was generally well tolerated in the study. Per interim data from the first 4 weeks of Part C of Study 0145, the majority of subjects received TD-9855 10-mg QD.

Based on the results of the human positron-emission tomography study in healthy volunteers, the estimated IC_{50} of TD-9855 for NET inhibition is 1.21 ng/mL. Accordingly, based on the population PK-pharmacodynamic model for TD-9855 in healthy and diseased subjects, 10-mg dose of TD-9855 is expected to achieve >80% NET inhibition in a majority of subjects. Thus, 10-mg dose of TD-9855 is considered adequate to achieve the desired pharmacological and clinical effect while minimizing the risk for safety concerns in subjects with symptomatic nOH.

3.4. Study Endpoints

3.4.1. Primary Endpoint

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

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

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

3.4.2. Secondary Endpoints

The secondary endpoints include:

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

3.4.3. 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
- C-SSRS

3.4.4. Exploratory Endpoints

Exploratory endpoints include:

- Standing SBP during orthostatic standing test at Week 6 post randomization (V9, D155)
- Change from baseline in OHQ overall composite score at Week 6 post randomization (V9, D155)
- Change from baseline in EQ-5D-5L at Week 6 post randomization (V9, D155)
- NMSS at Week 6 post randomization (V9, D155)
- HADS at Week 6 post randomization (V9, D155)
- BSFC-s at Week 6 post randomization (V9, D155)
- PK and pharmacodynamic parameters

For subjects with PD

- Change from baseline in UPDRS at Week 6 post randomization (V9, D155)
- Change from baseline in PDQ-8 at Week 6 post randomization (V9, D155)

For subjects with MSA

- Change from baseline in UMSARS at Week 6 post randomization (V9, D155)
- Change from baseline in COMPASS-31 at Week 6 post randomization (V9, D155)

3.5. Minimization of Bias

This is a randomized withdrawal study, including an OL and a placebo controlled double-blind randomized withdrawal phases. 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 to study treatment during the randomized withdrawal period, except in the event of a medical emergency as outlined in Section 3.5.1.

3.5.1. Blinding

This section is only applicable to the randomized withdrawal part of the study.

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 in the OL part of the study, the PI or their delegate will use the RTSM system to provide TD-9855 to the subject and dispense study medication accordingly.

Once the subject has been determined to be eligible to receive study treatment in the randomized withdrawal part of the study, 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 (for De Novo Group only)

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 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.

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 applicable inclusion criteria and none of the applicable exclusion criteria defined below.

4.1. Inclusion Criteria

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

Inclusion Criteria (For 0169 Completers Group):

101. Completion of 4 weeks of double-blind treatment in Study 0169 (V6) and, in the opinion of the Investigator, could benefit from continued treatment with TD-9855. No minimum score of OHSA#1 is required to enter V1 of Study 0170.
102. The subject has a minimum of 80% study medication compliance in Study 0169.
103. The subject must be able to understand the nature of the study and must provide written informed consent prior to the conduct of any study procedures (including an understanding that entry to Study 0170 may result in changes occurring in the subject's current therapeutic regimen).
104. The subject must be willing to continue on treatment regardless of the possibility of randomization to either TD-9855 or PBO during the randomized withdrawal phase and must continue to meet the inclusion criteria for the preceding study (Study 0169) with the exception that tilt-table test, ESC review and approval of eligibility are not required for entry into Study 0170.

Inclusion Criteria (For De Novo Group):

1. Subject is male or female and at least 30 years old.
2. If subject is female, the subject must be non-pregnant and non-lactating. 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 beta human chorionic gonadotropin (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.
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 ≥60^{o} from a supine position as determined by a tilt-table test.
5. Subject must score at least a 4 on the OHSA#1 at V1.
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 understand 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 applicable criteria is not eligible for study enrollment:

Exclusion Criteria (For 0169 Completers Group):

101. Subject may not be enrolled in another clinical trial (other than exiting Study 0169).
102. Subject has psychiatric, neurological, or behavioral disorders that may interfere with the ability of subjects to give informed consent or interfere with the conduct of the study.
103. Medical, laboratory, or surgical issues deemed by the Investigator to be clinically significant.
104. Uncooperative attitude or reasonable likelihood of non-compliance with the protocol.
105. 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.

Exclusion Criteria (For De Novo Group):

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.
4. Subject has used strong CYP1A2 inhibitors or inducers within 7 days or 5 half-lives, whichever is longer, prior to V1 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 V1.
    - Midodrine and droxidopa (if applicable) must be tapered off at least 7 days prior to V1.
6. Subject has known or suspected alcohol or substance abuse within the past 12 months (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR®] definition of alcohol or substance abuse).
7. Subject has a clinically unstable coronary artery disease or has had a 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 V1.
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 had 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 drug that is not approved by a regulatory agency (e.g., Food and Drug Administration [FDA]).

19. Subject has a clinically significant abnormal laboratory finding (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/1.73 m^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

4.4. Continuation Criteria

- At V3 (Week 4), following the initial 4-week OL treatment, subjects must demonstrate a reduction in OHSA#1 of at least 2 points compared to the baseline value, as determined in Study 0169 for subjects entering from Study 0169 and from V1 for de novo subjects, in order to continue in Study 0170.

4.5. Randomization Criteria for Double-Blind Period

A subject who meets the following criteria will be eligible for randomized withdrawal period

201. Subject has OHSA#1 score of ≤7.
202. Subject's unused OL study medications (10 mg TD-9855 tablets) are returned to site.
203. The subject has a minimum of 80% study medication compliance in OL treatment period.
204. Subjects without excessive deterioration of disease or symptoms during the OL phase and in the opinion of the Investigator, would benefit from continued participation in the study.

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

For OL treatment period:

All subjects will receive TD-9855 once daily through the end of the treatment period.

For randomized treatment period:

Subjects will be randomized in a 1:1 ratio to receive either TD-9855 (test product) or PBO (reference product) once daily through the end of the treatment period.

Further details regarding study medication handling, storage, and destruction are found in a separate pharmacy manual.

5.1.1. TD-9855 Test Product

For OL treatment period:

All subjects will receive TD-9855 and continue to take the study medication once daily starting on Day 2 through the end of the treatment period. The test product will be TD-9855 supplied as a 10-mg tablet in 35-count high-density polyethylene bottles.

For randomized treatment period:

Subjects randomized to TD-9855 will receive TD-9855 tablets and continue to take the study medication once daily starting in the morning post randomization (Day 2) through the end of the treatment period. The test product will be TD-9855 supplied as a 10-mg tablet in 35-count or 5-count high-density polyethylene bottles labeled in a blinded fashion (i.e., bottle label for test product will be indistinguishable from reference product except for a coded, unique bottle number).

5.1.2. Placebo Reference Product

For OL treatment period:

No subjects will receive the reference product.

For randomized treatment period:

Subjects randomized to PBO will receive PBO tablets that are supplied to match TD-9855 tablets in excipient content (except for the absence of TD-9855), appearance, tablet count, and in packaging (i.e., bottle label for reference product will be indistinguishable from test product except for a coded, unique bottle number).

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' dosing 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 (i.e., < 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 114 mL. 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 S (De Novo Group Only)

Screening visit assessments will be performed in clinic between 28 and 7 days prior to Day 1.

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

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

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

- Orthostatic standing test
- Vital signs
- HR, systolic BP (SBP), and diastolic BP (DBP)
- Respiratory rate (RR) and body temperature
- Height (in cm) and weight (in kg)
- Physical examination
- Neurological examination

- 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)
- Pregnancy test (in women of childbearing potential only)
- Blood collection
- Hematology
- Chemistry
- NE sample collection (after being seated for approximately 30 minutes)
- Urine collection
- Urinalysis
- ESC (for confirmation of diagnosis)
- 24-hour ambulatory BP device provision (device collection prior or on Visit 2)
- Wearable device provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, adverse event of special interest [AESIs])
- 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 1

De Novo Group subjects meeting all applicable eligibility criteria, including ESC confirmation of diagnosis, following completion of the screening assessments, will continue towards enrollment assessments on Day 1. Prior to dosing, 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 following assessments or procedures will be performed within 24-hours prior to the subject taking the study medication as part of study 0170 (pre-dose).

For 0169 Completers Group subjects, Study 0169 procedures conducted at V6 will serve as the baseline assessments for V1 of Study 0170.

Beginning on Day 2, subjects will receive a single dose of 10-mg TD-9855 once daily (QD) and continue thereafter for the 16-week duration of the OL treatment period. Following this 16-week OL treatment period, subjects will be randomized to either continue on the active treatment or PBO for a period of 6 weeks.

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

- Written informed consent (signed and dated) after the nature of the study has been explained and before any study procedure is performed (0169 Completers only)
- Review of protocol inclusion and exclusion criteria prior to beginning subject evaluations
- Review concomitant medications and smoking usage

- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS

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

- NMSS
- HADS
- PD subject assessments
  - UPDRS
  - PDQ-8
- MSA subject assessments
  - UMSARS
  - COMPASS-31
- EQ-5D-5L
- BSFC-s
- Orthostatic standing test
- Vital signs
  - HR, SBP, and DBP
  - RR and body temperature
- Weight (in kg)
- Physical examination
- Neurological examination
- 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)
- Pregnancy test (in women of childbearing potential only)
- Blood collection
  - Hematology
  - Chemistry
- Urine collection
  - Urinalysis
- Pharmacodynamic sampling (after being seated for approximately 30 minutes)
- 24-hour ambulatory BP device collection and re-provision
- Wearable device collection and re-provision

- Incidence of Falls and ABPM position diaries
- Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Dispense study medication

6.3.3. Treatment Day 15 – Visit 2

The following procedures will be performed on the Day 15 visit (+/- 3 days) after the daily dose of TD-9855:

- Review concomitant medications and smoking usage
- Vital signs
  - HR, SBP, and DBP
  - RR and body temperature
- Physical examination
- Blood collection
  - Hematology
  - Chemistry
- Urine collection
  - Urinalysis
- 24-hour ambulatory BP device collection
- Incidence of Falls and ABPM position diaries
- Dosing and Midodrine rescue medication diaries dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)

6.3.4. Treatment Day 29 – Visit 3

At V3 (Day 29), following the initial 4-week OL treatment, subjects must demonstrate a reduction in OHSA#1 of at least 2 points compared to the baseline value, as determined in Study 0169 for subjects entering from Study 0169 and from V1 for de novo subjects, in order to continue in Study 0170.

