CLINICAL STUDY PROTOCOL

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

Study Short Title: TD-9855 Phase 2 in Neurogenic Orthostatic Hypotension (nOH)

Sponsor Study No.: 0145

Date: 08 November 2017, [redacted]

Test Product: TD-9855

Sponsor: Theravance Biopharma R&D, Inc.
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901 Gateway Boulevard
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This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0145: A Phase 2 Study to Assess the Effect and Safety of TD-9855 in Subjects with Neurogenic Orthostatic Hypotension

Study Short Title: TD-9855 Phase 2 in Neurogenic Orthostatic Hypotension (nOH)

Estimated Number of Study Centers and Countries or Regions: Approximately [redacted] study centers in the United States.

Background and Rationale: [redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

Objectives: The primary objective of the study is as follows:

- To determine if TD-9855 has an acute (Parts A and B) and sustained (Part C) pressor response and improves symptoms of orthostatic intolerance in subjects with nOH due to MSA, PAF, or Parkinson's disease.

The secondary objective(s) of the study is as follows:

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

Study Design:

This is a multicenter, randomized, 3 part, single-blind (Part A), double-blind (Part B), and open-label multiple dose extension (Part C) study of TD-9855 versus placebo in subjects with nOH. However, beginning with Amendment 2 of this protocol, Part B of the study has been discontinued. Therefore, any new subjects enrolled after Amendment 2 will not be enrolled in Part B. Details regarding Part B are still included in this document but where appropriate the reader is referred to prior version of this protocol for more specific information related to Part B.

This study now consists of 2 Parts, A and C. Part A follows a daily, single, escalating dose design starting with placebo on Day 1, followed by a dose of [redacted] TD-9855 on Day 2, and proceeding to escalating higher doses of TD-9855 on a daily basis up to a maximum dose of [redacted] based on safety, tolerability, and determination of a pressor effect. In Part C, subjects who demonstrate a pressor effect in Part A, who complete Part A, and remain otherwise eligible will have the option to receive open-label TD-9855 by tablet daily for up to [redacted]

Study Procedures:

Part A – Dose Escalation

On Day -2 of Part A, eligible subjects will be admitted to the clinical research center (CRC), where they will remain during the entire dose escalation period. On Day 1, subjects will receive a single dose of placebo in a single-blind manner (ie, subject remains blinded). This will be followed by daily single-blind dose escalations, beginning with [redacted] of TD-9855 on Day 2. On each subsequent day, subjects will receive a single escalating dose of TD-9855

PROTOCOL SYNOPSIS (CONTINUED)

[redacted] [Day 3], [redacted] [Day 4], [redacted] [Day 5]) until Day 5 or until reaching the preset stopping criteria described below, whichever occurs first. The stopping criteria are:

- A determination from the Investigator (in collaboration with the Sponsor) that administration of the subsequent dose may pose a safety concern
- SBP ≥ 180 mm or DBP ≥ 110 mm in the sitting position replicated 2 more times over an hour
- Intolerable side effects as determined by the Investigator
- Received maximum dose of study medication specified by the protocol

Once the subject meets any of the above criteria, no further dose escalation will be performed. However, based on the daily evaluation of tolerability, the Investigator (in collaboration with the Sponsor), may decide to not escalate the dose, but rather re-administer the previous dose from the prior day. Once the decision has been made to not escalate the dose, the subject may remain at the current dose through Day 5 of dosing. Following a post dosing observation day in the clinic, the subject will have discharge procedures completed and will be released from the CRC.

Subjects who do not demonstrate a clinically meaningful pressor effect based on Investigator determination (in collaboration with the Sponsor), or who discontinue study drug prior to reaching the stopping criteria, should have discharge procedures completed, but will not continue to study Part C.

Washout Period

Following the completion of Part A, eligible subjects will be discharged from the CRC and undergo a washout period ([redacted] On a daily basis during the first 72 hours from discharge, and then weekly for the first 4 weeks after discharge from Part A during the washout period, the Investigator or designee will contact the subject by telephone to review the subject's health status. Any adverse events reported by phone will be recorded and followed as medically appropriate determined by the Investigator. Under the direction of the Investigator, subjects will manage their nOH symptoms using fludrocortisone as prescribed.

Part B – Randomized, Double-blind, Parallel Design

Beginning with Amendment 2 of this protocol, Part B of the study has been discontinued. Refer to prior versions of this protocol for specific details regarding Part B.

Part C – Open Label Extension

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

The dose level administered on Day 1 in Part C will be equal to [redacted] of the highest tolerated dose level (rounded-up to the nearest 1 mg) administered during Part A for that subject (or a lower dose at the discretion of the principal investigator to manage individual subject safety). Subjects will be discharged from the research clinic on Day 2, and continue at the same dose level as Day 1 of Part C. At the subsequent scheduled visits until Day 29, the Investigator has the option to double the subject's dose level at their discretion, if in their opinion the subject will benefit from, and can tolerate, a higher dose level. After Day 29, dose increases will need to be discussed with the Sponsor. It is recommended that the subject receives at least 7 daily doses of TD-9855 at any single dose level before escalation to a higher dose to allow TD-9855 exposure to reach steady state at the lower dose. [redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted] The schedule for potential dose increases is shown in the table below.

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

In the case where a subject develops the presence or worsening of supine hypertension (as determined by the Investigator with agreement from the Sponsor) or other adverse events suggesting intolerability, the dose can be withheld for 3 days and resumed at a dose level 50% (rounded up to the nearest 1 mg) of the prior dose level. If supine hypertension or other adverse events persist after the dose has been reduced, dosing in that subject should be discontinued and appropriate alternative therapy and care provided to the subject as determined by the principal investigator.

In Part C, subjects will enter the research center on Day -2 and remain resident in the research facility to undergo safety, PD, PK and diseases assessments through the morning of Day 2 of Part C, after which they will be discharged home. Subjects will return on an outpatient basis and undergo safety, PK/PD and disease assessments as described in the schedule of assessments. In addition, telephone assessments for safety and disease assessment will be performed on a weekly (during Month 1) and monthly basis (Months 2 through 5) where no clinic visit is scheduled. In such a case that the dose is reduced, the subject should be scheduled for a clinic visit to occur within approximately 2 weeks of the dose reduction. Following completion of the [redacted] dosing period, or in the case of early discontinuation from the study, subjects will return 2 and 4 weeks after the final dose for follow-up visits to undergo safety, PK/PD and diseases assessments and end of study procedures. In cases where the subject is unable to return to the clinic due to significant physical or geographic limitations, or at the Investigator's discretion, a nurse may be sent to the subject's home and the study visit procedures performed in the subject's home, except for the day 29 visit which must be done within the research center.

Adverse events will be assessed throughout the study duration in each Part and will be recorded in the case report form when reported.

Study procedures are further described in Table 1 for Part A and Table 2 for Part C and in Section 6.

Duration of Study Participation:

The duration of study involvement for each subject will be up to approximately 36 days for Part A (including up to 30 days for screening), and 169 days for Part C.

PROTOCOL SYNOPSIS (CONTINUED)

Number of Subjects per Group:

Up to [redacted] will be enrolled. Subjects who demonstrate a pressor effect in Part A, who complete Part A, and who remain otherwise eligible are eligible to participate in Part C. [redacted]

Study Population:

This study will enroll adult subjects with confirmed nOH due to MSA, PAF, or Parkinson's disease and who meet other inclusion and exclusion criteria defined below.

Inclusion Criteria:

1. Male or female at least 40 years of age.
2. Subject is able to communicate well with the Investigator and understands the expectations of the study.
3. Subject is willing and able to comply with the study procedures, requirements and restrictions, and to understand and signed the informed consent form.
4. Subject has been diagnosed with symptomatic orthostatic hypotension due to Parkinson's disease, multiple system atrophy, or pure autonomic failure, (ie, neurogenic orthostatic hypotension).
5. Subjects must meet the diagnostic criteria of neurogenic orthostatic hypotension, as demonstrated by a ≥30 mm Hg drop in SBP within 5 minutes of standing. If additional Autonomic Function Testing is required to confirm the diagnosis of autonomic dysfunction, sinus arrhythmia and Valsalva maneuver may be conducted, as appropriate.
6. Impaired autonomic reflexes, as determined by absence of BP overshoot during phase IV of the Valsalva maneuver, in subjects where Valsalva is performed, as appropriate.
7. Experiencing dizziness, light-headedness, or fainting when standing.
8. Absence of other identifiable causes of autonomic neuropathy.
9. Female subjects must be non-pregnant and non-lactating. If a female subject is of childbearing potential, must have a documented negative pregnancy test at screening.

   NOTE: All females are considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 2 years) or documented to be surgically sterile (bilateral tubal ligation or total hysterectomy). A subject may be admitted to the study on the basis of a negative urine pregnancy test (local lab), pending the result of the serum pregnancy test.
10. If sexually active, must agree to use a highly effective method of birth control with partners of childbearing potential during the study and for 1 month after study drug dosing.
    NOTE: A highly effective method of birth control is defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intra-uterine devices (IUDs), sexual abstinence, or a vasectomized partner. Male subjects must agree to use medically

PROTOCOL SYNOPSIS (CONTINUED)

acceptable birth control for at least 1 month following last dose of study medication. A vasectomy or a condom used with a spermicide is a medically acceptable birth control method for males.

Additional criteria for subjects participating in Part C only:

11. Demonstrated a pressor effect in Part A and completed dosing in Part A.
12. Willing to sign an IRB-approved informed consent form for Part C.
13. Able to comply with the visit requirements for Part C.

