Protocol Number: 0171

Official Title: A Phase 3, 182-week, Open-Label Extension Study to Investigate the Safety and Tolerability of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension (symptomatic nOH) in Subjects with Primary Autonomic Failure

NCT Number: NCT04095793

Document Date: 05 August 2020

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, 182-week, Open-Label Extension Study to Investigate the Safety and Tolerability of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension (symptomatic nOH) in Subjects with Primary Autonomic Failure
Study Short Title:	Phase 3 Open-Label Extension Study of TD-9855 for Treating symptomatic nOH in Subjects with Primary Autonomic Failure
Sponsor Study No.:	0171
Date:	05 August 2020 [redacted]
	[redacted]
Test Product:	TD-9855 (ampreloxetine hydrochloride) tablets
US IND:	129797
EudraCT No.:	2019-002425-30
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
Clinical Study Director:	[redacted] Theravance Biopharma US, Inc. [redacted]

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

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0171: A Phase 3, 182-week, Open-Label Extension Study to Investigate the Safety and Tolerability Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension (symptomatic nOH) in Subjects with Primary Autonomic Failure

Study Short Title: Phase 3 Open-Label Extension Study of TD-9855 for Treating symptomatic nOH in Subjects with Primary Autonomic Failure

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

Background and Rationale: [redacted]

[redacted]

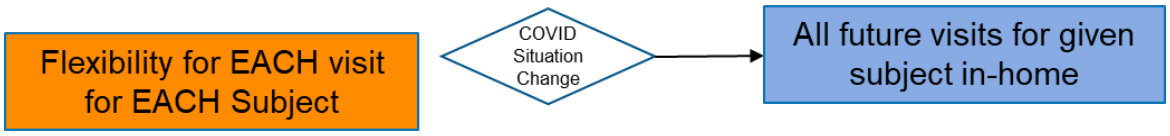
Objectives:

The primary objective of the study is to evaluate the long-term safety of TD-9855 over a 182-week period.

The exploratory objective of the study is to assess the patient reported outcome using EuroQoL Five-Dimensional Questionnaire (EQ-5D-5L).

Study Design:

This is a Phase 3, multi-center, open-label study to evaluate the safety and tolerability of TD-9855 in subjects with primary autonomic failures (MSA, PD, and PAF) and symptomatic nOH over 182 weeks. Given the challenges presented by the COVID-19 pandemic the trial utilizes an operational design featuring the ability to conduct protocol required visits as either in clinic or remote visits. Based upon discussion with the subject, the Investigator may conduct each study visit for a given subject either in clinic or remotely. The Investigator is recommended to conduct in clinic study visits consistent either with the standard of care for a subject outside of a clinical trial or at a minimum once per year for each subject. Tools and systems are available to sites and subjects to support remote visits (e.g., direct to subject shipping of study medication and other study supplies, standardized HIPAA/GDPR compliant telemedicine platform, in-home health nurses).



Due to the potential for resurgence of COVID-19 and its impact on both sites and subjects, these tools, mechanisms, and processes will be made available to sites and subjects who have selected the in clinic visit modality.

All sites are allowed at Investigator discretion to conduct either in clinic or remote unscheduled visit(s) for subject safety or unexpected subject medical needs outside of the regular visit schedule. Data collected during these visits may include any protocol-specified assessments which will be captured in the clinical database.

Refer to Appendix 6 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

Subjects who complete Study 0170 will be eligible for this study. Following signing of the informed consent, subjects will enter Study 0171 Visit 1, which will be conducted on the same day as Visit 9 of Study 0170.

Eligible subjects will receive a single dose of [redacted] TD-9855 [redacted]) for 182 weeks.

Subjects will complete study visits as outlined below:

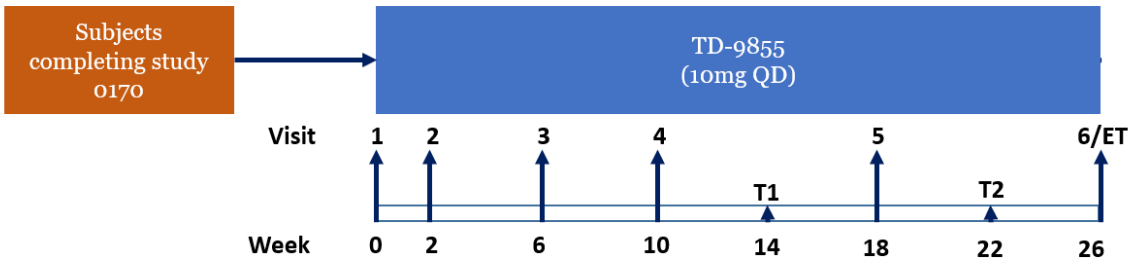
- Visit 2 (Week 2)
- Visit 3 (Week 6)
- Visit 4 (Week 10)
- Visit 5 (Week 18)
- Visit 6 (Week 26)
- Visit 7 (Week 38)

- Visit 8 (Week 50)
- Visit 9 (Week 74)
- Visit 10 (Week 98)
- Visit 11 (Week 122)
- Visit 12 (Week 146)
- Visit 13 (Week 170)
- Visit 14 (Week 182)

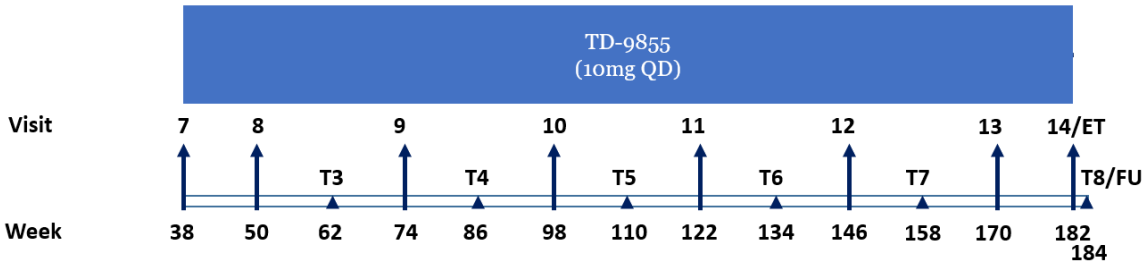
Telephone contact will be made to assess patient safety at Weeks 14, 22, 62, 86, 110, 134, 158, and 184.

The schematic representation is as shown below:

Visits 1 to 6



Visits 7 to Telephone 8



Assessments will be conducted as outlined in the Schedule of Study Procedures (Table 1). Refer to Appendix 6 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

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

- A determination from the Investigator that further administration of the investigational product may pose a safety concern to the subject.

- Sustained (at least 4 hours) SBP >180 mmHg or diastolic BP (DBP) >110 mmHg after 3 min of standing or after 5 min in the sitting position, or a sustained (at least 4 hours) SBP >180 mmHg or DBP >110 mmHg measured in the supine state (head/torso elevated at approximately 30^{o} from horizontal position).
- Intolerable AE as determined by the Investigator.
- Subject becomes pregnant.

No dose reduction is permitted at any time.

Safety assessments for the first 26 weeks will include a physical examination, neurological examination, vital signs (HR, BP, RR and body temperature), ECGs, safety laboratory tests (hematology, chemistry, and urinalysis), C-SSRS, and AEs. Safety assessments for the remaining 158 weeks will include evaluation of adverse events and concomitant medications.

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

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

Duration of Study Participation: Subjects will participate in this study for approximately 182 weeks of treatment and 2 weeks of follow up.

Number of Subjects: [redacted]

Study Population:

This study will enroll adult subjects with confirmed symptomatic nOH due to MSA, PD or PAF and who meet the inclusion and none of the exclusion criteria defined below. Eligible subjects will be subjects who complete Study 0170.

Inclusion Criteria:

1. Completion of Study 0170 and, in the opinion of the Investigator, would benefit from long-term treatment with TD-9855.
2. The subject must be able to understand the nature of the study and must provide written informed consent prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen).
3. The subject must be willing to continue on treatment and must continue to meet all the inclusion criteria for the preceding study (Study 0170) except, a score of $\geq$4 in OHSA#1.

Exclusion Criteria:

1. Subjects may not be enrolled in another clinical trial, with the exception of purely observational studies, which are allowed.

2. Psychiatric, neurological, or behavioral disorders that may interfere with the ability of subjects to give informed consent or interfere with the conduct of the study.
3. Medical, laboratory, or surgical issues deemed by the Investigator to be clinically significant.
4. Hypersensitivity to TD-9855 or the formulation excipients.