The following procedures will be performed on the Day 29 visit (+/- 3 days) after the daily dose of TD-9855:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S

- C-SSRS

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

- BSFC-s
- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- 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)
- 24-hour ambulatory BP device and position diary provision for all subjects
- Wearable device collection and re-provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions
- Dosing and Rescue medication diary dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Collect, review, and dispense study medication

6.3.5. Treatment Day 57 – Visit 4

The following procedures will be performed on the Day 57 visit (+/- 3 days) after the daily dose of TD-9855:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS

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

- NMSS
- HADS
- UPDRS (only for patients with PD)
- PDQ-8 (only for patients with PD)
- UMSARS (only for patients with MSA)
- COMPASS-31 (only for patients with MSA)
- EQ-5D-5L
- BSFC-s

- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- Blood collection
  - Hematology
  - Chemistry
- Urine collection
  - Urinalysis
- Pharmacokinetic sampling
- Pharmacodynamic sampling (after being seated for approximately 30 minutes)
- 24-hour ambulatory BP device collection
- Wearable device collection and re-provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions
- Dosing and Rescue medication diary dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Collect, review, and dispense study medication

6.3.6. Treatment Day 85 – Visit 5

The following procedures will be performed on the Day 85 visit (+/- 3 days) after the daily dose of TD-9855:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS

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

- BSFC-s
- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- Wearable device collection and re-provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions

- Dosing and Rescue medication diary dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Collect, review, and dispense study medication

6.3.7. Treatment Day 113 – Visit 6

At V6 (Day 113), following the OL treatment, only subjects with OHSA#1 score of ≤7 will be eligible for randomization for the double-blind treatment period. Ensure "Randomization Criteria" is met prior to continuation. First dose date of the randomized treatment should be used to determine the subsequent visits during the randomized treatment period (first dose date + 13 days for Day 127 [Visit 7], first dose date + 27 days for Day 141 [Visit 8], first dose date + 41 days for Day 155 [Visit 8]).

The following procedures will be performed on the Day 113 visit (+/- 3 days) after the daily dose of TD-9855:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS
- Randomization via a RTSM system (after all procedures have been completed and subject is confirmed eligible to be randomized per randomization criteria

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

- NMSS
- HADS
- UPDRS (only for patients with PD)
- PDQ-8 (only for patients with PD)
- UMSARS (only for patients with MSA)
- COMPASS-31 (only for patients with MSA)
- EQ-5D-5L
- BSFC-s
- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- Weight (kg)
- Physical examination
- Neurological examination

- 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)
- Pregnancy test (in women of childbearing potential only)
- Blood collection
  - Hematology
  - Chemistry
- Urine collection
  - Urinalysis
- PK sampling
- Wearable Device collection and re-provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions
- Dosing and Rescue medication diary dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Collect, review, and dispense study medication

6.3.8. Treatment Day 127 – Visit 7

The following procedures will be performed on the Day 127 visit (+/- 3 days) after the daily dose of TD-9855:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS

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

- BSFC-s
- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- PK sampling
- Wearable Device collection and re-provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions

- Dosing and Rescue medication diary dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Collect, review, and dispense study medication, if applicable

6.3.9. Treatment Day 141 – Visit 8

The following procedures will be performed on the Day 141 visit (+/- 3 days) after the daily dose of TD-9855:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS

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

- BSFC-s
- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- Wearable device collection and re-provision
- Incidence of falls – subject diary, dispensation and review of diary completion instructions
- Dosing and Rescue medication diary dispensation and review of diary completion instructions
- AE assessment (AEs, SAEs, AESIs)
- Collect, review, and dispense study medication

6.3.10. Treatment Day 155 – Visit 9/ Early Termination

Subjects completing Day 155 (V9) can proceed to Study 0171 following this visit. The following procedures will be performed on the Day 155 visit (+/- 3 days) after the daily dose of TD-9855/Early Termination:

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

- Review concomitant medications and smoking usage
- OHQ subject training
- OHQ (OHSA and OHDAS)
- PGI-S
- C-SSRS

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

- NMSS
- HADS
- UPDRS (only for patients with PD)
- PDQ-8 (only for patients with PD)
- UMSARS (only for patients with MSA)
- COMPASS-31 (only for patients with MSA)
- EQ-5D-5L
- BSFC-s
- Orthostatic standing test
- Vital signs: HR, SBP, and DBP; RR and body temperature
- Weight (kg)
- Physical examination
- Neurological examination
- 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)
- Pregnancy test (in women of childbearing potential only)
- Blood collection
  - Hematology
  - Chemistry
- Urine collection
  - Urinalysis
- Wearable device collection
- Incidence of falls – subject diary review for completion
- Dosing and Rescue medication diary review for completion
- AE assessment (AEs, SAEs, AESIs)
- Collect and review study medication

6.3.11. Follow-up Day 169 – Visit 10

The follow-up visit is applicable only for those subjects that will not proceed to Study 0171 and will be completed two weeks from the date of the last dose.

The following procedures will be performed on the Day 169 visit (+/- 3 days):

- Review concomitant medications and smoking usage
- C-SSRS

- Vital signs: HR, SBP, and DBP; RR and body temperature
- Weight (kg)
- 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 patient 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.

For De Novo Group subjects, inclusion and exclusion criteria will be assessed at screening and on Day 1 prior to OL treatment. 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).

For 0169 Completers Group subjects, the data would be confirmed with information captured in Study 0169.

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 ≥60^{o} from a supine position, ideally between 60^{o} to 65^{o}. 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 enrollment. Tilt-table test is only applicable for De Novo group. 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 (). 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.

6.4.5. OHQ Subject Training

Empirical evidence exists that the OHQ can accurately evaluate the severity of symptoms and the functional impact of symptomatic nOH as well as assess the efficacy of treatment[9]. To ensure that subjects are able to complete the OHQ questionnaires successfully with a complete understanding of the individual point differences on the scale as associated with their symptoms and to standardize the manner of completion of the 11-point scale from 0 to 10, the subjects will undergo OHQ training. Subjects should be rested prior to beginning the training. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1).

6.4.6. Efficacy Assessments

6.4.6.1. Orthostatic Hypotension Questionnaire

The 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 OHDAS[9]. 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 Severity

Patient Global Impression of Severity is a 1-item patient rated questionnaire designed to assess the patient's impression of symptom severity. The PGI-S item asks the respondent to best describe the current severity of symptoms of his/her neurogenic orthostatic hypotension on a 5-category scale, where a higher score is associated with greater symptom severity. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.6.3. Wearable Device

A wearable device, such as an activity monitor, that provides date- and time-stamped activity information will be used to collect raw motion data to measure the time spent in supine, sitting, and standing positions.

In countries where the wearable devices are available, 2 consecutive days of device use will be required on the days shown in Table 1. The 2 consecutive days of device use should be within 5 days before the subsequent visit. Site coordinators will monitor subject compliance. If the site coordinator becomes aware that a subject has not used the device for the required time, they will contact the subject and remind them to use the device. Subjects will be identified by subject ID and no personally identifiable information is collected or stored.

In countries where the devices are available, assessments will be performed as specified in the Schedule of Study Procedures (Table 1).

6.4.6.4. Unified Parkinson's Disease Rating Scale

Unified Parkinson's disease Rating Scale, a clinical rating scale for PD, has nearly comprehensive coverage of motor symptoms and its clinimetric properties, including reliability and validity. The UPDRS is only for subjects with PD. It is made up of 6 parts, namely, 1: evaluation of mentation, behavior, and mood; 2: self-evaluation of the activities of daily living (ADLs), including speech, salivation, swallowing, handwriting, cutting food/handling utensils, dressing, hygiene, turning in bed/adjusting bedclothes, falling, freezing when walking, tremor, and sensory complaints; 3: clinician-scored monitored motor evaluation; 4: complications of therapy; 5: modified Hoehn and Yahr staging of severity of PD; and 6: modified Schwab and England ADL scale. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). The UPDRS scale should be completed in an ON state, and within 2-4 hours of taking the PD medications. All UPDRS Parts will be completed on Day 1 for De Novo Group subjects, while only Parts 2 and 3 of the questionnaire would be completed for 0169 Completers Group, and for subsequent visits. An example of the instrument is provided in Appendix 2.

6.4.6.5. The Parkinson's Disease Questionnaire-8

The PDQ-8 is derived from the Parkinson's Disease Questionnaire-39 (PDQ-39) and is only for subjects with PD. The short-form 8-item PDQ-8 was developed to reflect scores on the PDQ-39 single index, but with a smaller number of items, placing less burden upon respondents. In the original formulation, 1 item was selected from each of the 8 dimensions of the PDQ-39. The item selected being the one that correlated most strongly with the dimension total to which it contributes. These 8 items constitute the PDQ-8 and are then summed to produce a single figure. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1).

An example of the instrument is provided in Appendix 2.

6.4.6.6. Unified Multiple System Atrophy Rating Scale

The UMSARS is only for subjects with MSA and comprises the following components: Part 1, historical review, 12 items; Part 2, motor examination, 14 items; Part 3, autonomic examination; and Part 4, global disability scale. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.6.7. Composite Autonomic Symptom Score-31

The COMPASS-31 is a refined, internally consistent, and markedly abbreviated quantitative measure of autonomic symptoms. It is based on the original Autonomic Symptom Profile (ASP) and Composite Autonomic Symptom Score (COMPASS), applies a more simplified scoring algorithm, and is suitable for widespread use in autonomic research and practice. It is only used for subjects with MSA. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.6.8. Incidence of Falls – Subject Diary

Falls in subjects with symptomatic nOH 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.

6.4.6.9. Orthostatic Standing Test

The orthostatic standing test (including SBPs) will be performed at the time points described in the Schedule of Study Procedures (Table 1).

At each time point, BP and HR measurements will be recorded with automated (or manual) sphygmomanometer while resting supine (with the torso and head elevated 30 degrees from horizontal), for a total of 10 minutes, with measurements taken at 5 and 10 minutes. Followed by, seated for a total of 10 minutes, with measurements taken at 5 and 10 minutes. Lastly, standing for up to a total of 10 minutes, with measurements taken at 1, 3, 5, and 10 minutes while standing. The standing time will be measured with a chronometer and the duration of standing will be recorded. The total duration of standing may occur in between the time points (i.e., 1, 3, 5, and 10 minutes) for the standing test. In either case, the total duration should be recorded. The BP and HR collected after 10 minutes supine and seated from the orthostatic standing test can be used for safety vital sign assessment. The assessments should be performed at approximately (±2 hour) the same time of day on Day 1 (except Screening). Subjects should abstain from eating for at least 90 minutes prior to this assessment.