Exclusion Criteria:

1. Systemic illnesses known to produce autonomic neuropathy, including but not limited to diabetes mellitus, amyloidosis, and autoimmune neuropathies.
2. Known intolerance to other NRIs or SNRIs.
3. Pre-existing sustained hypertension (BP ≥ 150/100 mm Hg in the sitting position determined from three independent assessments), and not explained by the use of pressor agents.
4. Concomitant use of vasoconstricting agents for the purpose of increasing BP such as ephedrine, dihydroergotamine, or midodrine must be stopped at least 2 days or five half-lives (whichever is longer) prior to dosing on Day 1 of Part A and C, and throughout the duration of Part C. Subjects previously enrolled in Part A under previous versions of the protocol will continue taking fludrocortisone during the washout period and in Part C at the dose and regimen used in Part A. For new subjects enrolling in Part A under Amendment 3, fludrocortisone use in both Parts of the study and during the washout period will be limited to 0.1 mg QD.
5. Concomitant use of anti-hypertensive medication for the treatment of essential hypertension unrelated to autonomic dysfunction.
6. Have changed dose, frequency or type of prescribed medication, within two weeks of dosing on Day 1 with the following exceptions:
   - Vasoconstricting agents such as ephedrine, dihydroergotamine, midodrine, or fludrocortisone
   - Short courses (less than 2 weeks) of medications or treatments that do not interfere with, or exacerbate the subject's condition under study (eg, antibiotics)
7. Known or suspected alcohol or substance abuse within the past 12 months (DSM-IV definition of alcohol or substance abuse).
8. Clinically unstable coronary artery disease, or major cardiovascular or neurological event in the past 6 months.
9. Use of any monoamine oxidase inhibitor (MAO-I) within 14 days of dosing on Day 1.
10. 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.
11. Any significant uncontrolled cardiac arrhythmia.
12. Myocardial infarction in the past 6 months, or current unstable angina.

PROTOCOL SYNOPSIS (CONTINUED)

13. Congestive heart failure (NYHA Class 3 or 4).
14. Diabetes insipidus, insulin-dependent diabetes mellitus, or diabetic neuropathy.
15. History of cancer within the past 2 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma or cervical cancer in situ.
16. Gastrointestinal condition, which in the Investigator's judgment, may affect the absorption of study drug (eg, ulcerative colitis, gastric bypass).
17. Any major surgical procedure within 30 days of dosing on Day 1.
18. Any other significant cardiovascular, pulmonary, renal, endocrine, hepatic, neurologic, psychiatric, immunologic, hematologic, gastrointestinal, or metabolic disease not currently controlled with medical treatment (eg, a stable medication dosing regimen).
19. Currently receiving any investigational drug or have received an investigational drug within 30 days of dosing on Day 1. An investigational drug is defined as non-FDA approved drug.
20. Allergic to or unable to drink apple juice (Part A only).
21. Any condition or laboratory test result which, in the Investigator's judgment, might result in an increased risk to the subject, or would affect their participation in the study.
22. Additionally, the Investigator has the ability to exclude a subject if for any reason they feel the subject is not a good candidate for the study or will not be able to follow study procedures.

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

Detailed storage and preparation instructions for test product will be provided in a separate pharmacy manual.

[redacted]

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

In Parts A (and previously in Part B which was discontinued), placebo solution for individual subject administration will be prepared to match TD-9855 doses but will not contain TD-9855. Details regarding placebo preparation will be provided in a separate pharmacy

PROTOCOL SYNOPSIS (CONTINUED)

manual. Part C is open-label and all eligible subjects will receive active TD-9855.

Study Evaluations

Safety Assessments:

- Adverse events (AE) [including serious adverse events (SAE)], clinical laboratory tests (including hematology, serum chemistry, and urinalysis), vital signs (including supine blood pressure), 12-lead ECGs, use of concomitant medications, and physical examination will be used to assess safety.

Efficacy Assessments:

- Efficacy assessments include measurement of seated and standing systolic blood pressure and completion of Orthostatic Hypotension Symptom Assessment (OHSA) questionnaire.

Pharmacokinetic Assessments:

- In Part A, blood samples for assessment of TD-9855 plasma concentration will be taken before dosing (within 30 minutes before the dose) and again between 6 and 9 hours post dose on dosing Days 3 (5 mg) and 5 (20 mg) as appropriate. One additional PK sample will be taken at 24 hours post dose following the last administered dose after the subject has reached the stopping criteria or at the end of the dose escalation sequence.
- In Part B, refer to prior versions of this Protocol for specific information related to Part B which was discontinued in Amendment 2.
- In Part C, PK samples are collected at selected visits as indicated in the schedule of assessments Table 2.

Pharmacodynamic Assessments:

- In Part A, blood samples for analysis of NE and dihydroxyphenylglycol (DHPG) will be collected on dosing Days 1 (placebo), 3 (5 mg) and 5 (20 mg), as appropriate, at the time points including once before dosing (after sitting for 10 minutes) and once again between 6 and 9 hours post dose (after sitting for 10 minutes). One additional PD sample will be taken at 24 hours post dose following the last administered dose after the subject has reached the stopping criteria or at the end of the dose escalation sequence
- In Part B, refer to prior versions of this Protocol for specific information related to Part B which was discontinued since Amendment 2.
- In Part C, PD samples are collected at selected visits as indicated in the schedule of assessments.

Details related to PK and PD sample collection, handling, storage and shipping will be provided in a separate manual.

Statistical Methods

Sample Size:

[redacted]

PROTOCOL SYNOPSIS (CONTINUED)

[redacted]

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

Study Endpoints:
For Part A, the primary study endpoint is the change from time-matched placebo in seated systolic blood pressure at 6 to 8 hours after drug administration. For Part C, the primary endpoint is the improvement from baseline in the Likert scale "dizziness, lightheadedness, feeling faint, or feeling like you might black out" (OHSA, question 1) at week 4.

The secondary endpoints for Part A include:

- Improvement in the Likert scale for "dizziness, lightheadedness, feeling faint, or feeling like you might black out" (OHSA, question 1).
- The composite OHSA score.
- Change from time-matched placebo in standing SBP
- Change from time-matched placebo in seated SBP (area under the curve for 0-12 hours following drug administration).
- Duration of standing during the orthostatic standing test

The secondary endpoints for Part C include:

- The composite OHSA and OHDAS score.
- Change from time-matched placebo in standing SBP
- Change from time-matched placebo in seated SBP (area under the curve for 0-12 hours following drug administration).
- Duration of standing during the orthostatic standing test

PROTOCOL SYNOPSIS (CONTINUED)

For all Parts of the study, safety and tolerability assessments will include adverse events, laboratory abnormalities, ECGs, and vital sign measurements including supine blood pressure. Exploratory PK and PD analysis will also be performed for all parts of the study.

Analysis:

All analyses will be presented separately by part. [redacted]

SCHEDULE OF STUDY ASSESSMENTS

Table 1: Schedule of Study Procedures/Assessments – Part A

Procedure	Screening (Day -30 to -1)	Admission (Day -2)	Admission (Day -1)	(Day 1[a])	Dose Escalation (Day 2 - 5)	Discharge (Day 3, 4, 5, or 6)[b]	Washout Min (8 days)
Overnight residency and Standardized Meal		X	X	X	X		
Informed Consent (may be signed up to 30 days prior to screening)	X						
Review Inclusion/Exclusion Criteria	X		X				
Medication and Medical History	X	X[c]	X[c]				
Height/Weight/BMI[d]	X		X[d]	X[d]	X[d]	X[d]	
Temperature and respiratory rate	X[q]		X[q]	X[q]	X[q]	X[q]	
Autonomic Function Testing[e]	X[e]						
Orthostatic Standing Test[f]	X[f]		X[f]	X[f]	X[f]	X[f]	
Supine Blood Pressure (after supine for 10 mins)[g]				X[g]	X[g]		
ECG (12-lead)[h]	X[h]		X[h]	X[h]	X[h]	X[h]	
Physical Examination[i]	X[g]		X[i]	X[i]	X[i]	X[i]	
Pregnancy Test (females only)[j]	X[j]						
Hematology, Serum Chemistry, and Urinalysis	X		X			X	
Urine Drug Screen	X						
Urine Collection and Volume Measurement			X[k]	X[k]	X[k]	X[k]	
PK Sampling[l]					X[l]	X[l]	
PD Sampling: NE and DHPG[m]				X[m]	X[m]	X[m]	
OH Questionnaire (OHSA)[n]	X[n]		X[n]	X[n]	X[n]	X[n]	
Clinician's/Subject's Global Impression[p]			X[p]	X[p]	X[p]	X[p]	
Concomitant Medications	X	X	X	X	X	X	
Adverse Events[o]	X	X	X	X	X	X	X[o]
Study Drug Administration (placebo/TD-9855)				X	X		

a. Study Day 1 is defined as the day of first study dosing (placebo). The preceding day is Study Day -1. Note that there is no Study Day 0.

b. Actual day of discharge will be on day following preset stopping criteria.

c. History update, if any changes since the Screening Visit, will be obtained.

SCHEDULE OF STUDY ASSESSMENTS (CONTINUED)

d. Body weight will be measured daily during Days -1 through 5 in the AM (predose) and PM (approximately 12 hours post dose), and the AM of Day 6 (or on discharge). The Day -1 "postdose" weight assessment should be prospectively calculated, based on the target Day 1 dosing time. Measurements will occur at approximately the same time each day (± 15 minutes) using the same scale and without clothing (or where necessary with the same light clothing).

e. Where appropriate, autonomic function testing will be conducted to confirm the diagnosis of autonomic dysfunction.

f. During Day -1 through Day 6, the orthostatic standing test will be performed in the morning at approximately the same time of day for each test, under fasting conditions after midnight to avoid the confounding effect of post-prandial hypotension. Additionally, during Days 1 through 5, the standing test will be repeated at 4, 7, 9 and 12 hours after dosing. At each time point, BP and HR measurements will be recorded with automated (or manual) sphygmomanometer while supine at 5 and 10 min (with the torso and head elevated 30 degrees from horizontal), after seated at 5 and 10 min and after 1, 3, 5, and 10 min while standing. The standing time will be measured with a chronometer and the duration of standing will be recorded. Additionally at each time point, the standing time will be measured with a chronometer and the duration of standing will be recorded.

g. Additional supine (30 degree head up) blood pressure readings will be measured at 14, 16, 18, and 20 hours after dosing each day in Part A for safety assessment. All times have a window of ± 15 minutes.

h. Electrocardiogram (12-lead) will be collected at Screening, on Day -1, predose and between 6 and 8 hours post dose on Days 1 through 5, and on Discharge.

i. Physical examinations after the Screening Visit may be abbreviated, focusing on abnormalities identified on the Screening examination and as related to adverse events.

j. For women of child bearing potential a serum pregnancy test will be performed at screening.

k. Where feasible, beginning with the morning void on Day -1, all urine will be collected and the volume measured and recorded at each void or as a total daily volume through discharge.

l. Blood samples for assessment of TD 9855 plasma concentration will be taken before dosing (within 30 minutes before the dose) and again between 6 and 9 hours post dose on dosing Days 3 and 5 as appropriate. One additional PK sample will be taken at 24 hours post dose following the last administered dose after the subject has reached the stopping criteria or at the end of the dose escalation sequence.