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

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

Study Evaluations

Safety Assessments:

- Physical examination
- Neurological examination
- Vital signs
- Resting ECGs
- Clinical laboratory tests including biochemistry, hematology, and urinalysis.
- Concomitant medication
- AEs
- Subject compliance to study treatment
- Incidence of falls
- Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Methods

[redacted]

[redacted]

Study Endpoints:

Primary safety and tolerability endpoints include:

- Physical examination
- Neurological examination
- Vital signs
- Resting ECGs
- Clinical laboratory tests including biochemistry, hematology, and urinalysis.
- Concomitant medication
- AEs
- Subject compliance to study treatment
- Incidence of falls
- Columbia Suicide Severity Rating Scale (C-SSRS)

[redacted]

Analysis:

The FAS (Full Analysis Set) and Safety analysis set will be identical and is defined as all enrolled subjects who have received at least one dose of TD-9855 in this study. Descriptive summaries will be provided for demographics and baseline characteristics.

Safety data will be listed by subject and summarized using the frequency of event or descriptive statistical summaries, as appropriate. Summary tables will be provided for adverse events, hematology, biochemistry and urinalysis laboratory evaluations, vital signs, 12 lead ECG findings, and concomitant medications.

Incidence of falls will be descriptively summarized using number of falls per subject, number and percentage of subjects with at least 1 fall since the previous study visit.

[redacted]

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures (Visits 1 – 6)

Each study visit for each subject may be conducted either in clinic or remotely									
Study Week (Visit/Telephone):	**Week 0 Visit 1 (0170 Visit 9)**	**Week 2 Visit 2 +/- 3 days**	**Week 6 Visit 3 +/- 3 days**	**Week 10 Visit 4 +/- 7 days**	**Week 14 Telephone 1 +/- 3 days**	**Week 18 Visit 5 +/- 7 days**	**Week 22 Telephone 2 +/- 3 days**	**Week 26 Visit 6 +/- 7 days**	**Early Termination up to Week 26**
Informed Consent	X								
Inclusion / exclusion criteria	X								
Medical history, including smoking history	X								
Concomitant Medications	X[a]	X	X	X	X	X	X	X	X
C-SSRS	X[a]	X	X	X		X		X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]
Vital signs (heart rate, blood pressure, respiratory rate and body temperature)	X[a, b]	X[b]	X[b]	X[b]		X[b]		X[b]	X[b]
Physical examination	X[a]			X				X	X
Neurological examination	X[a]			X				X	X
12-lead electrocardiogram[e]	X[a]			X				X	X
Pregnancy Test	X[a, c]			X[c]				X[c]	X[c]
Safety Labs (chemistry, hematology, urinalysis)	X[a]			X				X	X
Dosing, Incidence of Falls, and Midodrine Diaries	X[a]	X	X	X		X		X	X
Adverse Events	X[a]	X	X	X	X	X	X	X	X
Dispense Study Drug	X[d]	X[d]	X[d]	X[d]		X[d]		X[d]	
Study Drug Dosing	X[d]								
Collect Study Drug		X	X	X		X		X	X

a. Study 0170 procedures conducted at Visit 9 will serve as the baseline assessment for Visit 1 of Study 0171.
b. Vital signs will be assessed after the subject has been resting for at least 5 minutes in the seated or supine position.

c. In women of childbearing potential only, urine beta human chorionic gonadotropin (βhCG) test will be performed and if positive, confirmation with serum βhCG test is required. The pregnancy test must be confirmed negative for a subject to be eligible for this study.
d. Study drug will be ingested in the morning at approximately the same time of day with 8 ounces of water. The exact time and day of dosing will be recorded on the mornings of study visits. Subjects must be reminded to maintain an adequate fluid intake during their scheduled visits. Subjects will start taking study drug on the day after Visit 1.
e. ECGs are done in triplicate after the subject has been resting for at least 5 minutes in a seated or supine position before the first reading, with each replicate separated by at least 1 minute.