Assessments will be performed as specified in the Schedule of Study Procedures (Table 1).

6.4.7. Pharmacokinetic Assessments

A sparse PK sampling strategy is being employed in this study. At the time points described in the Schedule of Study Procedures (Table 1), blood samples for PK assay of TD-9855 will be collected, centrifuged, and split into aliquots. Detailed instructions and collection kits for sample collection, handling, and shipping will be provided in the laboratory manual.

All PK sampling times will be accurately recorded by collection date, hour, and minute. Study medication dosing time on the day before each PK collection and on the day of each PK collection will be accurately recorded by dosing date, hour, and minute by the study staff using time recorded in Dosing Diary by Subjects.

Assessments will be performed as specified in the Schedule of Study Procedures (Table 1).

6.4.8. Pharmacodynamic Assessments

At the time points described in the Schedule of Study Procedures (Table 1), blood samples for pharmacodynamic markers may be measured. Detailed instructions and collection kits for sample collection, handling, and shipping will be provided in the laboratory manual.

Blood samples for pharmacodynamic markers (DHPG and NE) will be collected at select study visits as defined in the Schedule of Study Procedures after the subject has been seated for 30 minutes. Note that all pharmacodynamic marker samples should be collected at approximately (±1 hour) the same time of day. Time-matched sampling will enable time-matched analysis, which is critical for biomarkers of the NE pathway owing to diurnal variations.NE alone will also be collected at Screening Visit as part of the eligibility criteria evaluations.

Assessments will be performed as specified in the Schedule of Study Procedures (Table 1).

6.4.9. Exploratory Assessments

6.4.9.1. EQ-5D-5L Descriptive System

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled, "The best health you can imagine" and "The worst health you can imagine." The EQ VAS can be used as a quantitative measure of health outcome that reflect the subject's own judgment. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.9.2. Non-Motor Symptom Scale

The NMSS is a 30-item scale for the assessment of non-motor symptoms. The NMSS contains 9 domains: cardiovascular including falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, GI tract, urinary, sexual function, and miscellaneous. The NMSS can be used to assess the frequency and severity of non-motor symptoms in patients across all stages in conjunction with the validated non-motor questionnaire. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.9.3. Hospital Anxiety and Depression Scale

The HADS is a brief questionnaire comprised of 2 domains including anxiety (7-items) and depression (7-items). It has been validated for in-clinic and out-patient settings. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 2.

6.4.9.4. Burden Scale for Family Caregivers – Short Version

The burden experienced by family caregivers is the most important caregiver-related variable in care at home of a chronically-ill person. The extent of subjective burden has significant impact on the emotional and physical health of the family caregiver, and even influences the mortality of spouse caregivers. It affects the way the family caregiver deals with the care-receiver and determines the time of institutionalization. The shorter version consists of the 10 statements of the BSFC-s and are rated on a 4-point scale ranging from 0 (strongly disagree) to 3 (strongly agree). 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. 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 V1 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.

Subjects entering from Study 0169 (0169 Completers Group): Adverse events that start after signing of Study 0170 informed consent, but before the first dose of study drug is taken on Day 2, are to be captured in Study 0169 database. Adverse events started in Study 0169 but which worsen in severity or seriousness during Study 0170 should be reported as a new adverse event.

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 AE must be recorded in the subject's 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 (for De Novo subjects only) and will include evaluation of 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 2 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/ GI system; extremities; lymphatic system [lymph nodes]; and nervous system).

Subsequent physical examinations, after the screening visit, 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. 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)

6.4.10.6. 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.

6.4.10.7. 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 orthostatic standing test 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.

6.4.10.8. 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 to allow for any appropriate action, if required.

6.4.10.9. 24-hour Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) equipment will be provided to the subject during the screening visit for De Novo Group subjects, and on V1 for 0169 Completers Group subjects. Beginning approximately 72 to 24-hours before a subject returns to the scheduled clinic visits that require the procedure, 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 will log their posture at the time of each BP measurement in the provided ABPM Position Diary (Appendix 4). More details regarding the ambulatory monitoring will be provided in a separate manual. ABPM will be performed as specified in the Schedule of Study Procedures (Table 1).

6.4.10.10. Laboratory Tests

Laboratory tests will be performed as specified in the 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.

6.4.10.10.1. 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).

6.4.10.10.2. 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.

6.4.10.10.3. Urinalysis

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

6.4.10.11. 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 V1. 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 return 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 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.

6.5. Concomitant Medications

For the De Novo Group, subjects should not have changed dose, frequency, or type of prescribed medication for orthostatic hypotension within 7 days prior to V1/D1.

Concomitant use of antihypertensive medication for the treatment of essential hypertension is not allowed.

Subjects can continue on a stable dosing regimen of fludrocortisone if the regimen was initiated at least 7 days prior to V1/D1.

Cannabinoids usage for medical reasons is permissible at a stable dosing regimen established at least 7 days prior to V1/D1 in countries where cannabinoids are permissible.

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

Preliminary results from the clinical drug-drug interaction study suggest that concomitant administration of itraconazole (CYP3A4 inhibitor) resulted in minimal impact on the exposure of TD-9855 while concomitant administration of fluvoxamine (CYP1A2 inhibitor) resulted in significant increase in TD-9855 exposure. Additionally, TD-9855 exposure was lower in subjects who are smokers as compared to nonsmokers. Accordingly, it is expected that TD-9855 metabolism is primarily driven by the CYP1A2 enzyme. Restrictions on the concomitant use of strong CYP1A2 inhibitors and inducers are described in Section 6.7.

6.5.2. Impact of TD-9855 on Other Medications

In vitro evaluation indicates that clinical drug-drug interactions due to CYP450 metabolism or transporters with TD-9855 as the perpetrator are not anticipated in humans. Thus, no clinical studies have been conducted and no impact on exposure of concomitant medications is expected.

6.6. Rescue Medications

Usage of any rescue medications is discouraged during the course of the study. However, under exceptional circumstances, based on the discretion of the Investigator and to ensure subject's safety, midodrine is permitted as follows:

- A maximum of 10mg (increments of 2.5mg are available) may be administered, one day per week
- Cannot be used on the assessment days

Dosing instructions will be provided by the Investigator as dosing for this medication will differ between subjects. Subjects will record their use of midodrine in the Midodrine Rescue Medication Diary. Midodrine use will be captured in the database. Refer to Appendix 6.

6.7. Prohibitions and Restrictions

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

- For the De Novo Group, subjects must stop the concomitant use of strong CYP1A2 inhibitors and inducers 7 days or 5 half-lives, whichever is longer, prior to V1. This restriction applies to concomitant medications, herbal supplements (e.g., St. John's Wort), and ordinary dietary intake. Refer to Appendix 7 for a list of prohibited medications.
- Prescribed medications for OH other than fludrocortisone are prohibited
- Alpha blockers are prohibited (e.g., Prazosin, Terazosin, Doxazosin, Silodosin, Alfuzosin, Tamsulosin)
- Norepinephrine reuptake inhibitors (NRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are prohibited
  - NRIs (e.g. atomoxetine and reboxetine) and SNRIs (e.g. duloxetine, milnacipran, levomilnacipran, venlafaxine, desvenlafaxine)

- Psychostimulants (e.g. amphetamine, dextroamphetamine, methylphenidate, pemoline) are prohibited
- Subjects will be requested to refrain from making any significant dietary changes throughout the duration of the study. During their scheduled visits, subjects should be reminded to maintain an adequate fluid intake.

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:

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

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 IDMC (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 10-mg TD-9855 dose. Thus, application of pregnancy prevention measures for 30 days 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 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 30 days 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 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 (ICF) 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 ICF 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 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 AESI reports will be completed and submitted.

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

Theravance Biopharma Clinical Safety
Fax: (650) 808-3786
Email: 0170_Safety@theravance.com

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

Medical Monitor Contact Information:
Telephone: +1 (650) 449-8840 (US) /
353-1-566-8682 (Ireland)
Email: 0170_Medical@theravance.com

For sites located in Mexico, Peru, Chile or Argentina:
Email: 0170_Medical_LATAM@theravance.com

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). ***Exception for Subjects entering from Study 0169 (0169 Completers Group)**:* Adverse Events, including Serious Adverse Events, that start after the Study 0170 ICF is signed, but before the first dose on Study 0170 is taken, are considered events originating in Study 0169. 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 reports 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
Fax: (650) 808-3786
Email: 0170_Safety@theravance.com

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

Medical Monitor Contact Information:

Telephone: +1 (650) 449-8840 (US) /
353-1-566-8682 (Ireland)
Email: 0170_Medical@theravance.com

For sites located in Mexico, Peru, Chile or Argentina:
Email: 0170_Medical_LATAM@theravance.com

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 SAS software (SAS Institute, Cary, North Carolina, US).

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 for each phase of the study (OL or double-blind randomized withdrawal phase), 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

Assuming that 60% are eligible for randomization at the end of the 16-week OL period, approximately 258 subjects will be enrolled such that 154 subjects are expected to continue into the randomized treatment period. For the De Novo Group, the goal is to enroll at least 40% of MSA subjects.

The primary analysis will occur when all subjects in the Full analysis set (FAS) (Section 8.3.2) of double-blinded randomized withdrawal phase of the study have either completed the primary endpoint assessment (OHSA#1 and PGI-S at Week 6 post randomization) (V9, D155)) or discontinued earlier and the database has been cleaned and locked. A sample size of 154 at randomization will provide an overall power of 90% to detect a difference of 25% (25% TD-9855 vs. 50% PBO) in the primary endpoint of proportion of subjects that meet the criteria of treatment failure at Week 6 (V9, D155) during the double-blind randomized withdrawal phase at two-sided alpha level of 0.05.

8.3. Analysis Sets

All efficacy analyses in the double-blind randomized withdrawal phase will be performed based on the FAS using the assigned randomized treatments. The FAS of the double-blind randomized withdrawal phase is defined as all randomized subjects who have received at least 1 dose of study medication post randomization.