m. Blood samples for analysis of PD (NE and DHPG) will be collected once before dosing (after sitting for 10 minutes) and once again between 6 and 9 hours post dose (after sitting for 10 minutes) on dosing Days 1 (placebo), 3 and 5 (20 mg) as appropriate. One additional PD sample will be taken at 24 hours post dose (after sitting for 10 minutes) following the last administered dose after the subject has reached the stopping criteria or at the end of the dose escalation sequence. Please refer to the PK manual for more specific information related to sample handling, labeling, storage and shipping.

n. OHSA to be administered at screening, on Day -1, daily on Day 1 through Day 5 both predose and between 6 and 8 hours following dosing, and on the day of discharge (approximately 24 hours after the last dose). Assessments should be performed by a trained clinician or qualified designee and recorded on a standardized paper form.

o. On a daily basis during the first 72 hours from discharge, and then weekly during the first 4 weeks after discharge in Part A, the Investigator or designee will contact the subject by telephone to review the subject's health status. Any adverse events reported by phone will be recorded and followed as medically appropriate determined by the Investigator. Under the direction of the Investigator, subjects will manage their nOH symptoms using fludrocortisone as prescribed.

p. The Clinician's/Subject's Global Impression scale are to be administered on Day -1, daily on Day 1 through Day 5 both predose and between 6 and 8 hours following dosing, and on the day of discharge. The Clinician's Global Impression scale must be administered by a trained clinician. The subject will complete the Subject's Global Impression scale under supervision of the Investigator or qualified designee.

q. On dosing days (Days 1 through 5), temperature and respiratory rate will be measured twice – predose and then again between 6-8 hours postdose.

SCHEDULE OF STUDY ASSESSMENTS (CONTINUED)

Table 2: Schedule of Study Procedures/Assessments – Part C

	Admit		Treatment period									Follow-up	
Visit number	1				2	3	4	5	6	7	8	9	10	11 EOS
Study week (beginning of week except Day 140)			1		2	3	4	5	9	13	17	20	23	25
Procedure (Study Day)	Admit Day -2	Day -1[b]	Day 1[b]	Day 2[b]	Day 8	Day 15	Day 22	Day 29	Day 57	Day 85	Day 113	Day 140[m]	Day 155	Day 169
Overnight Residency	X[a]	X[a]	X[a]											
Informed Consent	X													
Review Inclusion/Exclusion Criteria	X	X												
Medication and Medical History	X[c]													
Weight/BMI & Temperature	X	X	X	X		X		X		X		X	X	X
Orthostatic Standing Test including supine blood pressure[d]		X[d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]	X[d]	X[d]
Supine blood pressure[e]	X[e]				X[e]		X[e]		X[e]		X[e]			
24 hour blood pressure monitoring[f]		X[f]				X[f]		X[f]		X[f]				X[f]
ECG (12-lead)		X												X
Physical Examination[g]		X[g]	X[g]	X[g]		X[g]		X[g]		X[g]		X[g]	X[g]	X[g]
Urine Pregnancy Test[h]	X[h]													
Safety labs: Hematology, Chemistry, and UA	X[o]													X
PK Sampling[i]			X[i]	X[i]		X[i]		X[i]		X[i]			X[i]	
DHPG Sampling[j]			X[j]	X[j]				X[j]						
NE Sampling[k]			X[k]					X[k]						
OHQ (OHSA and OHDAS)[l]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Clinician's/Subject's Global Impression[l]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[m]			X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]		
Subject Satisfaction Survey[n]		X[n]				X[n]		X[n]				X[n]		
Telephone Assessments (highlighted in gray)					X		X		X		X			

SCHEDULE OF STUDY ASSESSMENTS (CONTINUED)

a. Subjects will admit to the research unit on Day -2 and remain resident through the completion of study procedures on the morning of Day 2.

b. The timing of Day -1 "postdose" assessments should be prospectively calculated, based on the target Day 1 dosing time (eg, orthostatic standing test and Clinical Impression and OHQ assessments). Study Day 1 is defined as the day of first study dosing with TD-9855 in Part C. On Day 2 subjects are discharged from the research facility after all study procedures are completed the morning of Day 2.

c. History update, if any changes since participation in Part A (and B if appropriate) of the study.

d. The orthostatic standing test will be performed in the morning before eating breakfast at approximately the same time of day each visit under fasting conditions after midnight to avoid the confounding effect of post-prandial hypotension. In addition, at least 4 hours after dosing (but no more than 7 hours) and before lunch, the standing test will be repeated. At each time point, BP and HR measurements will be recorded with automated (or manual) sphygmomanometer while supine at 5 and 10 min (with the torso and head elevated 30 degrees from horizontal), after seated at 5 and 10 min and after 1, 3, 5, and 10 min while standing. The standing time will be measured with a chronometer and the duration of standing will be recorded. More details related to the sequence of dosing and orthostatic assessments are described below. For the Day 155 and 169 assessments, the timing of the "postdose" orthostatic test should be calculated based on the Day 1 dosing time.

e. On Days 8, 22, 57 and 113, supine blood pressures will be collected twice in the morning before eating (after 5 and 10 minutes resting at 30° elevation), and twice again at least 4 hours after dosing (but no more than 7 hours and before lunch) after 5 and 10 minutes resting at 30° elevation. On Day -2, supine blood pressures should be measured (after 5 and 10 minutes resting at 30° elevation).

f. In Part C, at sites where ambulatory blood pressure monitoring equipment is available, on Day -1, beginning approximately 24 hours before dosing on Day 1, ambulatory blood pressure monitoring equipment will be attached to the subject and blood pressure monitored during the 24 hour period before dosing. In addition, approximately 72 to 48 hours before a subject returns to the clinic for the Day 15, Day 29, Day 85 and Day 169 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. In addition, subjects should be instructed to manually initiate 2 recordings to occur approximately 30 and 20 minutes before eating each morning after sitting supine (30 degree elevation) for at least 10 minutes. During each 24-hour session subjects should also maintain a log of their posture at the time of each blood pressure measurement. For sites where ambulatory equipment are not available, desk top blood pressure devices may be used and provided to the subject for home use. Subjects will be instructed to measure and record blood pressure on the days and time points described above and in Table 2. More details regarding the ambulatory monitoring will be provided in a separate manual.

g. Physical examinations after the Day -1 visit may be abbreviated, focusing on abnormalities identified on the Day -1 examination and as related to adverse events.

h. For women of child bearing potential a urine pregnancy test will be performed at screening. If urine pregnancy test is positive, confirm with serum pregnancy test.

i. Blood collection for PK analysis will be collected on Day 1 (within 30 minutes before dosing and again between 6 and 9 hours post dose), predose Day 2, and upon return to the clinic on Days 29, 85, and 155. Please refer to the central laboratory manual for more specific information related to sample handling, labeling, storage and shipping.

j. Blood collection for DHPG analysis will be collected on Day 1 (within 30 minutes before dosing and again between 6 and 9 hours post dose), predose on Day 2, and upon return to the clinic on Day 29. Please refer to the central laboratory manual.

k. Blood collection for NE analysis will be collected on Day 1 (within 30 minutes before dosing) and upon return to the clinic on Day 29. Please refer to the central laboratory manual.

SCHEDULE OF STUDY ASSESSMENTS (CONTINUED)

l. Clinician's/Subject's Global Impression and OHQ (OHSA and OHDAS components) to be administered during clinic visits by a trained clinician and recorded on standardized paper forms (See Appendix 4). In addition while at home, the Clinician's/Subject's Global Impression and OHQ will be completed by telephone with the study coordinator. On all visit days the OHQ and Global Impression assessments should be completed at least 4 hours after dosing (but no more than 7 hours) and before lunch. For the Day 155 and 169 assessments, the timing of the "postdose" questionnaires should be calculated based on the Day 1 dosing time.

m. On the study visit days marked above, subjects will receive a dose of study medication in the morning after supine blood pressures and the orthostatic standing test has been completed. On non-study visit days the subjects should take their dose of study medication in the morning at approximately the same time of day. On study days where the subject is traveling to the clinic, the subject should take their dose of study medication at home before traveling to the clinic. Subjects will return to the clinic on the day of their final dose. Day 140 is the day of the last dose received at the end of 5 months (20 weeks).

n. Subjects will complete the Subject Satisfaction Survey on Days -1, 15, 29 and 140 (or at the time of early discontinuation) using the appropriate questionnaire listed in Appendix 5.

o. Safety labs should be collected Day -2 or on Day -1.

Sequence of study procedures during study visits (with *hypothetical* times for illustration):

- *7:00 am* -Wake up
- *7:30 am* - supine blood pressure after 5 and 10 minutes resting at 30 degrees elevation and orthostatic standing test (where applicable)
- *8:00 am* - Dose with TD-9855 and eat breakfast

After a minimum of 4 hours but no more than 7 hours after dosing and before lunch:

- *12:00 pm* - supine blood pressure after 5 and 10 minutes resting at 30 degrees elevation and orthostatic standing test (where applicable)
- *12:30 pm* - Clinician/subject impression and OH Questionnaires (OHDAS and OHSA)
- *12:45 pm* - lunch

TABLE OF CONTENTS

PAGE

TABLE OF CONTENTS (CONTINUED)

PAGE

TABLE OF CONTENTS (CONTINUED)

PAGE

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
5-HT	serotonin
ITT	Intent-To-Treat population
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CA	Cochran-Armitage linear trend test
CI	confidence interval
CFR	(United States) Code of Federal Regulations
CNS	central nervous system
CRC	clinical research center
CRF	case report form
CTSA	Clinical and Translational Science Award Center
DHPG	dihydroxyphenylglycol
DPB	diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	electrocardiogram
EDC	electronic data capture
FM	fibromyalgia
GCP	Good Clinical Practice
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intra-uterine device
LDH	lactose dehydrogenase
LS	least square
MAO-I	monoamine oxidase inhibitor
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MSA	multiple system atrophy
NE	norepinehprine

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
NET	norepinephrine transporter
nOH	neurogenic orthostatic hypotension
NRI	norepinephrine Reuptake Inhibitor
NYHA	New York Heart Association
OH	Orthostatic Hypotension
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHQ	Orthostatic Hypotension Questionnaire
OHSA	Orthostatic Hypotension Symptom Assessment
PAF	pure autonomic failure
PD	Parkinson's disease
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	preferred term
QTcF	corrected QT interval
REB	Research Ethics Board
SA	sinus arrhythmia
SAE	serious adverse event
SBP	systolic blood pressure
SERT	serotonin transporter
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TOEPH	heterogeneous banded Toeplitz structure
WBC	white blood cell count

1 INTRODUCTION

1.1 Background and Rationale

[redacted]

[redacted]

1.2 Nonclinical Profile

A review of the nonclinical profile of TD-9855 can be found in the current version of the TD-9855 Investigator's Brochure (IB).