Table 2: Schedule of Study Procedures (Visits 7 – 14 Extension)

Study Week (Visit/Telephone):	**Wk 38 Visit 7 +/-7 days**	**Wk 50 Visit 8 +/-7 days**	**Wk 62 Telephone 3 +/-7 days**	**Wk 74 Visit 9 +/-7 day**	**Wk 86 Telephone 4 +/-7 days**	**Wk 98 Visit 10 +/-7 days**	**Wk 110 Telephone 5 +/-7 days**	**Wk 122 Visit 11 +/-7 days**	**Wk 134 Telephone 6 +/-7 days**	**Wk 146 Visit 12 +/-7 days**	**Wk 158 Telephone 7 +/-7 days**	**Wk 170 Visit 13 +/-7 days**	**Wk 182 Visit 14 End of Treatment Early Termination after Week 26 +/-7 days**	**Wk 184 Telephone 8 Follow-up +/-7 days**
Procedure														
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
Pregnancy Test[a]		X		X		X		X		X			X	
Dispense Study Drug	X	X		X		X		X		X		X		
Study Drug Dosing	X[b]													
Collect Study Drug	X	X		X		X		X		X		X	X	

a. In women of childbearing potential only, urine beta human chorionic gonadotropin (βhCG) test will be performed.
b. Study drug will be ingested in the morning at approximately the same time of day with 8 ounces of water.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
5-HT	Serotonin
ADHD	Attention-deficit hyperactivity disorder
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
βhCG	Beta human chorionic gonadotropin
BP	Blood pressure
CFR	(United States) Code of Federal Regulations
C_{max}	Maximum concentration recorded
CNS	Central Nervous System
eCOA	Electronic Clinical Outcome Assessment
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Early Termed
[redacted]	[redacted]
FAS	Full analysis set
FM	Fibromyalgia
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	Gastrointestinal
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intra-uterine devices
MAD	Multiple ascending dose
MAP	Mean arterial pressure
MAR	Missing at random

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MMRM	Mixed Model for Repeated Measures
MSA	Multiple System Atrophy
NE	Norepinephrine
NET	Norepinephrine transporter
nOH	Neurogenic Orthostatic Hypotension
NOAEL	No observed adverse event level
NRI	Norepinephrine reuptake inhibitor
OH	Orthostatic Hypotension
OHSA#1	Orthostatic Hypotension Symptom Assessment Question 1
PAF	Pure Autonomic Failure
PD	Parkinson's disease
P-gp	p-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per-protocol
PT	Preferred term
QD	Daily
QTcF	Corrected QT interval using the Fridericia's formula
REB	Research Ethics Board
RR	Respiratory rate
RTSM	Randomization and trial supply management
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SERT	Serotonin Reuptake Transporter
symptomatic nOH	Symptomatic Neurogenic Orthostatic Hypotension
SNRI	Serotonin norepinephrine reuptake inhibitor
SOC	System organ class
SOP	Standard Operating Procedure
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TD-9855	Laboratory code for ampreloxetine hydrochloride
US	United States
V1, V2, V3, etc.	Study Visits

1. INTRODUCTION

1.1. Background and Rationale

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

[redacted]

1.2. Nonclinical Profile

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

1.2.1. [redacted]

[redacted]

SERT over DAT and various other transporter, receptor, ion channel, and enzyme targets [redacted]

[redacted]

1.2.2. [redacted]

[redacted]

1.2.3. [redacted]

[redacted]

1.2.4. [redacted]

[redacted]

[redacted]

1.3. [redacted]

[redacted]

[redacted]

Overall, of the 34 subjects dosed in the study, 3 subjects discontinued study drug due to [redacted]

1.3.1. [redacted]

[redacted]

1.4. Risks and Benefits

Results from preclinical and clinical studies indicate that TD-9855 is [redacted] Efficacy of TD-9855 is being further evaluated in confirmatory studies (Studies 0169 and 0170). Study 0171 provides access to drug for subjects who participated in Study 0170 and for whom Investigators believe could benefit from longer term treatment with TD-9855.

[redacted]

[redacted]

To help ensure subject safety, subjects will be closely monitored during this study. Study visits will be conducted in the Investigator's autonomic disorders clinic or appropriately qualified research facility, or remotely using a telemedicine platform, under the supervision of qualified site personnel with help from a health care provider. The schedule of procedures requires subjects to be closely monitored on a regular basis during the dosing and follow-up periods. If any subject should incur any unexpected and untoward event during the testing procedures, the Investigator is instructed to provide the subject immediate and appropriate care as needed, including unscheduled in-clinic or remote visits.