The per-protocol (PP) analysis set of the double-blind randomized withdrawal phase comprises all subjects in the FAS with no major analysis protocol deviations (Section 8.3.2). If the number of FAS subjects excluded from the PP analysis set is <5% per treatment group, PP analyses will not be performed. Otherwise, both the FAS and the PP analysis set will be used for selected efficacy summaries and analyses.

The safety analysis set (Safety set) of the double-blind randomized withdrawal phase is comprised of all randomized subjects who receive at least 1 dose of study medication. The safety analysis set will be the analysis set for both general (baseline, exposure, and compliance) and safety analyses in the double-blind randomized withdrawal phase. Subjects in the safety analysis set will be grouped according to the actual study treatments they receive.

The FAS and Safety set for OL phase will be identical and is defined as all enrolled subjects who have received at least one dose of TD-9855.

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

Protocol deviations will be identified separately for each phase of the study. The following protocol deviations are defined as major and would be considered to have an impact on the interpretation of efficacy results:

- Poor study medication compliance (as calculated from drug accountability data), defined as compliance <80% over the interval from first to last dose in each phase of the study
- Not meeting efficacy-related inclusion criteria or meeting efficacy-related exclusion criteria (criteria to be listed in the applicable SAP)
- Using efficacy-related prohibited concomitant medications (to be listed in the applicable SAP)

Additional criteria may be specified in the SAP. Subjects with major analysis protocol deviations will be identified before the database lock and provided in a listing. In addition, a listing of all protocol deviations will be provided.

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 and described in the SAP if deemed appropriate.

The demographics, baseline characteristics, medical history and safety will be summarized separately for OL phase and double-blind randomized withdrawal phase. In the OL phase, data will be summarized for all subjects and by enrollment group (De Novo Group or 0169 Completers Group). In the double-blind randomized withdrawal phase, data will be summarized by treatment group.

All data as collected will be listed by subject.

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 descriptively summarized.

8.4.2. Medical History

Descriptive summary of medical history will be provided.

8.5. Analysis of Efficacy

8.5.1. Efficacy Endpoints

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

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

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

The secondary endpoints are:

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

The exploratory endpoints are:

- Standing systolic blood pressure during orthostatic standing test at Week 6 post randomization (V9, D155)
- Change from baseline in OHQ overall composite score at Week 6 post randomization (V9, D155)
- Change from baseline in EQ-5D-5L at Week 6 post randomization (V9, D155)
- Non-Motor Symptom Scale (NMSS) at Week 6 post randomization (V9, D155)
- Hospital Anxiety and Depression Scale (HADS) at Week 6 post randomization (V9, D155)
- Burden Scale for Family Caregivers – short version (BSFC-s) at Week 6 post randomization (V9, D155)

For subjects with PD

- Change from baseline in UPDRS at Week 6 post randomization (V9, D155)
- Change from baseline in PDQ-8 at Week 6 post randomization (V9, D155)

For subjects with MSA

- Change from baseline in UMSARS at Week 6 post randomization (V9, D155)
- Change from baseline in COMPASS-31 at Week 6 post randomization (V9, D155)

8.5.1.1. Primary Efficacy Evaluation

The primary study endpoint is the proportion of treatment failure at Week 6 during the double-blind randomized withdrawal phase. Treatment failure is defined as subjects who meet the following criteria at Week 6 following randomization:

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

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

Logistic regression model will be used to compare treatment differences based on the FAS. The model will include fixed effect class terms of treatment, baseline disease type (MSA, PAF, PD), and continuous covariate of baseline OHSA#1 score, and baseline PGI-S score. Odds Ratio with 95% confidence intervals will be calculated and presented, least-square proportion and 95% confidence intervals on the differences between TD-9855 and placebo groups will be calculated and presented. In addition, the proportion of subject with treatment failure along with proportion of subjects failing separately due to worsening of OHSA#1 and PGI-S will be reported.

Sensitivity analyses on the primary endpoint will be carried out (1) using per-protocol set which excludes subjects with major protocol deviations, (2) using multiple imputation for subject missing OHSA#1 and/or PGI-S score at Week 6 post randomization (V9, D155) and (3) by excluding subjects with missing data on primary endpoint. Additional sensitivity analyses may be defined in the SAP.

The primary analysis will be repeated on a set of pre-specified subgroups (e.g., disease type) and presented in graphical format. Details will be specified in the Statistical Analysis Plan (SAP).

8.5.1.2. Secondary and Other Efficacy Evaluations

Secondary efficacy endpoints involving assessment of change from baseline at multiple time points such as OHSA#1, OHSA composite score, OHDAS composite score, and percent of time spent in supine, sitting and standing position as measured by a wearable device, will be analyzed using mixed model for repeated measures (MMRM) to compare treatment differences based on the FAS. The model will include fixed effect class terms of treatment, baseline disease type (MSA, PD, PAF), week, and continuous covariate of baseline score of the respective measure, a random subject effect, with an unstructured covariance structure. 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 PBO will be calculated and presented.

Exploratory endpoints involving assessment of change from baseline at multiple time points such as standing SBP during orthostatic standing test will be analyzed using mixed model for repeated measures (MMRM) to compare treatment differences based on the FAS.

Exploratory endpoints involving assessment of change from baseline but only at Week 6 such as PDQ-8, UPDRS, UMSARS, and COMPASS-31 an analysis of covariance (ANCOVA) will be used to compare treatment differences based on the FAS. The model will include fixed effect of treatment, baseline disease type (MSA, PD, PAF) and continuous covariate of baseline score of the respective scales.

All other efficacy endpoints will be analyzed descriptively as supportive analysis.

In addition, descriptive analysis of efficacy data collected during OL phase will be carried out for all subjects and summarized by enrollment group (De Novo Group or 0169 Completers Group).

8.5.2. Multiplicity Adjustment

If the treatment effect of the primary efficacy endpoint has been demonstrated, secondary efficacy endpoints (Section 8.5.1) will be tested via a statistical testing procedure, to be described in the SAP, that will protect the family-wise Type I error rate at 2-sided significance level of 5%. No statistical significance will be claimed after a failure to reject the null hypothesis has occurred.

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

For all supportive analyses including other efficacy endpoints and sensitivity analyses of the primary efficacy endpoint, p-values and confidence intervals will be evaluated descriptively at 2-sided 5% significance level with no adjustment for multiplicity.

8.5.3. Analysis of Pharmacokinetics

All PK data collected in the study will be listed. PK analyses will follow the PK SAP and be reported in a separate Population-PK report.

8.5.4. Analysis of Pharmacodynamics

All pharmacodynamic data collected will be listed. Pharmacodynamic analyses will be detailed as appropriate in a separate report.

8.6. Safety Analyses

Safety data, including C-SSRS, will be descriptively summarized separately for OL phase and double-blind randomized withdrawal phase.

The OL phase data will be summarized for all subjects and by enrollment group (De Novo Group or 0169 Completers Group), and the double-blind randomized withdrawal phase data will be summarized by treatment group according to treatment subjects received. 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

Extent of exposure will be calculated from the study medication administration page of the CRF and summarized. Dosing information for individual subjects will be listed. Reasons for study medication discontinuation will be summarized. For each subject, treatment compliance over the interval from first to last dose will be calculated from the study medication administration and drug accountability pages of the CRF. Treatment compliance will be summarized for all subjects and by enrollment group in OL phase and by treatment group in the double-blinded randomized withdrawal phase.

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 be presented by system organ class (SOC), PT, and severity (mild, moderate, severe), along with the number and percentage of subjects for whom events were reported.

For subjects continuing from OL phase to the double-blinded randomized withdrawal phase, an AE that begins on or after the date of the first dose of TD-9855 up to the date of last dose of TD-9855 in OL phase will be considered TEAE for OL phase. For subjects discontinuing the study during the OL phase, an AE that begins on or after the date of the first dose of TD-9855 and up to the date of last dose of TD-9855 plus 14 days follow-up period will be considered TEAE for OL phase.

In the double-blinded randomized withdrawal phase, a TEAE is defined as any AE that begins on or after the date of the first dose of study medication post randomization and up to the date of last dose of study medication plus 14 days follow-up period.

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

- All AEs, by SOC and PT and also by PT (by descending overall frequency)
- All AEs, by SOC, PT, and severity
- All study medication-related AEs, by SOC and PT
- All study medication-related AEs, by SOC, PT, and severity

- All AEs leading to premature discontinuation of study medication, by SOC and PT
- All AEs leading to temporary interruption of study medication, by SOC and PT
- All SAEs, by SOC and PT
- All study medication-related SAEs, by SOC and PT

All AEs reported will be listed by subject. A separate listing will be provided for all subjects who experience an SAE. Separate 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 by nominal visit.

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, SBP and DBP, 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

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 and excluding subjects with missing data on primary endpoint.

Rules for imputation of missing safety data (e.g., missing or partial AE start dates) will be specified in the SAP. General principles are to count AEs as treatment emergent if they might have been, given the data obtained, and likewise to count medications as concomitant if they might have been, given the data obtained. There will be no imputation of missing safety assessments (e.g., laboratory test results).

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

Subject-level data will be collected to capture details around any deviations resulting from COVID-19. Data may include discontinuation of treatment, withdrawal from the trial, use of alternative or rescue treatments, missed endpoint ascertainment, and visit modality (e.g., in clinic vs remote visit). This information will be incorporated into the planned primary analysis and sensitivity analyses to assess potential impact associated with COVID-19. Further details will be provided in SAP.

8.8. Independent Data Monitoring Committee

There will be an external IDMC comprising 2 clinicians and a biostatistician. The sponsor will also perform ongoing blinded review of the safety data.

The IDMC will act in an advisory capacity to the sponsor. The IDMC responsibilities will be detailed in a charter and will include but not be limited to the following:

- Review the following documents before commencing activities as an IDMC: draft IDMC charter, Investigator brochure, study protocols, template informed consent form, blank case report forms, and data monitoring plans
- Evaluate the progress of the study; timeliness and quality of the data; subject recruitment, accrual, and retention; risk versus benefit to subjects; and other factors that might affect the outcome of the study
- Consider relevant information that may have an impact on subject safety or the ethics of the study
- Make recommendations to the sponsor concerning continuation, termination, or other modifications to the study based on their observations of the study and its data.
- Conduct routine review of efficacy and safety data according to a preplanned schedule.