1.3 Clinical Experience

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Risks and Benefits

[redacted] suggesting that TD-9855 has the potential to provide a novel treatment option for 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 heart rate
- Increase in BP
- Syncope

Possible risks to subjects participating in this study include adverse events associated with other 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. The study will be conducted in the Clinical and Translational Science Awards Centers (CTSAs) of the respective participating institutions comprising the Autonomic Disorders Consortium whenever possible. When a CTSA is not available, study visits will be conducted in the Investigator's autonomic disorders clinic or appropriately qualified research facility. The schedule of procedures conducted during the open-label out-patient extension requires subjects to return to the clinic on a regular basis during the dosing and follow up periods and participate in telephone based evaluations on a weekly basis. If subjects are unable to return to the clinic as indicated by the schedule of procedures, home visits will be conducted by protocol-trained nurses. If any participant should incur any unexpected and untoward event during the testing procedure, the emergency caregivers (cardiologists, anesthesiologists, social workers, and psychologists) would become available on an immediate basis to provide necessary emergent management.

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

2 OBJECTIVES

The primary objective of the study is as follows:

- To determine if TD-9855 has an acute (Parts A and B) and sustained (Part C) pressor response and improves symptoms of orthostatic intolerance in subjects with nOH due to MSA, PAF, or Parkinson's disease.

The secondary objective(s) of the study is as follows:

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

3 STUDY DESIGN

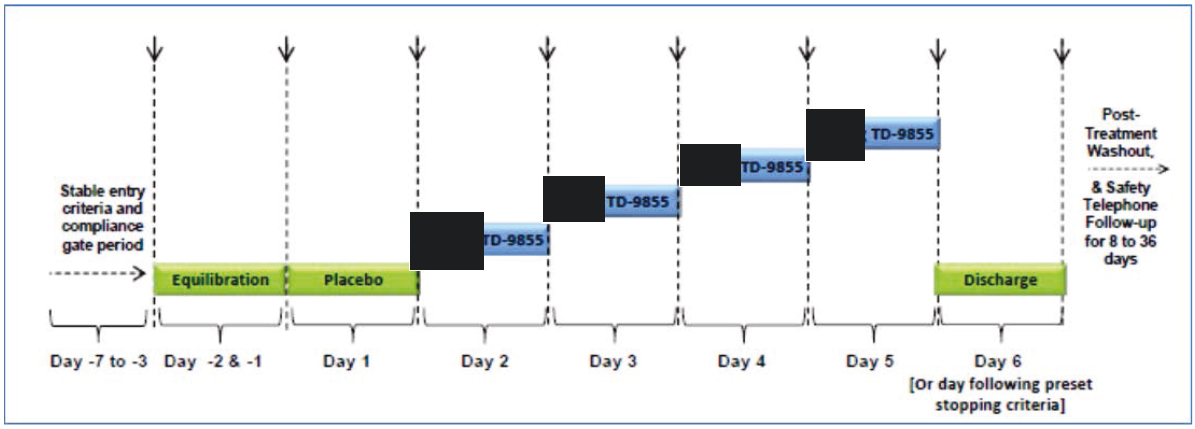
3.1 Overview

This is a multicenter, randomized, 3 part, single-blind (Part A), double-blind (Part B), and open-label multiple dose extension (Part C) study of TD 9855 versus placebo in subjects with nOH. However, beginning with Amendment 2 of this protocol, Part B of the study has been discontinued. Therefore, any new subjects enrolled after Amendment 2 will not be enrolled in Part B. Details regarding Part B are still included in this document but where appropriate the reader is referred to the prior version of this protocol for more specific information related to Part B.

This study now consists of 2 Parts, A and C. Part A follows a daily, single, escalating dose design starting with placebo on Day 1, followed by a dose of [redacted] TD-9855 on Day 2, and proceeding to escalating higher doses of TD-9855 on a daily basis up to a maximum dose of [redacted] based on safety, tolerability, and determination of a pressor effect. In Part C, subjects who demonstrate a pressor effect in Part A, who complete Part A, and remain otherwise eligible will have the option to receive open-label TD-9855 by tablet daily for up to [redacted]

Study Schematics

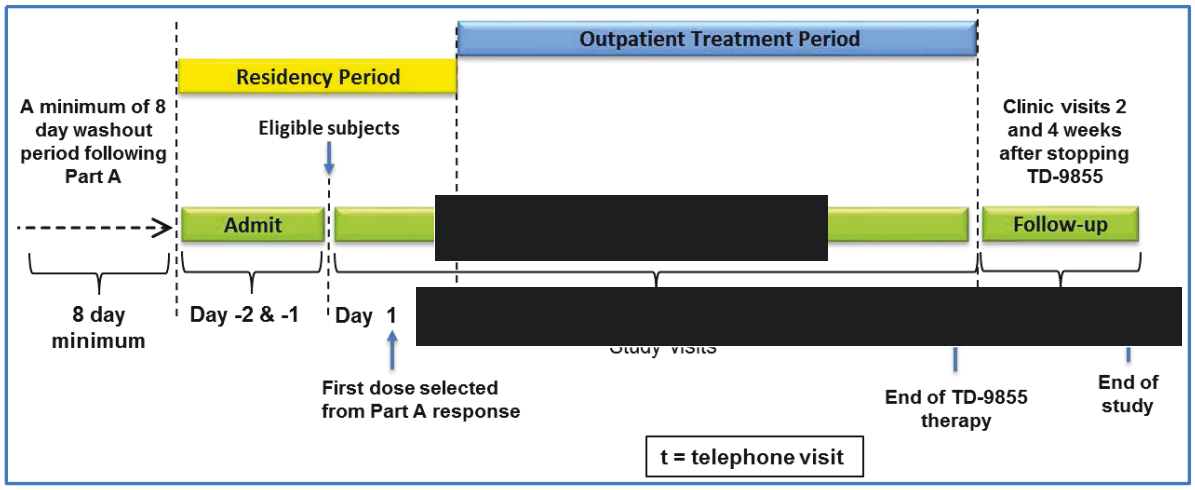
Part A – Single Blind, Dose-Escalation



Part B

Beginning with Amendment 2, Part B has been discontinued. Refer to prior versions of this protocol regarding more specific information pertaining to Part B.

Part C



3.2 Rationale for Study Design

This study is designed to evaluate the acute (Part A and B) and sustained (Part C) efficacy and safety of TD-9855 in improving BP and reducing orthostatic symptoms in subjects with nOH. The study should provide important information between BP, orthostatic symptom relief and the potential correlation with changes in NE and dihydroxyphenylglycol (DHPG) release. The information to be learned could be useful in optimizing diagnosis and clinical management. Safety and tolerability will be assessed throughout the study treatment period via laboratory measurements (eg, hematology, chemistry, and urinalysis) and monitoring of AEs.

3.3 Selection of Doses and Regimen

This study aims to evaluate the effects of single and multiple doses of TD-9855 on systolic blood pressure, symptoms associated with nOH, safety, and tolerability. The current doses of TD 9855 for this trial were chosen using pharmacokinetic (PK) and pharmacodynamic (PD) modeling to achieve a range of NET inhibition and to determine a minimum dose required to yield an increase in sitting systolic blood pressure. An ascending dose design was chosen in Part A to allow the subjects to start at a low dose because of the intrinsic hyper adrenergic responsiveness in these patients. The maximum dose levels ([redacted] single dose or [redacted] multiple doses QD) were selected to provide maximal steady state NET inhibition in all subjects despite inter-individual PK variability. A single dose of [redacted] and multiple doses QD of [redacted] are below or equal to doses examined and tolerated in single and multiple dose studies in healthy volunteers respectively. The maximum dose in Part C [redacted] QD) is equal to the well-tolerated [redacted] dose that was studied in two Phase 2 trials in patients with ADHD and FM where [redacted] was administered over 6 to 8 weeks.

3.4 Study Endpoints

3.4.1 Primary and Secondary Endpoints

For Part A, the primary study endpoint is the change from time-matched placebo in seated systolic blood pressure at 6 to 8 hours after drug administration. For Part C, the primary endpoint is the improvement from baseline in the Likert scale “dizziness, lightheadedness, feeling faint, or feeling like you might black out” (OHSA, question 1) at week 4.

The secondary endpoints for Part A include:

- Improvement in the Likert scale for “dizziness, lightheadedness, feeling faint, or feeling like you might black out” (OHSA, question 1).
- The composite OHSA score.
- Change from time-matched placebo in standing SBP
- Change from time-matched placebo in seated SBP (area under the curve for 0-12 hours following drug administration).
- Duration of standing during the orthostatic standing test

The secondary endpoints for Part C include:

- The composite OHSA and OHDAS score.
- Change from time-matched placebo in standing SBP
- Change from time-matched placebo in seated SBP (area under the curve for 0-12 hours following drug administration).
- Duration of standing during the orthostatic standing test

3.4.2 Safety Endpoints

For all Parts of the study, safety and tolerability assessments will include adverse events, laboratory abnormalities, ECGs, and vital sign measurements including supine blood pressure. Exploratory PK and PD assessments will also be made in all parts of the study as indicated in the schedule of assessments.

3.5 Minimization of Bias

Bias will be minimized through the use of randomization and blinding.

3.5.1 Blinding

In Part A, study subjects will be blinded to dose levels and escalation. Pre-defined stopping rules will be used to guide procedures. For Part B, which has been discontinued, refer to previous versions of this protocol. Part C will be an open-label extension study and therefore blinding considerations are not applicable.

3.5.2 Treatment Assignment

Subjects in Part A will begin by receiving placebo in a single-blind manner (ie, subject remains blinded). This will be followed by daily dose escalations, beginning with [redacted] of TD-9855 on Day 2. On each subsequent day, subjects will receive a single escalating dose of TD-9855 [redacted] until Day 5 or until reaching the preset stopping criteria

(Section 5.2). However, based on the daily evaluation of tolerability, the Investigator (in collaboration with the Sponsor), may decide to not escalate the dose, but rather re-administer the previous dose from the prior day. Once the decision has been made to not escalate the dose, the subject should remain at the current dose through Day 5 of dosing.