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

2. OBJECTIVE

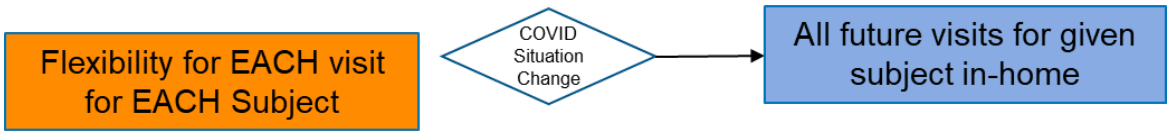
The primary objective of the study is to evaluate the long-term safety of TD-9855 over a 182-week period.

[redacted]

3. STUDY DESIGN

3.1. Overview

This is a Phase 3, multi-center, open-label study to evaluate the safety and tolerability of TD9855 in subjects with primary autonomic failures (MSA, PD, and PAF) and symptomatic nOH over 182 weeks. Given the challenges presented by the COVID-19 pandemic the trial utilizes an operational design featuring the ability to conduct protocol required visits as either in clinic or remote visits. Based upon discussion with the subject, the Investigator may conduct each study visit for a given subject either in clinic or remotely. The Investigator is recommended to conduct in clinic study visits consistent either with the standard of care for a subject outside of a clinical trial or at a minimum once per year for each subject. Tools and systems are available to sites and subjects to support remote visits (e.g., direct to subject shipping of study medication and other study supplies, standardized HIPAA/GDPR compliant telemedicine platform, in-home health nurses).



Due to the potential for resurgence of COVID-19 and its impact on both sites and subjects, these tools, mechanisms, and processes will be made available to sites and subjects who have selected the in clinic visit modality.

All sites are allowed at Investigator discretion to conduct either in clinic or remote unscheduled visit(s) for subject safety or unexpected subject medical needs outside of the regular visit schedule. Data collected during these visits may include any protocol-specified assessments which will be captured in the clinical database.

Subjects who complete Study 0170 will be eligible for this study. Following signing of the informed consent, subjects will enter Study 0171 Visit 1, which will be conducted on the same day as Visit 9 of Study 0170. Study 0170 procedures conducted at Visit 9 will serve as the baseline assessments for Visit 1 of Study 0171.

Beginning on the day after Visit 1, subjects will receive a single dose of [redacted] TD-9855 [redacted] and continue thereafter for the 182-week duration of the treatment period.

Subjects will complete study visits as outlined below:

- Visit 2 (Week 2)
- Visit 3 (Week 6)
- Visit 4 (Week 10)
- Visit 5 (Week 18)
- Visit 6 (Week 26)
- Visit 7 (Week 38)
- Visit 8 (Week 50)
- Visit 9 (Week 74)
- Visit 10 (Week 98)

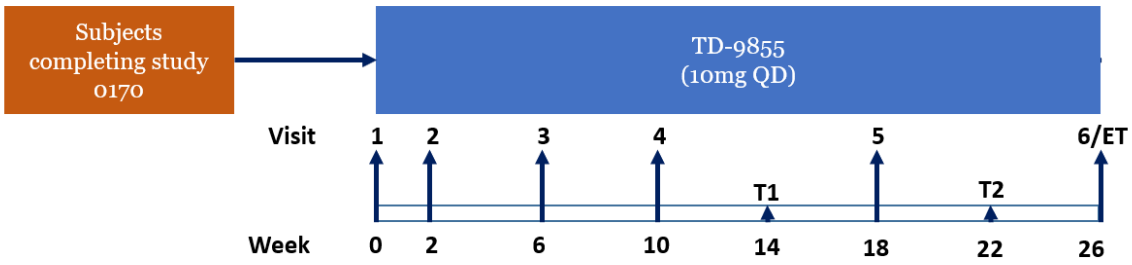
- Visit 11 (Week 122)
- Visit 12 (Week 146)
- Visit 13 (Week 170)
- Visit 14 (Week 182)

Telephone contact will be made to assess patient safety on Weeks 14, 22, 62, 86, 110, 134, 158, and 184.