The Sponsor has enlisted an Independent Statistical Supporting Group (ISRG) to prepare and present reports to the IDMC to facilitate their data reviews.

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 designated 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 US 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, 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, year 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

1. Metzler M, Duerr S, Granata R, Krismer F, Robertson D, Wenning GK. Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. J Neurol. 2013 Sept;260(9):2212-9. doi: 10.1007/s00415-012-6736-7. Epub 2012 Nov 20.
2. Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. Circulation. 2009 Jan 6;119(1):139-46. doi: 10.1161/CIRCULATIONAHA.108.805887.
3. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol. 2006 Sep;13(9):930-6.
4. Goldstein DS, Holmes C, Cannon RO 3rd, Eisenhofer G, Kopin IJ. Sympathetic cardioneuropathy in dysautonomias. N Eng J Med. 1997 Mar 6;336(10):696-702.
5. Ehringer H, Hornykiewicz O. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Parkinsonism Relat Disord. 1998 Aug;4(2):53-7.
6. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004 Oct;318(1):121-34. Epub 2004 Aug 24.
7. Shibao C, Raj SR, Gamboa A, Diedrich A, Choi L, Black BK, et al. Norepinephrine transporter blockade with atomoxetine induces hypertension in patients with impaired autonomic function. Hypertension. 2007 Jul;50(1):47-53. Epub 2007 May 21.
8. Ramirez CE, Okamoto LE, Arnold AC, Gamboa A, Diedrich A, Choi L, et al. Efficacy of atomoxetine versus midodrine for the treatment of orthostatic hypotension in autonomic failure. Hypertension. 2014 Dec;64(6):1235-40. doi: 10.1161/HYPERTENSIONAHA.114.04225. Epub 2014 Sep 2.
9. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res. 2012 Apr;22(2):79-90. doi: 10.1007/s10286-011-0146-2. Epub 2011 Nov 2.

APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0170
Protocol Title:	A Phase 3, 22-week, Multi-center, Randomized Withdrawal Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension in Subjects with Primary Autonomic Failure
Version:	1.0 (Amendment 4)
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: 0170													Bracket®
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:		
Visit	Subject ID Number													
	1	7	0	-						-				

#

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

Protocol: 0170																
Visit	Subject ID Number													Rater Initials		
	1	7	0	-						-						

#

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 ☐

Appendix 2-2

Theravance Biopharma	Protocol: 0170														Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:			
Visit	Subject ID Number														
	1	7	0	-						-					

Burden Scale for Family Caregivers – Short Form BSFC-s

We are asking you for information about your present situation. The present situation comprises your caregiving deduced from the illness of your family member (or friend).

The following statements often refer to the type of your assistance. This may be any kind of support up to nursing care.

Please draw an "X" for the best description of your present situation. Please answer every question!

	strongly agree	agree	disagree	strongly disagree
1. My life satisfaction has suffered because of the care.	☐	☐	☐	☐
2. I often feel physically exhausted.	☐	☐	☐	☐
3. From time to time I wish I could "run away" from the situation I am in.	☐	☐	☐	☐
4. Sometimes I don't really feel like "myself" as before.	☐	☐	☐	☐
5. Since I have been a caregiver my financial situation has decreased.	☐	☐	☐	☐
6. My health is affected by the care situation.	☐	☐	☐	☐
7. The care takes a lot of my own strength.	☐	☐	☐	☐
8. I feel torn between the demands of my environment (such as family) and the demands of the care.	☐	☐	☐	☐
9. I am worried about my future because of the care I give.	☐	☐	☐	☐
10. My relationships with other family members, relatives, friends and acquaintances are suffering as a result of the care.	☐	☐	☐	☐

Thank you very much!

Appendix 2-3

Theravance Biopharma	Protocol: 0170													Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:		
Visit	Subject ID Number													
	1	7	0	-						-				

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

HADS - USA/English - Version of 15 Apr 08 - Mapi Research Institute.
ID4577

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		A	D
		I feel tense or "wound up"		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Never		
		I enjoy the things I used to enjoy		
	0	Definitely		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and fairly badly		
2		Yes, but not too badly		
1		Sometimes, but it doesn't worry me		
0		Never		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Never		0
		I get a sort of anxious feeling like "butterflies" in the stomach		
		Never	0	
		Occasionally	1	
		Often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		Often I don't take as much care as I should		2
		Sometimes I don't take as much care as I should		1
		I take just as much care as ever		0

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D			A	D
		I feel tense or "wound up"	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Never	Never		0
		I enjoy the things I used to enjoy	**I get a sort of anxious feeling like "butterflies" in the stomach**		
	0	Definitely	Never	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and fairly badly	Definitely		3
2		Yes, but not too badly	Often I don't take as much care as I should		2
1		Sometimes, but it doesn't worry me	Sometimes I don't take as much care as I should		1
0		Never	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Definitely	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Never	Never	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever have		0
2		A lot of the time	Somewhat less than I used to		1
1		Not too often	Much less than I used to		2
0		Almost never	Rarely		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often	3	
	2	Not often	Often	2	
	1	Sometimes	Not very often	1	
	0	Most of the time	Never	0	
		I can sit at ease and feel relaxed	**I can enjoy a good book, radio or television program**		
0		Always	Often		0
1		Usually	Sometimes		1
2		Not often	Not often		2
3		Never	Very seldom		3

Please make sure you have answered all the questions.

	A	D
TOTAL		

Appendix 2-4

Theravance Biopharma	Protocol: 0170		Bracket
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	
Visit	Subject ID Number		Rater Initials
	1 7 0 -	-	

Non-Motor Symptom Scale

Symptoms assessed over the last month. Each symptom scored with respect to:

Severity: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (< 1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week); 4 = Very Frequent (daily or all the time).

Domains will be weighed differentially. Yes/No answers are not included in final frequency x severity calculation. (Bracketed text in questions within the scale is included as an explanatory aid).

	Severity	Frequency	Frequency x Severity
Domain 1: Cardiovascular including falls			
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐
Domain 2: Sleep/fatigue			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reading).	☐	☐	☐
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	☐	☐	☐
5. Does the patient have difficulties falling or staying asleep?	☐	☐	☐
6. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	☐	☐	☐
SCORE:			☐

Appendix 2-5

Theravance Biopharma	Protocol: 0170														Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:			
Visit	Subject ID Number														
	1	7	0	-						-					

EQ-5D-5L

Health Questionnaire

English version for the USA

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

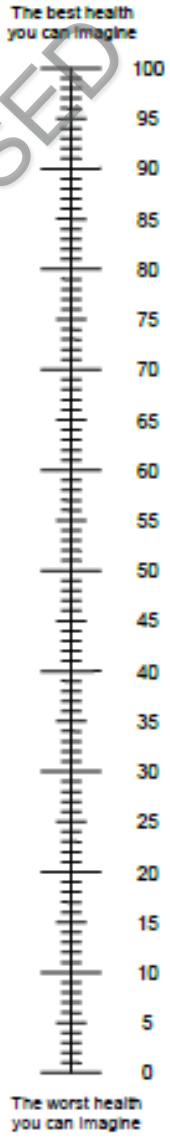
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Protocol: 0170																
Visit	Subject ID Number													Rater Initials		
	1	7	0	-						-						

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Appendix 2-6

Theravance Biopharma	Protocol: 0170		Bracket
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	

Visit	Subject ID Number	Rater Initials
	1 7 0 - -	

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 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.

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

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

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).

Protocol: 0170																		
Visit	Subject ID Number															Rater Initials		
	1	7	0	-						-								

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.).

Protocol: 0170																		
Visit	Subject ID Number															Rater Initials		
	1	7	0	-						-								

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.

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

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."*

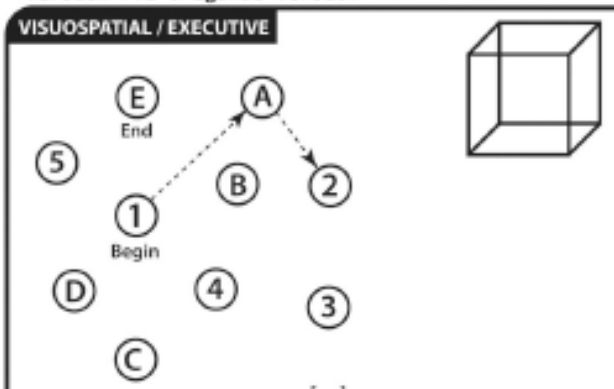
Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

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.

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE



Copy cube

[ ] [ ]

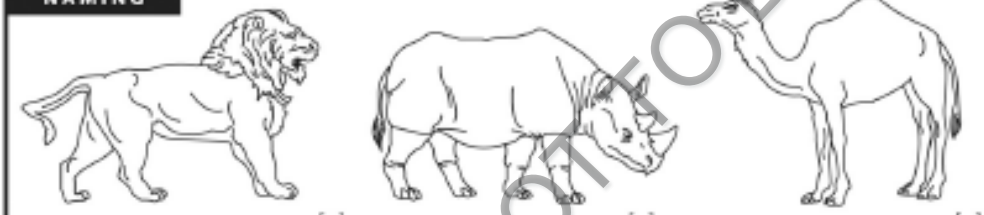
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS

__/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

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix 2-7

Theravance Biopharma	Protocol: 0170														Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:			
Visit	Subject ID Number														Rater Initials
	1	7	0	-						-					

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

Protocol: 0170																		
Visit	Subject ID Number															Rater Initials		
	1	7	0	-						-								

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 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?* 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.