The dose level administered on Day 1 in Part C will be equal to 50% of the highest tolerated dose level (rounded up to the nearest 1 mg) administered during Part A for that subject (or a lower dose at the discretion of the principal investigator to manage individual subject safety). Subjects will be discharged from the research clinic on Day 2 and continue at the same dose level as Day 1 of Part C. At the subsequent scheduled visits until Day 29, the Investigator has the option to double the subject's dose level at their discretion, if in their opinion the subject will benefit from, and can tolerate, a higher dose level. After Day 29, dose increases will need to be discussed with the Sponsor. It is recommended that the subject receives at least 7 daily doses of TD-9855 at any single dose level before escalation to a higher dose to allow TD-9855 exposure to reach steady state at the lower dose. Due to the half-life of TD-9855 multiple dose increases within a 7 day period might lead to greater than 2-fold increase in TD-9855 exposure and are not recommended. The maximum dose administered to any subject is [redacted] The schedule for dose increases is shown in Table 3.

Table 3: Weekly Dose Escalation Plan for Subject in Part C

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

In the case where a subject develops the presence or worsening of supine hypertension (as determined by the Investigator with agreement from the Sponsor) or other adverse events suggesting intolerability, the dose can be withheld for 3 days and resumed at a dose level 50% (rounded up to the nearest 1 mg) of the prior dose level. If supine hypertension or other adverse events persists after the dose has been reduced, dosing in that subject should be discontinued and appropriate alternative therapy and care provided to the subject as determined by the principal investigator.

4 STUDY POPULATION

Subjects who meet all of the inclusion and none of the exclusion criteria will be eligible for enrollment into this study.

4.1 Inclusion Criteria

1. Male or female at least 40 years of age.
2. Subject is able to communicate well with the Investigator and understands the expectations of the study.
3. Subject is willing and able to comply with the study procedures, requirements and restrictions, and to understand and signed the informed consent form.
4. Subject has been diagnosed with symptomatic orthostatic hypotension due to Parkinson's disease, multiple system atrophy, or pure autonomic failure (ie, neurogenic orthostatic hypotension).
5. Subjects must meet the diagnostic criteria of neurogenic orthostatic hypotension, as demonstrated by a ≥30 mm Hg drop in SBP within 5 minutes of standing. If additional Autonomic Function Testing is required to confirm the diagnosis of autonomic dysfunction, sinus arrhythmia and Valsalva maneuver may be conducted, as appropriate.
6. Impaired autonomic reflexes, as determined by absence of BP overshoot during phase IV of the Valsalva maneuver, in subjects where Valsalva is performed, as appropriate.
7. Experiencing dizziness, light-headedness, or fainting when standing.
8. Absence of other identifiable causes of autonomic neuropathy.
9. Female subjects must be non-pregnant and non-lactating. If a female subject is of childbearing potential, must have a documented negative pregnancy test at screening. NOTE: All females are considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 2 years) or documented to be surgically sterile (bilateral tubal ligation or total hysterectomy). A subject may be admitted to the study on the basis of a negative urine pregnancy test (local lab), pending the result of the serum pregnancy test.
10. If sexually active, must agree to use a highly effective method of birth control with partners of childbearing potential during the study and for 1 month after study drug

dosing.

NOTE: A highly effective method of birth control is defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intra-uterine devices (IUDs), sexual abstinence, or a vasectomized partner. Male subjects must agree to use medically acceptable birth control for at least 1 month following last dose of study medication.
A vasectomy or a condom used with a spermicide is a medically acceptable birth control method for males.

Additional criteria for subjects participating in Part C only:

11. Demonstrated a pressor effect in Part A and completed dosing in Part A.
12. Willing to sign an IRB-approved informed consent form for Part C.
13. Able to comply with the visit requirements for Part C.

4.2 Exclusion Criteria

1. Systemic illnesses known to produce autonomic neuropathy, including but not limited to diabetes mellitus, amyloidosis, and autoimmune neuropathies.
2. Known intolerance to other NRIs or SNRIs.
3. Pre-existing sustained hypertension (BP ≥ 150/100 mm Hg in the sitting position determined from three independent assessments, and not explained by the use of pressor agents).
4. Concomitant use of vasoconstricting agents for the purpose of increasing BP such as ephedrine, dihydroergotamine, or midodrine must stop taking these drugs at least 2 days or five half-lives (whichever is longer) prior to dosing on Day 1 of Part A and C, and throughout the duration of Part C. Subjects previously enrolled in Part A under previous versions of the protocol will continue taking fludrocortisone during the washout period and in Part C at the dose and regimen used in Part A. For new subjects enrolling in Part A under Amendment 3, fludrocortisone use in both Parts of the study and during the washout period will be limited to 0.1 mg QD.
5. Concomitant use of anti-hypertensive medication for the treatment of essential hypertension unrelated to autonomic dysfunction.
6. Have changed dose, frequency or type of prescribed medication, within two weeks of dosing on Day 1 with the following exceptions:

- Vasoconstricting agents such as ephedrine, dihydroergotamine, midodrine, or fludrocortisone
- Short courses (less than 2 weeks) of medications or treatments that do not interfere with, or exacerbate the subject's condition under study (eg, antibiotics)

7. Known or suspected alcohol or substance abuse within the past 12 months (DSM-IV definition of alcohol or substance abuse).
8. Clinically unstable coronary artery disease, or major cardiovascular or neurological event in the past 6 months.
9. Use of any monoamine oxidase inhibitor (MAO-I) within 14 days of dosing on Day 1.
10. 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.
11. Any significant uncontrolled cardiac arrhythmia.
12. Myocardial infarction in the past 6 months, or current unstable angina.
13. Congestive heart failure (NYHA Class 3 or 4).
14. Diabetes insipidus, insulin-dependent diabetes mellitus, or diabetic neuropathy.
15. History of cancer within the past 2 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma or cervical cancer in situ.
16. Gastrointestinal condition, which in the Investigator's judgment may affect the absorption of study drug (eg, ulcerative colitis, gastric bypass).
17. Any major surgical procedure within 30 days of dosing on Day 1.
18. Any other significant cardiovascular, pulmonary, renal, endocrine, hepatic, neurologic, psychiatric, immunologic, hematologic, gastrointestinal, or metabolic disease not currently controlled with medical treatment (eg, a stable medication dosing regimen).
19. Currently receiving any investigational drug or have received an investigational drug within 30 days of dosing on Day 1. An investigational drug is defined as a non-FDA approved drug.
20. Allergic to or unable to drink apple juice (Part A only).

21. Any condition or laboratory test result which, in the Investigator's judgment, might result in an increased risk to the subject, or would affect their participation in the study.
22. Additionally, the Investigator has the ability to exclude a subject if for any reason they feel the subject is not a good candidate for the study or will not be able to follow study procedures.

5 STUDY DRUGS

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

5.1 Description of Study Drugs

In Part A (and previously in Part B of the study which was discontinued), TD-9855 will be provided by the Sponsor as a bulk active pharmaceutical ingredient (API), appearing as a white powder. Doses for individual subject administration will be prepared as a solution in filtered apple juice by the designated unblinded pharmacist at the CRC. In Part C, TD-9855 will be provided as a [redacted] packaged in open-labeled 40-count high density polyethylene bottles. Detailed storage and preparation instructions will be provided in a separate pharmacy manual.

5.2 Dosage and Administration

Part A Dose Escalation

On Day -2 of Part A, eligible subjects will be admitted to the CRC, where they will remain during the entire dose escalation period. On Day 1, subjects will receive a single dose of placebo in a single-blind manner (ie, subject remains blinded). This will be followed by daily dose escalations, beginning with [redacted] TD-9855 on Day 2. On each subsequent day, subjects will receive a single escalating dose of TD-9855 [redacted] [Day 3], [redacted] [Day 4], and [redacted] [Day 5]) until Day 5 or until reaching the preset stopping criteria described below, whichever occurs first.

The stopping criteria are:

- A determination from the Investigator (in collaboration with the Sponsor) that administration of the subsequent dose may pose a safety concern
- SBP ≥ 180 mm or DBP ≥ 110 mm in the sitting position replicated 2 more times over an hour
- Intolerable side effects as determined by the Investigator

- Received maximum dose of study medication specified by the protocol

Once the subject meets any of the above criteria, no further dose escalation will be performed. However, based on the daily evaluation of tolerability, the Investigator (in collaboration with the Sponsor), may decide to not escalate the dose, but rather re-administer the previous dose from the prior day. Once the decision has been made to not escalate the dose, the subject should remain at the current dose through Day 5 of dosing. Following a post dosing observation day in the clinic, the subject will have discharge procedures completed and will be released from the CRC.

Subjects who do not demonstrate a clinically meaningful pressor effect based on Investigator determination (in collaboration with the Sponsor), or who discontinue study drug prior to reaching the stopping criteria, should have discharge procedures completed, but will not continue to Part C of the study.

Washout Period

Following the completion of Part A, subjects will be discharged from the CRC and undergo a washout period (minimum 8 days). On a daily basis following the first 72 hours from discharge, and then at least weekly during the first 4 weeks after discharge, the Investigator or designee will contact the subject by telephone to review the subject's health status. Any adverse events reported by phone will be recorded and followed as medically appropriate determined by the Investigator. Under the direction of the Investigator, subjects will manage their nOH symptoms using fludrocortisone as prescribed.

Part B – Randomized Parallel Design

In Part B, refer to prior versions of this Protocol for specific information related to Part B which was discontinued in Amendment 2.

Part C – Outpatient Extension

The dose level administered on Day 1 in Part C will be equal to 50% of the highest tolerated dose level (rounded-up to the nearest 1 mg) administered during Part A for that subject (or a lower dose at the discretion of the principal investigator to manage individual subject safety). Subjects will be discharged from the research clinic on Day 2, and continue at the same dose level as Day 1 of Part-C. At the subsequent scheduled visits until Day 29, the Investigator has the option to double the subject's dose level at their discretion, if in their opinion the subject will benefit from, and can tolerate, a higher dose level. After Day 29,

dose increases will need to be discussed with the Sponsor. It is recommended that the subject receives at least 7 daily doses of TD-9855 at any single dose level before escalation to a higher dose to allow TD-9855 exposure to reach steady state at the lower dose. [redacted] The maximum dose administered to any subject is [redacted] The schedule for potential dose increases is shown below in Table 3.