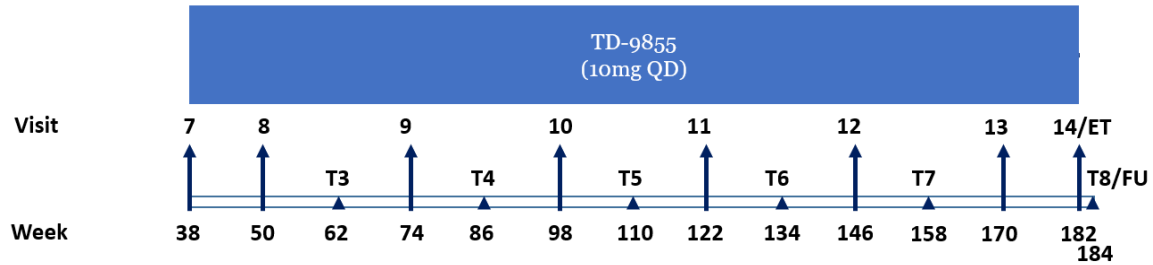
The study consists of 3 periods: (i) 26-week treatment, (ii) 156-week treatment extension and (iii) 2-week follow-up. The schematic representation is as shown below:

Figure 1: Study Schematic

Visits 1 to 6



Visits 7 to Telephone 8



No dose reduction is permitted during the treatment periods.

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

Assessments will be conducted as outlined in the Schedule of Study Procedures (Table 1). Refer to Appendix 6 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

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

- A determination from the PI (in discussion with the Sponsor's medical monitor) that further administration of the investigational product may pose a safety concern to the subject.

- Sustained (at least 4 hours) SBP >180 mmHg or diastolic BP (DBP) >110 mmHg after 3 min of standing or after 5 mins in the sitting position, or a sustained (at least 4 hours) SBP >180 mmHg or DBP >110 mmHg measured in the supine state (head/torso elevated at approximately 30° from horizontal position).
- Intolerable AE, as determined by the PI.
- Subject becomes pregnant.

During the first 26 weeks, safety assessments will include a physical examination, neurological examination, vital signs (HR, BP, respiratory rate [RR] and body temperature), 12-lead electrocardiograms (ECGs), laboratory tests (hematology, chemistry, and urinalysis), Columbia Suicide Severity Rating Scale (C-SSRS), and monitoring of AEs. Safety assessments after Week 26 will include assessments of AEs and Concomitant Medications.

[redacted]

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

Subjects will complete the Early Termination Visit if they terminate from the study prior to Week 26. All subjects will complete the End of Treatment Visit (Visit 14) upon completion of the 182-week treatment period or if terminating early after Week 26. The Follow-up visit must be completed within 2 weeks (+/- 7 days) from the date of the last dose for all subjects who complete the 182-week treatment period or who terminate the study early at any point.

3.2. [redacted]

[redacted]

[redacted]

3.3. [redacted]

[redacted]

Based on the results of the human positron-emission tomography study in healthy volunteers, [redacted]

3.4. Study Endpoints

Study Endpoints:

Primary safety and tolerability endpoints include:

- Physical examination
- Neurological examination
- Vital signs
- Resting ECGs
- Clinical laboratory tests including biochemistry, hematology, and urinalysis.
- Concomitant medication
- AEs
- Subject compliance to study treatment
- Incidence of falls
- Columbia Suicide Severity Rating Scale (C-SSRS)

[redacted]

4. STUDY POPULATION

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

4.1. Inclusion Criteria

Subjects who meet the following criteria will be eligible for study enrollment:

1. Completion of Study 0170 and, in the opinion of the Investigator, would benefit from long-term treatment with TD-9855.
2. The subject must be able to understand the nature of the study and must provide written informed consent prior to the conduct of any study procedures (including any changes occurring in the subject's current therapeutic regimen).
3. The subject must be willing to continue on treatment and must continue to meet all the inclusion criteria for the preceding study (Study 0170) except, a score of $\geq$4 in OHSA#1.

4.2. Exclusion Criteria

Subjects who satisfy any of the following criteria are not eligible for study enrollment:

1. Subjects may not be enrolled in another clinical trial, with the exception of purely observational studies, which are allowed.
2. Psychiatric, neurological, or behavioral disorders that may interfere with the ability of subjects to give informed consent or interfere with the conduct of the study.
3. Medical, laboratory, or surgical issues deemed by the Investigator to be clinically significant.
4. Hypersensitivity to TD-9855 or the formulation excipients.