	Most Severe	Most Severe
Lifetime - *Most Severe Ideation:* ____ *Type # (1-5)* ____ *Description of Ideation* Past 12 Months - *Most Severe Ideation:* ____ *Type # (1-5)* ____ *Description of Ideation*		
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	____	____

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐	Yes ☐ No ☐ Total # of Attempts _____ 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* _____

Appendix 2-8

Theravance Biopharma	Protocol: 0170														Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)					
												:			
Visit	Subject ID Number														Rater Initials
	1	7	0	-						-					

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

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: 0170																		
Visit	Subject ID Number															Rater Initials		
	1	7	0	-						-								

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?* If yes, describe:	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 ☐
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 ☐
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?* If yes, describe:	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 ☐

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	___

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ 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 _____

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ 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* _____

Appendix 2-9

Theravance Biopharma	Protocol: 0170		Bracket
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
Visit	Subject ID Number		Rater Initials
	1 7 0 -		

PATIENT GLOBAL IMPRESSION SEVERITY (PGI-S)

Please choose the response below that best describes the overall severity of your neurogenic orthostatic hypotension symptoms **over the past week**

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

Appendix 2-10

Theravance Biopharma	Protocol: 0170		Bracket
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	

Visit	Subject ID Number	Rater Initials
	1 7 0 - -	

PART I. MENTATION, BEHAVIOR AND MOOD (RATE ITEMS 1 TO 4 BY INTERVIEW)

1. Intellectual Impairment
0 = None
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

Score: ____

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

Score: ____

3. Depression
0 = Not present.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

Score: ____

4. Motivation / Initiative
0 = Normal
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

Score: ____

ENTER TOTAL SCORE for PART I. MENTATION, BEHAVIOR AND MOOD:
(from items 1 to 4 - maximum score = 16)

Total score: ____

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

PART II. ACTIVITIES OF DAILY LIVING (RATE ITEMS 5 TO 17 BY INTERVIEW)

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.
Score: ____

6. Salivation
0 = Normal
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.
Score: ____

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.
Score: ____

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.
Score: ____

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.
Score: ____

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.
Score: ____

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.
Score: ____

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

PART II. ACTIVITIES OF DAILY LIVING

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.
Score: ____

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.
Score: ____

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have start-hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.
Score: ____

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.
Score: ____

16. Tremor
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.
Score: ____

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.
Score: ____

ENTER TOTAL SCORE for PART II. ACTIVITIES OF DAILY LIVING:
(from items 5 to 17 - maximum score = 52)
Total score: ____

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

PART III MOTOR EXAMINATION (Acceptable responses are 0, 1, 2, 3, 4)

Please perform full UPDRS approximately 1 to 3 hours after the subject has taken a scheduled dose of their Parkinson's medication, preferably their morning dose). UPDRS in the ON state will be measured at a time representative of the ON state in that subject, not in "best" ON.

18. Speech

0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

Score: |___|

19. Facial Expression

0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

Score: |___|

20. Tremor at rest

Face, lips, chin |___| + Right hand |___| + Left hand |___| + Right foot |___| + Left foot |___| =

Score: |___|___|

0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

Right hand |___| + Left hand |___| =

Score: |___|

0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with subject relaxed in sitting position. Cogwheeling to be ignored.)

Neck |___| + RUE |___| + LUE |___| + RLE |___| + LLE |___| =

Score: |___|___|

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

PART III. MOTOR EXAMINATION

23. Finger Taps (Subject taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)

Right hand |____| + Left hand |____| = Score: |____|

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Subject opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)

Right hand |____| + Left hand |____| = Score: |____|

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)

Right hand |____| + Left hand |____| =
Score: |____|

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

PART III. MOTOR EXAMINATION

23. Finger Taps (Subject taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)

Right hand ____ + Left hand ____ = Score: ____

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Subject opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)

Right hand ____ + Left hand ____ = Score: ____

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)

Right hand ____ + Left hand ____ = Score: ____

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Subject taps heel on the ground in rapid succession picking up entire leg. Amplitude should be about 3 inches)

Right leg ____ + Left leg ____ = Score: ____

0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Subject attempts to arise from a straight-back wood or metal chair with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt. Score: ____
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side. Score: ____
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

PART III. MOTOR EXAMINATION

29. Gait
0 = Normal
1 = Walks slowly, may shuffle with short steps, but no festination or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

Score: ___

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while subject is erect, with eyes open and feet slightly apart. Subject is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

Score: ___

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude and poverty of movement in general)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

Score: ___

A. Indicate the subject's PD state during the examination (check one):
☐ "On" during exam
☐ Fluctuated during the exam
☐ "Off" during exam

ENTER TOTAL SCORE for PART III. MOTOR EXAMINATION:
(from items 18 to 31 - maximum score = 108)

Total score: ___

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

PART IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present?
(Historical information.)

0 = None
1 = 1-25% of day
2 = 26-50% of day
3 = 51-75% of day
4 = 76-100% of day

Score: |___|

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

Score: |___|

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

Score: |___|

35. Presence of Early Morning Dystonia (Historical information.)

0 = No
1 = Yes

Score: |___|

ENTER TOTAL SCORE for PART IV. A. Dyskinesias
(from items 32 to 35 - maximum score = 13)

Total score: |___|___|

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

PART IV. COMPLICATIONS OF THERAPY (In the past week)

B. CLINICAL FLUCTUATIONS

36. Are any "off" periods predictable as to timing after a dose of medication?
0 = No
1 = Yes
Score: ____

37. Are any "off" periods unpredictable as to timing after a dose of medication?
0 = No
1 = Yes
Score: ____

38. Do any of the "off" periods come on suddenly, e.g. over a few seconds?
0 = No
1 = Yes
Score: ____

39. What proportion of the waking day is the subject "off" on average?
0 = None
1 = 1-25% of day
2 = 26-50% of day
3 = 51-75% of day
4 = 76-100% of day
Score: ____

ENTER TOTAL SCORE for PART IV. B. Clinical Fluctuations
(from items 36 to 39 - maximum score = 7)
Total score: ____

C. OTHER COMPLICATIONS

40. Does the subject have anorexia, nausea, or vomiting?
0 = No
1 = Yes
Score: ____

41. Does the subject have any sleep disturbances, e.g. insomnia or hypersomnolence?
0 = No
1 = Yes
Score: ____

42. Does the subject have symptomatic orthostasis?
0 = No
1 = Yes
Score: ____

ENTER TOTAL SCORE for PART IV. C. Other Complications
(from items 40 to 42 - maximum score = 3)
Total score: ____

Protocol: 0170																	
Visit	Subject ID Number														Rater Initials		
	1	7	0	-						-							

Part V. MODIFIED HOEHN AND YAHR STAGING

Stage 0 = No signs of disease.
Stage 1 = Unilateral disease.
Stage 1.5= Unilateral plus axial involvement.
Stage 2 = Bilateral disease, without impairment of balance.
Stage 2.5= Mild bilateral disease, with recovery on pull test.
Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4 = Severe disability; still able to walk or stand unassisted
Stage 5 = Wheelchair bound or bedridden unless aided.

Part VI. MODIFIED SCHWAB AND ENGLAND ACTIVITIES ON DAILY LIVING SCALE

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

Appendix 2-11

Theravance Biopharma	Protocol: 0170														Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:			

Visit	Subject ID Number													
	1	7	0	-						-				

Parkinson's Disease Quality of Life Questionnaire (PDQ-8)

Due to having Parkinson's disease,
how often during the last month have you…

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	Had difficulty getting around in public?	☐	☐	☐	☐	☐
2.	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
3.	Felt depressed?	☐	☐	☐	☐	☐
4.	Had problems with your close personal relationships?	☐	☐	☐	☐	☐
5.	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
6.	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
7.	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
8.	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐

Appendix 2-12

Theravance Biopharma	Protocol: 0170		Bracket
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	

Visit	Subject ID Number	Rater Initials
	1 7 0 - -	

APPENDIX: UNIFIED MSA RATING SCALE (UMSARS)
Part I: Historical Review

Rate the average functional situation for the past 2 weeks (unless specified) according to the patient and caregiver interview. Indicate the score that best fits with the patient status. Rate the function independently from the nature of the signs.

1. Speech ____
   - 0 Not affected.
   - 1 Mildly affected. No difficulties being understood.
   - 2 Moderately affected. Sometimes (less than half of the time) asked to repeat statements.
   - 3 Severely affected. Frequently (more than half of the time) asked to repeat statements.
   - 4 Unintelligible most of the time.

2. Swallowing ____
   - 0 Normal.
   - 1 Mild impairment. Choking less than once a week.
   - 2 Moderate impairment. Occasional food aspiration with choking more than once a week.
   - 3 Marked impairment. Frequent food aspiration.
   - 4 Nasogastric tube or gastrostomy feeding.

3. Handwriting ____
   - 0 Normal
   - 1 Mildly impaired, all words are legible.
   - 2 Moderately impaired, up to half of the words are not legible.
   - 3 Markedly impaired, the majority of words are not legible.
   - 4 Unable to write.

4. Cutting food and handling utensils ____
   - 0 Normal.
   - 1 Somewhat slow and/or clumsy, but no help needed.
   - 2 Can cut most foods, although clumsy and slow; some help needed.
   - 3 Food must be cut by someone, but can still feed slowly.
   - 4 Needs to be fed.

5. Dressing ____
   - 0 Normal.
   - 1 Somewhat slow and/or clumsy, but no help needed.
   - 2 Occasional assistance with buttoning, getting arms in sleeves.
   - 3 Considerable help required, but can do some things alone.
   - 4 Completely helpless.

6. Hygiene ____
   - 0 Normal.
   - 1 Somewhat slow and/or clumsy, but no help needed.
   - 2 Needs help to shower or bathe; or very slow in hygienic care.
   - 3 Requires assistance for washing, brushing teeth, combing hair, using the toilet.
   - 4 Completely helpless.

7. Walking ____
   - 0 Normal.
   - 1 Mildly impaired. No assistance needed. No walking aid required (except for unrelated disorders).
   - 2 Moderately impaired. Assistance and/or walking aid needed occasionally.
   - 3 Severely impaired. Assistance and/or walking aid needed frequently.
   - 4 Cannot walk at all even with assistance.

8. Falling (rate the past month) ____
   - 0 None.
   - 1 Rare falling (less than once a month).
   - 2 Occasional falling (less than once a week).
   - 3 Falls more than once a week.
   - 4 Falls at least once a day (if the patient cannot walk at all, rate 4).

9. Orthostatic symptoms ____
   - 0 No orthostatic symptoms.*
   - 1 Orthostatic symptoms are infrequent and do not restrict activities of daily living.
   - 2 Frequent orthostatic symptoms developing at least once a week. Some limitation in activities of daily living.
   - 3 Orthostatic symptoms develop on most occasions. Able to stand > 1 min on most occasions. Limitation in most of activities of daily living.
   - 4 Symptoms consistently develop on orthostasis. Able to stand < 1 min on most occasions. Syncope/presyncope is common if patient attempts to stand.

   *Syncope, dizziness, visual disturbances or neck pain, relieved on lying flat.