Table 3: Weekly Dose Escalation Plan for Subject in Part C

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

In the case where a subject develops the presence or worsening of supine hypertension (as determined by the Investigator with agreement from the Sponsor) or other adverse events suggesting intolerability, the dose can be withheld for 3 days and resumed at a dose level 50% (rounded up to the nearest 1 mg) of the prior dose level. If supine hypertension or other adverse events persist after the dose has been reduced, dosing in that subject should be discontinued and appropriate alternative therapy and care provided to the subject as determined by the principal investigator.

In Part A, subjects will be administered study drug by qualified study personnel under the supervision of the Investigator. Study personnel will observe and record date and time of dosing and in the event any deviations or incomplete administrations will be noted in the source records.

In Part C, subjects will be administered study drug by qualified study personnel under the supervision of the Investigator on Day 1 and Day 2. On all other dosing days, subjects will record the date and time of their daily dose in a dosing diary. Any dose increases, missed doses, or issues with dosing should be noted in the dosing diary. Site staff will also record any dose increase in the subject's source documents. Subjects are expected to bring the

dosing diary and any empty and/or partially used bottles of study drug to the clinic on their return visits.

5.3 Drug Accountability and Reconciliation

The unblinded pharmacist or designee is responsible for maintaining accountability records for all study drug(s) received from the Sponsor, in accordance with applicable government regulations and study procedures. The accountability records for study medication (TD-9855) will be maintained in a secure location, accessible only to authorized staff members. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s).

The pharmacist must retain all unused, and expired product until the site monitor has confirmed accountability data. No study drug (used, partially used, and unused bottles) may be destroyed without prior approval from the Sponsor. Compliance with the dosing regimen will also be assessed by reconciliation of used and unused study drug.

Unused and expired study drugs will be disposed of in accordance with written instructions from the Sponsor. Copies of the study medication accountability records will be provided to the Sponsor at completion of the study and will be made available for review by the site monitor during the course of the study.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

The schedule of study procedures/assessments are summarized in Table 1 for Part A and Table 2 for Part C of the study. Study procedures listed in each row of the table should be performed at the visits designated in each column where an "X" is marked, and as indicted in the footnote, where applicable. Further information related to each study procedure type are described in Section 6.3.3.

The calendar day of the first study drug administration is designated as Day 1; subsequent calendar days are Days 2, 3, etc. Note that each parts of the study (Parts A and C) has their own unique numbering of calendar days.

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. Part C, which is an optional long-term extension study will require subjects to sign a separate informed consent form from that in Part A.

The site should make every effort to perform procedures at the scheduled times, and the actual time should be recorded in the source documents and on the case report forms. Acceptable deviations from the timing of assessments are as follows:

- Day 8 through Day 29: ± 3 days
- Day 57 through Day 169: ± 7 days

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

In Part C, in cases where the subject is unable to return to the clinic for a clinic visit for reasons due to significant physical or geographic limitations, or at the Investigator's discretion, a protocol-trained nurse may be sent to the subject's home and the study visit procedures performed in the subject's home. The only exception to this is for the day 29 visit of Part C which must be done at the research center.

6.2 Total Blood Volume

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

6.3 Description of Study Procedures / Assessments

6.3.1 Informed consent

Written informed consent using an IRB-approved informed consent form must be obtained prior to performing any protocol specific procedures. Within 30 days 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. Part C, which is an optional long-term extension study will require subjects to sign a separate informed consent form from that in Part A.

6.3.2 Overnight Residency, Standardized Meals, and Restrictions

Subjects will be admitted and remain resident in the clinical research center (CRC) beginning Day -2 through the morning of Day 6 in Part A, and Day -2 through the morning of Day 2 for Part C.

[redacted]

[redacted]

Should there be a clinically significant change between Screening and Day 1 of either Part A or Part C such that subjects no longer meet the eligibility criteria, they will no longer be eligible for the study and should be listed as a screen failure.

6.3.3 Inclusion and Exclusion Criteria

Section 4 provides a listing of inclusion criteria which subjects must meet to be eligible. Any subjects meeting exclusion criteria should not be enrolled in the study.

6.3.4 Medication and Medical History

Complete medication record and medical history at the pretreatment screening evaluation will include evaluation and therapies for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, or any other diseases or disorders. If any worsening in severity or frequency occurs for an existing condition or a new event occurs after signing of the informed consent, this must be recorded as an AE. Prior to initiating Part C, the medication and medical history should be reevaluated and updated accordingly. Any events occurring < 30 days since the last dose of study drug in part A (or Part B) should be recorded as an AE. Any event that occurs ≥ 30 days since the last dose of study drug in Part A (or Part B) but prior to Part C should be recorded as medical history (unless the Investigator deems the event related to prior study drug use).

6.3.5 Body Height, Weight and BMI

Body height and weight will be measured at the time points described in Table 1 for Part A and Table 2 for Part C. Care will be taken to ensure the measurements for weight occur at approximately the same time each day (± 15 minutes) using the same scale and without clothing (or where necessary with the same light clothing). BMI will be automatically calculated in the EDC system once weight and height are entered.

6.3.6 Temperature and Respiratory Rate

Temperature and respiratory rate are to be measured at the time points described in Table 1 for Part A.

Temperature is to be measured at time points described in Table 2 for Part C.

6.3.7 Orthostatic Standing Test

The orthostatic standing test (including supine blood pressures) will be performed at the time points listed in Table 1 for Part A and Table 2 for Part C and according to the details provided in the footnotes of each table.

At each time point, BP and HR measurements will be recorded with automated (or manual) sphygmomanometer while supine at 5 and 10 min (with the torso and head elevated 30 degrees from horizontal), after seated at 5 and 10 min and after 1, 3, 5, and 10 min 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 timepoints (ie, 1, 3, 5, and 10 minutes) for the standing test, or the subject may be able to stand for longer than the 10-minute standing test. In either case, the total duration should be recorded. More details related to the sequence of dosing and orthostatic assessments are described in Table 1 for Part A and Table 2 for Part C.

Blood pressure and HR collected after 10 minutes supine and seated from the orthostatic standing test will be used for safety vital sign assessment.

6.3.8 Supine Blood Pressure

Supine blood pressure will be measured at specified time points in the Schedule of Procedures / Assessments Table 1 for Part A and Table 2 for Part C.

In Part C, on Days 8, 22, 57 and 113, supine blood pressures will be collected twice in the morning before eating (after 5 and 10 minutes resting at 30° elevation), and twice again at least 4 hours after dosing (but no more than 7 hours and before lunch) after 5 and 10 minutes resting at 30° head and torso elevation (Table 2). On Day -2, supine blood pressures should be measured after 5 and 10 minutes resting at 30° head and torso elevation.

6.3.9 Autonomic Function Testing

Where appropriate, autonomic function testing will be conducted to confirm the diagnosis of autonomic dysfunction and will include the following assessments. Note that the results of this testing will be recorded in the subject source notes but will not be collected in the case report form.

- HR will be monitored by ECG and BP continuously with tonometry or finger plethysmography and intermittently with an oscillometric device. These tests include sinus arrhythmia and Valsalva maneuver.
- Deep breathing-vagally-mediated sinus arrhythmia (SA) is assessed during controlled breathing (pattern of 5 seconds inhalation and 5 seconds exhalation repeated over 90 seconds).

- Valsalva maneuver. The subject will exhale against a 40 mm Hg pressure. Changes in intrathoracic pressure produce autonomically modulated transient changes in HR and BP.

6.3.10 24-Hour Blood Pressure Monitoring

In Part C, at sites where ambulatory blood pressure monitoring equipment is available, on Day -1, beginning approximately 24 hours before dosing on Day 1, ambulatory blood pressure monitoring equipment will be attached to the subject and blood pressure monitored during the 24 hour period before dosing. In addition, approximately 72 to 48 hours before the subject returns to the clinic for the Day 15, Day 29, Day 85 and Day 169 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 after the monitoring device is powered on. In addition, subjects should be instructed to manually initiate 2 recordings to occur approximately 30 and 20 minutes before eating each morning after sitting supine (30 degree elevation) for at least 10 minutes. During each 24-hour session subjects should also maintain a log of their posture at the time of each blood pressure measurement. For sites where ambulatory equipment are not available, desk top blood pressure devices may be used and provided to the subject for home use. Subjects will be instructed to measure and record blood pressure on the days and time points described above and in Table 2. More details regarding the ambulatory monitoring will be provided in a separate manual.

6.3.11 Electrocardiogram

At time points specified in the Schedule of Study Procedures / Assessments (Table 1 for Part A and Table 2 for Part C) subject will have a 12-lead ECG following a 10 minute rest period. QTc corrections will be made using the Fredericia correction formula.

6.3.12 Physical Examination

The physical examinations at the pretreatment screening visit for Part A and the Day -1 visit for Part C will be performed by an appropriately qualified individual (eg, physician, nurse practitioner, physician's assistant or equivalent under the supervision of a physician), and will include examination of the following: general appearance; head, ears, eyes, nose, and

throat; neck, skin; cardiovascular system; respiratory system; abdominal system; lymphatic system, dermatologic system, musculoskeletal system, and nervous system. Subsequent physical examinations after the screening visit for Part A and the Day -1 visit for Part C can be abbreviated and symptomatic, largely focused on evaluation of AEs, if any, and any abnormalities identified on the screening (Part A)/Day -1 (Part C) examination.

6.3.13 Pregnancy Test

For female subjects of child bearing potential, serum beta–human chorionic gonadotropin pregnancy tests will be conducted at the screening visit in Part A.

For Part C, a urine pregnancy test will be conducted at the Day -2 visit. If the urine pregnancy test is positive, a serum pregnancy test will be done to confirm the result.

Pregnancy tests must be negative for a subject to participate in the study.

6.3.14 Laboratory Tests

Blood (for hematology and serum chemistry) and urine (for urinalysis) should be sent to the local or central laboratory according to the schedule of procedures/assessments in Table 1 for Part A and Table 2 for Part C.

6.3.14.1 Hematology

Hematology analytes to be tested include the following: hematocrit; hemoglobin; white blood cell count (WBC), including differential count by microscopy with percentage of immature neutrophils (bands), mature neutrophils, and eosinophils; and platelet count.