4.3. Pregnancy and Contraception

4.3.1. Females of Childbearing Potential

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

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

4.3.2. Contraception for Male and Female Subjects

All female subjects of childbearing potential and males who are able to father children must agree to abstain from sexual intercourse or to use a highly effective method of birth control during the study and for at least 30 days after the completion of study drug dosing (Section 6.9). A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly. Such methods include:

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

NOTE: Birth control methods which are not considered highly effective:

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

5. STUDY DRUG

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

5.1. [redacted]

[redacted].

5.1.1. [redacted]

[redacted]

5.2. Dosage and Administration

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

5.3. Treatment Compliance

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

The subjects' dosing diary entries will also be reviewed at applicable study visits to assess compliance with study drug administration per documentation of the daily dosing times. An example of the diary is provided in Appendix 3.

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

5.4. Drug Accountability and Reconciliation

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

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1 and Table 2. Assessments will be conducted as outlined in the Schedule of Study Procedures. Refer to Appendix 6 and the Study Reference Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

6.2. Total Blood Volume

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

6.3. Procedures by Visit

The Enrollment date for the Study is defined as Week 0/Visit 1.

6.3.1. Screening

All subjects enrolled into Study 0171 will roll over from Study 0170, therefore there is no screening visit. Study 0170 procedures conducted at Visit 9 will serve as the baseline assessments for Visit 1 of Study 0171.

6.3.2. Visit 1 – Week 0

Study 0170 procedures conducted at Visit 9 will serve as the baseline assessments for Visit 1 of Study 0171.

Beginning on the day after Visit 1, subjects will receive a single dose of [redacted] TD-9855 [redacted] and continue thereafter for the 182-week duration of the treatment period.

The following procedures must be completed first, and in the order below at the Week 0 Visit:

1. Written informed consent (signed and dated) after the nature of the study has been explained and before any study procedure is performed
2. Review of protocol inclusion and exclusion criteria prior to beginning subject evaluations
3. Medical history, including smoking history
4. Review concomitant medications

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

5. C-SSRS
6. [redacted]
7. Vital signs
    a. HR, systolic BP (SBP), and diastolic BP (DBP)
    b. Respiratory rate (RR) and body temperature

8. Physical examination
9. Neurological examination
10. 12-lead ECG (in triplicate separated by at least 1 minute for each replicate, after the subject has been resting for at least 5 minutes)
11. Pregnancy test (in women of childbearing potential only)
12. Blood collection:
    a. Hematology
    b. Chemistry
13. Urine collection: Urinalysis
14. Dosing Diary dispensation
15. Incidence of Falls Diary, dispensation and review of diary completion instructions
16. Midodrine Diary dispensation
17. AE assessment (AEs, SAEs, adverse event of special interest [AESIs])
18. Dispense study drug

6.3.3. Visit 2 – Week 2

The following procedures will be performed at the Week 2 visit:

1. Review concomitant medications
2. C-SSRS
3. [redacted]
4. Vital signs
    a. HR, SBP, and DBP
    b. RR and body temperature
5. Dosing Diary collection and review
6. Incidence of Falls Diary collection and review
7. Midodrine Diary collection and review
8. AE assessment (AEs, SAEs, AESIs)
9. Collect, review, and dispense study drug

6.3.4. Visit 3 – Week 6

The following procedures will be performed at the Week 6 visit:

1. Review concomitant medications
2. C-SSRS
3. EQ-5D-5L
4. Vital signs:
    a. HR, SBP, and DBP

b. RR and body temperature

5. Dosing Diary collection and review
6. Incidence of Falls Diary collection and review
7. Midodrine Diary collection and review
8. AE assessment (AEs, SAEs, AESIs)
9. Collect, review, and dispense study drug

6.3.5. Visit 4 – Week 10

The following procedures will be performed at the Week 10 visit:

1. Review concomitant medications
2. C-SSRS
3. [redacted]
4. Vital signs
   a. HR, SBP, DBP
   b. RR and body temperature
5. Physical examination
6. Neurological examination
7. 12-lead ECG (in triplicate separated by at least 1 minute for each replicate, after the subject has been resting for at least 5 minutes)
8. Pregnancy test (in women of childbearing potential only)
9. Blood collection: Hematology, Chemistry
10. Urine collection: Urinalysis
11. Dosing Diary collection and review
12. Incidence of Falls Diary collection and review
13. Midodrine Diary collection and review
14. AE assessment (AEs, SAEs, AESIs)
15. Collect, review, and dispense study drug