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

10. Urinary function*
0 Normal.
1 Urgency and/or frequency, no drug treatment required.
2 Urgency and/or frequency, drug treatment required.
3 Urge incontinence and/or incomplete bladder emptying needing intermittent catheterization.
4 Incontinence needing indwelling catheter. *Urinary symptoms should not be due to other causes. ____

11. Sexual function
0 No problems.
1 Minor impairment compared to healthy days.
2 Moderate impairment compared to healthy days.
3 Severe impairment compared to healthy days.
4 No sexual activity possible. ____

12. Bowel function
0 No change in pattern of bowel function from previous pattern.
1 Occasional constipation but no medication needed.
2 Frequent constipation requiring use of laxatives.
3 Chronic constipation requiring use of laxatives and enemas.
4 Cannot have a spontaneous bowel movement. ____

Total score Part I: ____

Part II: Motor Examination Scale

Always rate the worst affected limb.

1. Facial expression ____
   - 0 Normal.
   - 1 Minimal hypomimia, could be normal ("Poker face").
   - 2 Slight but definitely abnormal diminution of facial expression.
   - 3 Moderate hypomimia; lips parted some of the time.
   - 4 Masked or fixed facies with severe or complete loss of facial expression, lips parted 0.25 inch or more.

2. Speech ____
   The patient is asked to repeat several times a standard sentence.
   - 0 Normal.
   - 1 Mildly slow, slurred, and/or dysphonic. No need to repeat statements.
   - 2 Moderately slow, slurred, and/or dysphonic. Sometimes asked to repeat statements.
   - 3 Severely slow, slurred, and/or dysphonic. Frequently asked to repeat statements.
   - 4 Unintelligible.

3. Ocular motor dysfunction ____
   Eye movements are examined by asking the subject to follow slow horizontal finger movements of the examiner, to look laterally at the finger at different positions, and to perform saccades between two fingers, each held at an eccentric posit ion of approximately 30°. The examiner assesses the following abnormal signs: (1) broken-up smooth pursuit, (2) gaze-evoked nystagmus at an eye position of more than 45 degrees, (3) gaze-evoked nystagmus at an eye position of less than 45 degrees, (4) saccadic hypermetria. Sign 3 suggests that there are at least two abnormal ocular motor signs, because Sign 2 is also present.
   - 0 None.
   - 1 One abnormal ocular motor sign.
   - 2 Two abnormal ocular motor signs.
   - 3 Three abnormal ocular motor signs.
   - 4 Four abnormal ocular motor signs.

4. Tremor at rest (rate the most affected limb) ____
   - 0 Absent.
   - 1 Slight and infrequently present.
   - 2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
   - 3 Moderate in amplitude and present most of the time.
   - 4 Marked in amplitude and present most of the time.

5. Action tremor ____
   Assess postural tremor of outstretched arms (A) and action tremor on finger pointing (B). Rate maximal tremor severity in Task A and/or B (whichever is worse), and rate the most affected limb.
   - 0 Absent.
   - 1 Slight tremor of small amplitude (A). No interference with finger pointing (B).
   - 2 Moderate amplitude (A). Some interference with finger pointing (B).
   - 3 Marked amplitude (A). Marked interference with finger pointing (B).
   - 4 Severe amplitude (A). Finger pointing impossible (B).

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

6. Increased tone (rate the most affected limb) ____
Judged on passive movement of major joints with patient relaxed in sitting position; ignore cogwheeling.
0 Absent.
1 Slight or detectable only when activated by mirror or other movements.
2 Mild to moderate.
3 Marked, but full range of motion easily achieved.
4 Severe, range of motion achieved with difficulty.

7. Rapid alternating movements of hands ____
Pro-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately, rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cerebellar incoordination. Rate functional performance regardless of underlying motor disorder.
0 Normal.
1 Mildly impaired.
2 Moderately impaired.
3 Severely impaired.
4 Can barely perform the task.

8. Finger taps ____
Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand at least 15 to 20 seconds. Rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cerebellar incoordination. Rate functional performance regardless of underlying motor disorder.
0 Normal.
1 Mildly impaired.
2 Moderately impaired.
3 Severely impaired.
4 Can barely perform the task.

9. Leg agility ____
Patient is sitting and taps heel on ground in rapid succession, picking up entire leg. Amplitude should be approximately 10 cm, rate the worst affected leg. Note that impaired performance on this task can be caused by bradykinesia and/or cerebellar incoordination. Rate functional performance, regardless of underlying motor disorder.
0 Normal.
1 Mildly impaired.
2 Moderately impaired.
3 Severely impaired.
4 Can barely perform the task.

10. Heel-knee-shin test ____
The patient is requested to raise one leg and place the heel on the knee, and then slide the heel down the anterior tibial surface of the resting leg toward the ankle. On reaching the ankle joint, the leg is again raised in the air to a height of approximately 40 cm and the action is repeated. At least three movements of each limb must be performed for proper assessment. Rate the worst affected limb.
0 Normal.
1 Mildly dysmetric and ataxic.
2 Moderately dysmetric and ataxic.
3 Severely dysmetric and ataxic.
4 Can barely perform the task.

11. Arising from chair ____
Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.
0 Normal.
1 Clumsy, or may need more than one attempt.
2 Pushes self up from arms of seat.
3 Tends to fall back and may have to try more than once but can get up without help.
4 Unable to arise without help.

12. Posture ____
0 Normal.
1 Not quite erect, slightly stooped posture; could be normal for older person.
2 Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 Marked flexion with extreme abnormality of posture.

13. Body sway ____
Rate spontaneous body sway and response to sudden, strong posterior displacement produced by pull on shoulder while patient erect with eyes open and feet slightly apart. Patient has to be warned.
0 Normal.
1 Slight body sway and/or retropulsion with unaided recovery.
2 Moderate body sway and/or deficient postural response; might fall if not caught by examiner.
3 Severe body sway. Very unstable. Tends to lose balance spontaneously.
4 Unable to stand without assistance.

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

14. Gait ____

0 Normal.
1 Mildly impaired.
2 Moderately impaired. Walks with difficulty, but requires little or no assistance.
3 Severely impaired. Requires assistance.
4 Cannot walk at all, even with assistance.

Total score Part II: ____

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

14. Gait ____

0 Normal.
1 Mildly impaired.
2 Moderately impaired. Walks with difficulty, but requires little or no assistance.
3 Severely impaired. Requires assistance.
4 Cannot walk at all, even with assistance.

Total score Part II: ____

Part III: Autonomic Examination

Supine blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing. Orthostatic symptoms may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, neck and "coat-hanger" ache.

Systolic blood pressure
- Supine ____
- Standing (2 minutes) ____
- Unable to record ____

Diastolic blood pressure
- Supine ____
- Standing (2 minutes) ____
- Unable to record ____

Heart rate
- Supine ____
- Standing (2 minutes) ____
- Unable to record ____

Orthostatic symptoms
- Yes
- No

Part IV: Global Disability Scale

1. Completely independent. Able to do all chores with minimal difficulty or impairment. Essentially normal. Unaware of any difficulty.
2. Not completely independent. Needs help with some chores.
3. More dependent. Help with half of chores. Spends a large part of the day with chores.
4. Very dependent. Now and then does a few chores alone or begins alone. Much help needed.
5. Totally dependent and helpless. Bedridden.

Appendix 2-13

Theravance Biopharma	Protocol: 0170														Bracket
	Date of Assessment (DDMMMYYYY)									Time of Assessment (24-hour clock)		:			
Visit	Subject ID Number														
	1	7	0	-						-					

COMPASS 31

1. In the past week, have you ever felt faint, dizzy, "goofy", or had difficulty thinking soon after standing up from a sitting or lying position?
   1 Yes
   2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?
   1 Rarely
   2 Occasionally
   3 Frequently
   4 Almost Always

3. How would you rate the severity of these feelings or symptoms?
   1 Mild
   2 Moderate
   3 Severe

4. In the past week, have these feelings or symptoms that you have experienced:
   1 Gotten much worse
   2 Gotten somewhat worse
   3 Stayed about the same
   4 Gotten somewhat better
   5 Gotten much better
   6 Completely gone

5. In the past week, have you ever noticed color changes in your skin, such as red, white, or purple?
   1 Yes
   2 No (if you marked No, please skip to question 8)

6. What parts of your body are affected by these color changes? (Check all that apply)
   1 Hands
   2 Feet

7. Are these changes in your skin color:
   1 Getting much worse
   2 Getting somewhat worse
   3 Staying about the same
   4 Getting somewhat better
   5 Getting much better
   6 Completely gone

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

8. In the past week, what changes, if any, have occurred in your general body sweating?

1 I sweat much more than I used to
2 I sweat somewhat more than I used to
3 I haven't noticed any changes in my sweating
4 I sweat somewhat less than I used to
5 I sweat much less than I used to

9. Do your eyes feel excessively dry?

1 Yes
2 No

10. Does you mouth feel excessively dry?

1 Yes
2 No

11. For the symptom of dry eyes or dry mouth that you have had for the longest period of time, is this symptom:

1 I have not had any of these symptoms
2 Getting much worse
3 Getting somewhat worse
4 Staying about the same
5 Getting somewhat better
6 Getting much better
7 Completely gone

12. In the past week, have you noticed any changes in how quickly you get full when eating a meal?

1 I get full a lot more quickly now than I used to
2 I get full more quickly now than I used to
3 I haven't noticed any change
4 I get full less quickly now than I used to
5 I get full a lot less quickly now than I used to

13. In the past week, have you felt excessively full or persistently full (bloated feeling) after a meal?

1 Never
2 Sometimes
3 A lot of the time

14. In the past week, have you vomited after a meal?

1 Never
2 Sometimes
3 A lot of the time

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

15. In the past week, have you had a cramping or colicky abdominal pain?
    1 Never
    2 Sometimes
    3 A lot of the time

16. In the past week, have you had any bouts of diarrhea?
    1 Yes
    2 No (if you marked No, please skip to question 20)

17. How frequently does this occur?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per week
    4 Constantly

18. How severe are these bouts of diarrhea?
    1 Mild
    2 Moderate
    3 Severe

19. Are your bouts of diarrhea getting:
    1 Much worse
    2 Somewhat worse
    3 Staying the same
    4 Somewhat better
    5 Much better
    6 Completely gone

20. In the past week, have you been constipated?
    1 Yes
    2 No (if you marked No, please skip to question 24)

21. How frequently are you constipated?
    1 Rarely
    2 Occasionally
    3 Frequently _____ times per week
    4 Constantly