6.3.14.2 Serum Chemistry

Serum chemistry analytes to be tested include the following: potassium, magnesium, blood urea nitrogen (BUN), creatinine, C-reactive protein, creatine kinase, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

6.3.14.3 Urinalysis

Urinalysis analytes to be tested include the following: presence of blood, bilirubin, urobilinogen, nitrite, leukocytes, and (if dipstick positive) microscopic examination of sediment (sediment results will not be collected in the case report form).

6.3.14.4 Urine Drug Screen

At screening a urine drug screen for drugs of abuse will be performed.

6.3.15 Urine Collection and Volume Measurement

In Part A, at clinical sites where feasible, beginning with the morning void on Day -1 through discharge, all urine will be collected and the volume measured and recorded at each void or as a total volume for each day (eg, 7 am to 7 am). Urine will not be measured in Part C.

6.3.16 Pharmacokinetic Assessments

At the time points described in Table 1 for Part A and Table 2 for Part C blood samples for PK assay of TD-9855 will be collected, centrifuged, and split into aliquots. Collection and handling instruction will be provided in a separate manual.

6.3.17 Norepinephrine and Dihydroxyphenylglycol Assessments

At the time points described in Table 1 for Part A and Table 2 for Part C, blood samples for NE and the metabolite DHPG may be measured using high-performance liquid chromatography with electrochemical detection. Collection and handling instructions will be provided in a separate manual.

6.3.18 Orthostatic Hypotension Questionnaire

The Orthostatic Hypotension Questionnaire (OHQ) is a 2 components scale made up of a 6-item symptoms assessment scale referred to as Orthostatic Hypotension Symptom Assessment Questionnaire (OHSA) and a 4-item daily activity scale referred to as the Orthostatic Hypotension Daily Activity Scale (OHDAS) {6}. 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 be done for other reasons.” Activities that are marked as zero or ‘cannot be done for other reasons’ at baseline are not included in the scoring. Samples of the questionnaire for Part A are provided in Appendix 1 and for Part C in Appendix 2.

In Part A, only the OHSA will be used and will be assessed at the time points described in Table 1. In Part C both the OHSA and OHDAS will be used and will be assessed at the time points listed in Table 2 and as described in the table footnotes.

6.3.19 Clinician's / Subject's Global Impression

A Clinician's / Subject's Global Impression assessment (Appendix 3) for Part A and Appendix 4 for Part C will be completed at the time points described in the Schedule of Assessments / Procedures (Table 1 for Part A and Table 2 for Part C).

6.3.20 Concomitant Medications

[redacted]

6.3.21 Adverse Events

Adverse events will be reviewed and recorded from signing of the informed consent through the end of follow up or after 30 days following the final dose of TD-9855, whichever is

longer, in each part of the study. Adverse events may be observed by the site study personnel or spontaneously reported by the subject.

All adverse events must be recorded in the subject's case report form and, if applicable, reported as described in Section 7.

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

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

6.3.22 Subject Satisfaction Survey

Subjects will complete the Subject Satisfaction Survey (Appendix 5) on Day -1, Day 15, Day 29 and at the time of end of study therapy (either Day 140 or at the time of early discontinue, as appropriate).

6.3.23 Telephone Assessments

On a daily basis during the first 72 hours from discharge in Part A, and then weekly for the first 4 weeks after discharge from Part A during the washout period, the Investigator or designee will contact the subject by telephone to review the subject's health status. Any adverse events reported by phone will be recorded and followed as medically appropriate determined by the Investigator.

Additionally, in Part C, telephone visit assessments will occur at the designated visits and will include the procedures listed in Table 2.

6.4 Discontinuation

6.4.1 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 carried out. 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 or the Sponsor 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
- Subject choice
- Major violation of the protocol
- Termination of the study by the Sponsor
- Other

Subjects who discontinue study drug 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.

6.4.2 Subject Replacement

[redacted]

6.4.3 Study Discontinuation

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

6.5 Pregnancy

If a female subject becomes pregnant during the study, the Sponsor clinical study director (or designee) must be notified immediately. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7 ADVERSE EVENTS

7.1 Regulatory Definition of an Adverse Event

In the International Council for Harmonization (ICH) E6 Guideline for Good Clinical Practice, Section 7.2 defines an AE as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily 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 (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.2 Adverse Event Definition for the Purposes of This Study

For the purposes of this clinical study, AEs will be defined as follows:

An AE is any untoward medical occurrence in a subject who has signed an informed consent form and is participating in a clinical investigation. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered related to the study drug (investigational product).

Pre-existing events that increase in frequency or severity or change in nature during or as a consequence of participation in clinical studies will also be considered as adverse events. An AE may also include pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).

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

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 adverse event
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

7.3 Assessment of Adverse Events

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

Clinical severity should be recorded and graded using mild, moderate or severe as described below.

Mild	= Awareness of signs or symptoms, but easily tolerated
Moderate	= Discomfort sufficient to cause interference with usual activities
Severe	= Incapacitation with inability to work or perform usual activities

The relationship to study drug therapy should be assessed using the following definitions:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. 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 rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4 Serious Adverse Events

A SAE is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: 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

Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. In reports of death due to disease progression, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- 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 drug 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.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- “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.
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

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

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [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 adverse event or serious adverse event, as described in Sections 7.2 and 7.4, respectively.

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

7.6 Serious Adverse Event Reporting

Any SAE that occurs after a subject signs an informed consent form through the follow-up visit (or at the time a subject is determined to be ineligible for the study or who does not enroll in the study), regardless of causal relationship, must be reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. To report an SAE, complete and fax the Serious Adverse Event Report Form to the following:

Theravance Biopharma Clinical Drug Safety
Fax: [redacted]

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

Sponsor Medical Monitor Contact Information:
[redacted]
Telephone: [redacted]

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

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current Investigator's Brochure. 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.

7.7 Adverse Event Follow-up

A subject experiencing an AE 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 or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The Investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size and Power

[redacted]

[redacted]

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

8.2 Analysis Populations

[redacted]

8.3 Analyses

[redacted]

[redacted]

8.3.1 Demographics and Other Baseline Characteristics

[redacted]

8.3.2 Analysis of Efficacy

[redacted]

[redacted]

8.3.7 Adverse Event Data

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will be presented by system organ class (SOC), preferred term (PT) and severity, and the frequency and percentage of subjects reporting each observed event.

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

[redacted]

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

8.3.8 Concomitant Medications

Medications will be summarized both prior and during the treatment period.

8.3.9 Laboratory Data

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges. Listings will flag laboratory values that are outside of normal range.

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

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

8.3.10 Vital Signs Data

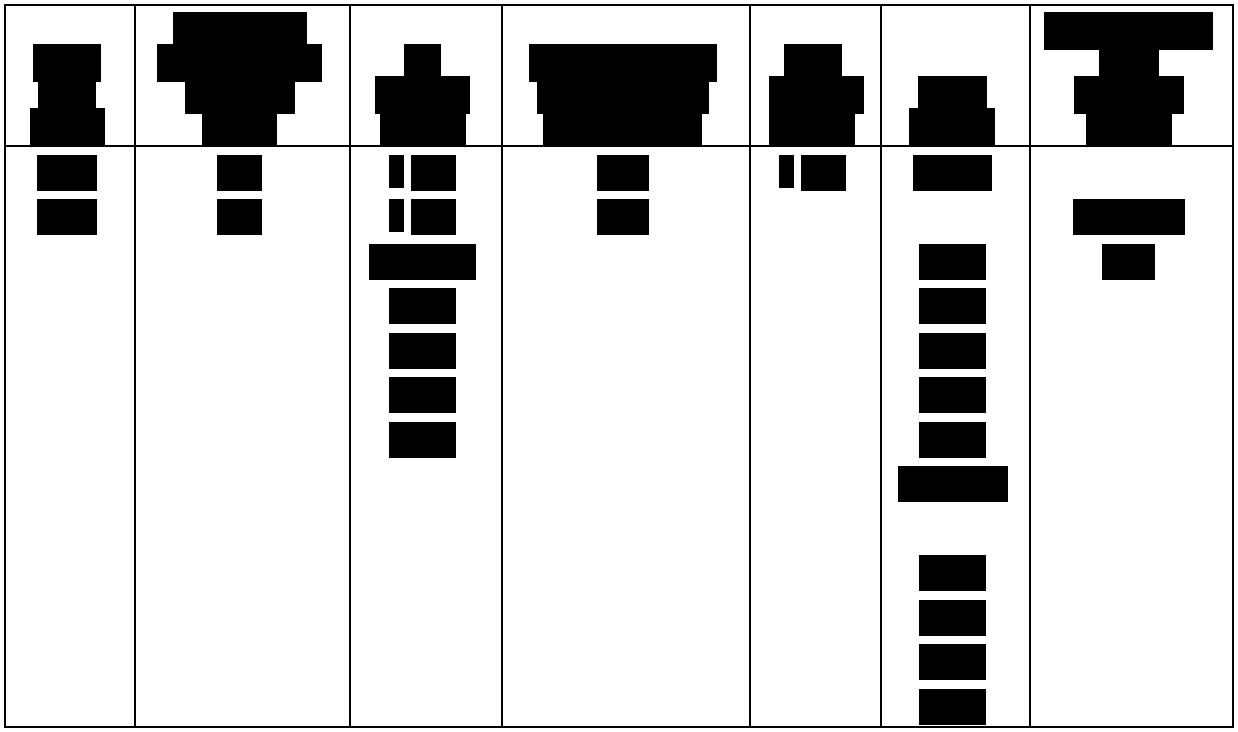
Vital signs data, including body weight, will be summarized in terms of observed values (by time point), changes from baseline (by time point).

When multiple values exist for the same nominal time point (eg, duplicate reading), the average of the readings taken for vital signs will be used in the data analysis. All recorded values for vital signs data will be presented in a by-subject listing.

8.3.11 ECG 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 [redacted]

[redacted]



[redacted]

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

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

8.3.12 Other Analyses

[redacted]

8.4 Handling of Missing Data

[redacted]

8.5 Data Monitoring Committees

There will be no data monitoring committee.

9 STUDY ADMINISTRATION

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

9.1 Principal Investigator Responsibilities

Before beginning the study, the Principal Investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator 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 [eg, associates, residents, research fellows].)

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.
- 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 requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the TD-9855 Investigator's Brochure, 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 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB, Independent Ethics Committee (IEC), or Research Ethics Board (REB) complies with the requirements of 21 CFR Part 56, 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 requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

9.2 Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the Investigator will obtain written confirmation that the IRB, IEC, or REB is properly constituted and compliant with ICH and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until 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 case report form (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.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, eg, electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (eg, 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 will be sent to the site for retention with other study documents after full completion of the study, ie, 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 (eg, 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 institutional review board (IRB) or independent ethics committee (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 United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the Investigator is responsible for documenting that no further data from the subject will be collected.