22. How severe are these episodes of constipation?
    1 Mild
    2 Moderate
    3 Severe

Protocol: 0170																	
Visit	Subject ID Number													Rater Initials			
	1	7	0	-						-							

23. Is your constipation getting:
    1 Much worse
    2 Somewhat worse
    3 Staying the same
    4 Somewhat better
    5 Much better
    6 Completely gone

24. In the past week, have you ever lost control of your bladder function?
    1 Never
    2 Occasionally
    3 Frequently _____ times per week
    4 Constantly

25. In the past week, have you had difficulty passing urine?
    1 Never
    2 Occasionally
    3 Frequently _____ times per week
    4 Constantly

26. In the past week, have you had trouble completely emptying your bladder?
    1 Never
    2 Occasionally
    3 Frequently _____ times per week
    4 Constantly

27. In the past week, without sunglasses or tinted glasses, has bright light bothered your eyes?
    1 Never (if you marked Never, please skip to question 29)
    2 Occasionally
    3 Frequently
    4 Constantly

28. How severe is this sensitivity to bright light?
    1 Mild
    2 Moderate
    3 Severe

29. In the past week, have you had trouble focusing your eyes?
    1 Never (if you marked Never, please skip to question 31)
    2 Occasionally
    3 Frequently
    4 Constantly

Protocol: 0170																
Visit	Subject ID Number													Rater Initials		
	1	7	0	-						-						

30. How severe is this focusing problem?

1 Mild
2 Moderate
3 Severe

31. Is the most troublesome symptom with your eyes (i.e. sensitivity to bright light or trouble focusing) getting:

1 I have not had any of these symptoms
2 Much worse
3 Somewhat worse
4 Staying about the same
5 Somewhat better
6 Much better
7 Completely gone

APPENDIX 3. INCIDENCE OF FALLS

Protocol 0170 - Fall Diary

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☐

If you checked "Yes", please remember to discuss the injury with the site staff at your next visit.

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: ________________

THR173023_0170_Fall_Diary_English(US)_v2.0_2018_Oct_26.docx 1

APPENDIX 4. AMBULATORY BLOOD PRESSURE MONITORING - POSITION DIARY

Protocol 0170 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: ________________

THR173023_0170_ABPM Log_English(US)_v1.0_2018_Oct_11.docx 1

APPENDIX 5. DOSING DIARY

Protocol 0170 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) Each "**Time**" entry should be immediately after taking the medication.
3) Dosing should occur every day at approximately the same time and AM or PM should be circled
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 maintain a constant smoking habit during the entire course of the study.

Day of the Week/ Date	Time	Comments (E.g.: -Reason for missed or partial dose -Significant Dietary Changes)
Day of the Week: Date:	_____:_____ AM / PM	
Day of the Week: Date:	_____:_____ AM / PM	
Day of the Week: Date:	_____:_____ AM / PM	
Day of the Week: Date:	_____:_____ AM / PM	
Day of the Week: Date:	_____:_____ AM / PM	
Day of the Week: Date:	_____:_____ AM / PM	
Day of the Week: Date:	_____:_____ AM / PM	

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: _____

THR173023_0170_Dosing_Diary_English(US)_v1.0_2018_Aug_17.docx 1

APPENDIX 6. MIDODRINE RESCUE MEDICATION DIARY

Protocol 0170 Midodrine Rescue Medication 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, midodrine dose, and any comments.
2) Each "**Midodrine Dose**" entry should be immediately after taking the medication.
3) Midodrine is permitted as follows:
   a. Up to 10 mg total daily dose, not to exceed more than one day in any given week
   b. Cannot be used on the assessment days

Day of the Week/ Date	Midodrine Dose	Comments (E.g.: Reason for taking midodrine)
Day of the Week: Date:	_____ mg	
Day of the Week: Date:	_____ mg	
Day of the Week: Date:	_____ mg	
Day of the Week: Date:	_____ mg	
Day of the Week: Date:	_____ mg	
Day of the Week: Date:	_____ mg	
Day of the Week: Date:	_____ mg	

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: _____

APPENDIX 7. PROHIBITED MEDICATIONS

The following are restricted during study participation as specified:

- Strong CYP1A2 inhibitors and inducers. This restriction applies to concomitant medications, herbal supplements, and ordinary dietary intake and include, but are not limited to the following:
  - Angelica root, St John's Wort, ciprofloxacin, clinafloxacin, enoxacin, fluvoxamine, oltipraz, rofecoxib, zafirlukast
- Prescribed medications (e.g. droxidopa, etc.) for OH other than fludrocortisone are prohibited
- Alpha blockers are prohibited (e.g., Prazosin, Terazosin, Doxazosin, Silodosin, Alfuzosin, Tamsulosin)
- Norepinephrine reuptake inhibitors (NRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are prohibited
  - NRIs (e.g. atomoxetine and reboxetine) and SNRIs (e.g. duloxetine, milnacipran, levomilnacipran, venlafaxine, desvenlafaxine)
- Psychostimulants (e.g. amphetamine, dextroamphetamine, methylphenidate, pemoline) are prohibited

APPENDIX 8. SAMPLE SCREENING VISIT FOR DENOVO SUBJECTS

Study Period:	**Screening**	
Study Day (Visit):	**Day -28 to -7 (Visit 1)**	
Procedure	**Start Time**	Approximate Time for Subject
Breakfast @ home and then travel	8:00 AM	1:00
Hospital Visit	9:00 AM	0:30
Informed consent (prior review)	9:30 AM	0:25
Inclusion /exclusion criteria	9:55 AM	0:15
Medical history (including smoking history)	10:10 AM	0:05
Concomitant medications (and smoking usage)	10:15 AM	0:05
MoCA	10:20 AM	0:10
C-SSRS	10:30 AM	0:10
OHQ subject training	10:40 AM	0:15
Tilt-table test	10:55 AM	0:30
Orthostatic standing test	11:25 AM	0:30
Vital Signs (Body Temperature, Heart Rate, Respiration Rate, Blood Pressure)	11:55 AM	0:05
Height (cm)	12:00 PM	0:02
Weight (kg)	12:02 PM	0:03
Physical examination	12:05 PM	0:05
Neurological examination	12:10 PM	0:05
12-lead electrocardiogram	12:15 PM	0:10
Pregnancy test	12:25 PM	0:05
Norepinephrine (NE)	12:30 PM	0:35
Safety laboratory test (chemistry, hematology, and urinalysis)	1:05 PM	0:10
Adverse events	1:15 PM	0:10
ESC (for confirmation of diagnosis)	1:25 PM	0:10
24-hour ambulatory BP device provision	1:35 PM	0:05
Wearables	1:40 PM	0:15
Incidence of Falls and ABPM position Diaries	1:55 PM	0:05
	Total Time (at Hospital):	5:00

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 De Novo subjects must be conducted in clinic, regardless of which visit modality is selected.

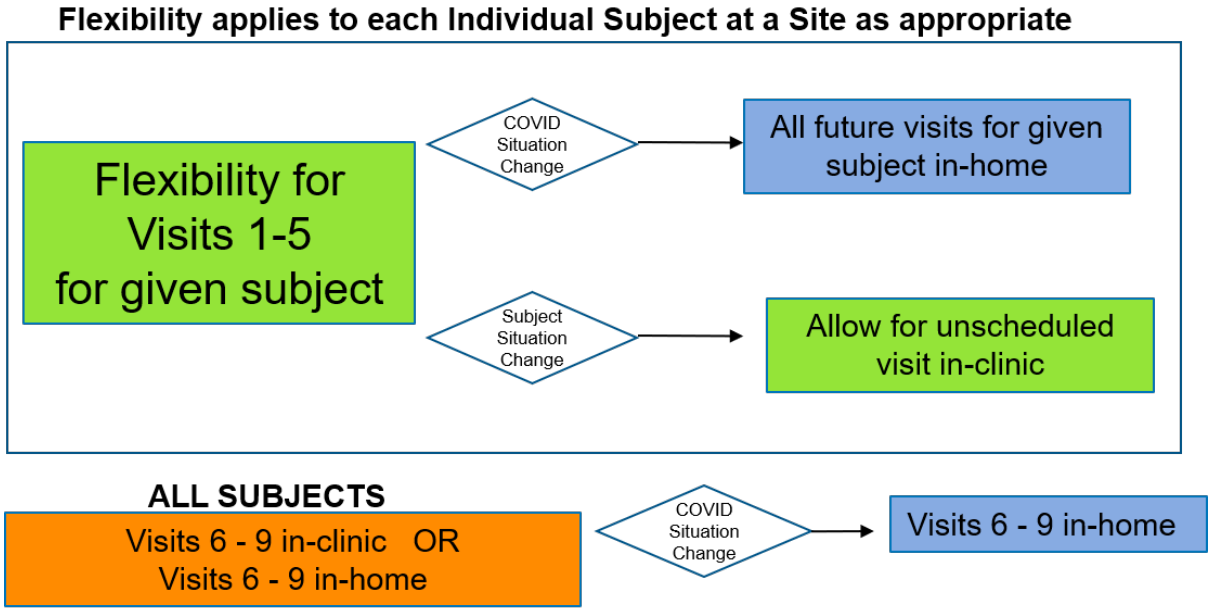
Investigators, in discussion with each individual subject at their site, will be required to elect to conduct study visits either in the clinic or remotely. Sites must conduct the randomization withdrawal visits 6 through 9 (V6/D113 - V9/D155) for a given subject in a consistent manner to reduce the possibility of variability in data collection and reporting.

Tools and systems are available to sites and subjects to support remote visits (e.g., direct to subject shipping of study medication and other study supplies, standardized HIPAA/GDPR compliant telemedicine platform, in-home health nurses).

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 the COVID-19 pandemic and its impact on both sites and subjects, the Sponsor will allow Investigators to request exceptions to the selected type of study visit modality for V6/D113 through V9/D155 due to COVID-19 or COVID-19 related circumstances. Approved exceptions will be recorded as COVID-19 related protocol deviations.



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

For De Novo subjects that have previously completed the Screening visit at the time regulatory and ethics approval for Amendment 4 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. For those subjects who are already randomized into the randomized withdrawal portion of Study 0170 and active in the study at the time regulatory and ethics approval for Amendment 4 is received, the Investigator and subject should continue the remaining study visits in the same visit modality as the Randomization Visit (V6/D113).

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