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

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

Before and during the conduct of the study, no study-related details may be disclosed, ie, 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 standard operating procedures (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. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology. 1996 May;46(5):1470.

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4. 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;50(1):47–53.

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11 APPENDICES

Appendix 1: Orthostatic Hypotension Questionnaire OHQ for Part A Only

AUTONOMIC DYSFUNCTION SCORES
ORTHOSTATIC HYPOTENSION QUESTIONNAIRE (OHQ)

Patient Instructions:

We are interested in measuring the symptoms that occur because of your problem with low blood pressure (orthostatic hypotension) and the degree that those symptoms may interfere with your daily activity. It is important that we measure the symptoms that are due ONLY to your low blood pressure, and not something else (like diabetes or Parkinson's disease). Many people know which of their symptoms are due to low blood pressure. Some people who have recently developed problems with low blood pressure may not easily distinguish symptoms of low blood pressure from symptoms caused by other conditions. In general, symptoms of your low blood pressure problem will appear either upon standing or after you have been standing for some time, and will usually improve if you sit down or lie down. Some patients even have symptoms when they are sitting which might improve after laying down. Some people have symptoms that improve only after sitting or lying down for quite some time.

Please answer the questions on the following pages keeping in mind that we want to know only about those symptoms that are from your problem with low blood pressure.

OH SYMPTOM ASSESSMENT (OHSA)

Please tick the number on the scale that best rates how severe your symptoms are from low blood pressure at this moment (right now).

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
   None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ Worst possible

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

Date completed: _____ time: _____ Initials: _____

Appendix 2: Orthostatic Hypotension Questionnaire (OHQ) for Part C Only

AUTONOMIC DYSFUNCTION SCORES
ORTHOSTATIC HYPOTENSION QUESTIONNAIRE (OHQ)

Patient Instructions:

We are interested in measuring the symptoms that occur because of your problem with low blood pressure (orthostatic hypotension) and the degree that those symptoms may interfere with your daily activity. It is important that we measure the symptoms that are due ONLY to your low blood pressure, and not something else (like diabetes or Parkinson's disease). Many people know which of their symptoms are due to low blood pressure. Some people who have recently developed problems with low blood pressure may not easily distinguish symptoms of low blood pressure from symptoms caused by other conditions. In general, symptoms of your low blood pressure problem will appear either upon standing or after you have been standing for some time, and will usually improve if you sit down or lie down. Some patients even have symptoms when they are sitting which might improve after laying down. Some people have symptoms that improve only after sitting or lying down for quite some time.

Please answer the questions on the following pages keeping in mind that we want to know only about those symptoms that are from your problem with low blood pressure.

OH SYMPTOM ASSESSMENT (OHSA)

Please tick the box 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, tick zero (O). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM.

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
   None 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ 8☐ 9☐ 10☐ Worst possible

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

Date completed: _____ time: _____ Initials: _____

OH Daily Activity Scale (OHDAS)													
*We are interested in how the low blood pressure symptoms you experience affect your daily life. Please rate each item by ticking the number that best represents how much on 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 tick the box at the right.*													
1. Activities that require standing for a short time													**Cannot do for other reasons**
No interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	Complete Interference	☐
2. Activities that require standing for a long time													
No interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	Complete Interference	☐
3. Activities that require walking for a short time													
No interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	Complete Interference	☐
4. Activities that require walking for a long time													
No interference	0☐	1☐	2☐	3☐	4☐	5☐	6☐	7☐	8☐	9☐	10☐	Complete Interference	☐

Date completed: _____ time: _____ Initials: _____

Appendix 3: Physician/Subject Global Impression for Part A Only

CLINICAL GLOBAL IMPRESSIONS – CLINICIAN (Part A only)

Clinical Global Impressions – Clinician

Questions to be answered at Day -1 (Admission), each Day of Dosing (Days 1 to 5 predose and at 6 to 8 hours post dose), and Day of Discharge (Final Evaluations).

1) Severity of Illness

Considering your total clinical experience with the particular population, how severe is the patient's orthostatic hypotension (OH) at this time?

0 – Not assessed
1 – Normal, no OH
2 – Borderline OH
3 – Mild OH
4 – Moderate OH
5 – Marked OH
6 – Severe OH
7 – Among those patients most extremely ill with OH

2) Global Improvement – Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to the patient's condition at Day -1 (Admission), how much has his/her orthostatic hypotension changed?

0 – Not assessed
1 – Very much improved
2 – Much improved
3 – Slightly improved
4 – No change
5 – Slightly worse
6 – Much worse
7 – Very much worse

Date completed: _____ time: _____ Initials: _____

CLINICAL GLOBAL IMPRESSIONS – PATIENT (Part A only)

Clinical Global Impressions – Patient

Questions to be answered at Day -1 (Admission), each Day of Dosing (Days 1 to 5 predose and 6 to 8 hours post dose), and Day of Discharge (Final Evaluations).

1) Severity of Illness

How severe is your orthostatic hypotension (OH) at this time?

0 – Not assessed
1 – Normal, no OH
2 – Borderline OH
3 – Mild OH
4 – Moderate OH
5 – Marked OH
6 – Severe OH
7 – Most extremely ill with OH

2) Global Improvement – Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to your condition at your Day -1 (Admission) visit when you rated the severty of your orthostatic hypotension after being off medication, how much has your condition changed?

0 – Not assessed
1 – Very much improved
2 – Much improved
3 – Slightly improved
4 – No change
5 – Slightly worse
6 – Much worse
7 – Very much worse

Date completed: _____ time: _____ Initials: _____

Appendix 4: Physician/Subject Global Impression for Part C Only

CLINICAL GLOBAL IMPRESSIONS – CLINICIAN (Part C only)

Clinical Global Impressions – Clinician

1) Severity of Illness

Considering your total clinical experience with the particular population, how severe is the patient's orthostatic hypotension (OH) at this time?

0 – Not assessed
1 – Normal, no OH
2 – Borderline OH
3 – Mild OH
4 – Moderate OH
5 – Marked OH
6 – Severe OH
7 – Among those patients most extremely ill with OH

2) Global Improvement – Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to the patient's condition at Day -1 (Admission) for Part C, how much has his/her orthostatic hypotension changed?

0 – Not assessed
1 – Very much improved
2 – Much improved
3 – Slightly improved
4 – No change
5 – Slightly worse
6 – Much worse
7 – Very much worse

Date completed: _____ time: _____ Initials: _____

CLINICAL GLOBAL IMPRESSIONS – PATIENT (Part C only)

Clinical Global Impressions – Patient

1) Severity of Illness

How severe is your orthostatic hypotension (OH) at this time?

0 – Not assessed
1 – Normal, no OH
2 – Borderline OH
3 – Mild OH
4 – Moderate OH
5 – Marked OH
6 – Severe OH
7 – Most extremely ill with OH

2) Global Improvement – Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to your condition at your Day -1 (Admission) visit when you rated the severty of your orthostatic hypotension after being off medication, how much has your condition changed?

0 – Not assessed
1 – Very much improved
2 – Much improved
3 – Slightly improved
4 – No change
5 – Slightly worse
6 – Much worse
7 – Very much worse

Date completed: _____ time: _____ Initials: _____

Appendix 5: Subject Satisfaction Survey

Patient Satisfaction Questionnaire – Day -1 Questions

To be completed by the subject on Study Day -1

1. Please circle the number below that represents how satisfied you are *currently* with your ability to manage your orthostatic hypotension (OH) symptoms. Consider both how effectively you can manage your symptoms and any side effects resulting from the products you currently use.

Very **Dissatisfied** w/ Current OH Symptoms Management						Very **Satisfied** w/ Current OH Symptoms Management
1	2	3	4	5	6	

Subject initials: _____

Date Completed: _____

Patient Satisfaction Questionnaire – Day 15 and Day 29 Questions

To be completed by the subject on Study Day 15 and Study Day 29

1. Thinking over the *past week*, please circle the number below that best indicates how satisfied you have been with the ability of the medication you are taking in this clinical trial to manage your orthostatic hypotension (OH) symptoms:

Very **Dissatisfied** with Trial Medication						Very **Satisfied** with Trial Medication
1	2	3	4	5	6	

2. Thinking over the *past week*, which statement best describes your impression of *how well* the study medication worked? *(check one)*

- ☐ The study medication didn't seem to work for me at all.
- ☐ The study medication provided some relief of my orthostatic hypotension (OH), but not as much as I would like.
- ☐ The study medication worked very well.

3. Thinking over the *past week*, which statement best describes your impression of the *side effects* that you experienced from the study medication? *(check one)*

- ☐ I experienced no/minimal side effects.
- ☐ I experienced some side effects, but they were acceptable given the efficacy of the study medication.
- ☐ I experienced significant side effects.

4. Thinking about your responses to questions 2 and 3 above; please circle the number that represents how likely would you be to continue taking this medication if you were <u>not</u> currently enrolled in a clinical trial?

Very Likely to **Discontinue**						Very Likely to **Continue**
1	2	3	4	5	6	

Subject initials: _____

Date Completed: _____

Patient Satisfaction Questionnaire – End of Therapy Visit Questions

To be completed by the subject at the end of study therapy (Study Day 140 or at the time of early discontinue, as applicable)

1. Based on your *overall experience thus far* in this clinical trial, how likely do you think you would be to use the medication if it were offered to you by a physician after it is approved by the FDA? *(check one)*

- ☐ Extremely likely
- ☐ Somewhat likely
- ☐ Somewhat unlikely *(answer Question 2)*
- ☐ Extremely unlikely *(answer Question 2)*

2. Answer only if you responded "Somewhat unlikely" or "Extremely unlikely" to Question 1, otherwise leave this question blank.

We'd like to understand, based on your *overall experience thus far* in this clinical study, why you would be unlikely to use the medication. Listed below are three reasons why you might choose not to use the medication. For each reason, please circle the number below that reflects the importance of each reason in explaining why you are unlikely to use the medication.

	Not at all important in deciding not to use					**Very important** in deciding not to use
Not effective enough	1	2	3	4	5	6
Side effects too bothersome	1	2	3	4	5	6
Assume that it would be too expensive	1	2	3	4	5	6

Subject initials: _____

Date Completed: _____