6.3.6. Telephone Contact 1 – Week 14

The following procedures will be performed at Week 14:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.7. Visit 5 – Week 18

The following procedures will be performed at the Week 18 visit:

1. Review concomitant medications
2. C-SSRS

3. [redacted]
4. Vital signs
    a. HR, SBP, DBP
    b. RR and body temperature
5. Dosing Diary collection and review
6. Incidence of Falls Diary collection and review
7. Midodrine Diary collection and review
8. AE assessment (AEs, SAEs, AESIs)
9. Collect, review, and dispense study drug

6.3.8. Telephone Contact 2 – Week 22

The following procedures will be performed at Week 22:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.9. Visit 6 – Week 26

The following procedures will be performed at the Week 26 visit.

1. Review concomitant medications
2. C-SSRS
3. [redacted]
4. Vital signs
    a. HR, SBP, DBP
    b. RR and body temperature
5. Physical examination
6. Neurological examination
7. 12-lead ECG (in triplicate separated by at least 1 minute for each replicate, after the subject has been resting for at least 5 minutes)
8. Pregnancy test (in women of childbearing potential only)
9. Blood collection: Hematology, Chemistry
10. Urine collection: Urinalysis
11. Dosing Diary collection and review
12. Incidence of Falls Diary collection and review
13. Midodrine Diary collection and review
14. AE assessment (AEs, SAEs, AESIs)
15. Collect, review, and dispense study drug

6.3.10. Early Termination Up to Week 26

Subjects terminating the study prior to Week 26 will complete all of the following procedures.

1. Review concomitant medications
2. C-SSRS
3. [redacted]
4. Vital signs
    a. HR, SBP, DBP
    b. RR and body temperature
5. Physical examination
6. Neurological examination
7. 12-lead ECG (in triplicate separated by at least 1 minute for each replicate, after the subject has been resting for at least 5 minutes)
8. Pregnancy test (in women of childbearing potential only)
9. Blood collection: Hematology, Chemistry
10. Urine collection: Urinalysis
11. Dosing Diary collection and review
12. Incidence of Falls Diary collection and review
13. Midodrine Diary collection and review
14. AE assessment (AEs, SAEs, AESIs)
15. Collect and review study drug

6.3.11. Visit 7 – Week 38

The following procedures will be performed at the Week 38 visit:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)
3. Collect, review, and dispense study drug

6.3.12. Visit 8 – Week 50

The following procedures will be performed at the Week 50 visit:

1. Review concomitant medications
2. Pregnancy test (in women of childbearing potential only)
3. AE assessment (AEs, SAEs, AESIs)
4. Collect, review, and dispense study drug

6.3.13. Telephone Contact 3 – Week 62

The following procedures will be performed at Week 62:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.14. Visit 9 – Week 74

The following procedures will be performed at the Week 74 visit:

1. Review concomitant medications
2. Pregnancy test (in women of childbearing potential only)
3. AE assessment (AEs, SAEs, AESIs)
4. Collect, review, and dispense study drug

6.3.15. Telephone Contact 4 – Week 86

The following procedures will be performed at Week 86:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.16. Visit 10 – Week 98

The following procedures will be performed at the Week 98 visit:

1. Review concomitant medications
2. Pregnancy test (in women of childbearing potential only)
3. AE assessment (AEs, SAEs, AESIs)
4. Collect, review, and dispense study drug

6.3.17. Telephone Contact 5 – Week 110

The following procedures will be performed at Week 110:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.18. Visit 11 – Week 122

The following procedures will be performed at the Week 122 visit:

1. Review concomitant medications
2. Pregnancy test (in women of childbearing potential only)
3. AE assessment (AEs, SAEs, AESIs)
4. Collect, review, and dispense study drug

6.3.19. Telephone Contact 6 – Week 134

The following procedures will be performed at Week 134:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.20. Visit 12 – Week 146

The following procedures will be performed at the Week 146 visit:

1. Review concomitant medications
2. Pregnancy test (in women of childbearing potential only)
3. AE assessment (AEs, SAEs, AESIs)
4. Collect, review, and dispense study drug

6.3.21. Telephone Contact 7 – Week 158

The following procedures will be performed at Week 158:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.3.22. Visit 13 – Week 170

The following procedures will be performed at the Week 170 visit:

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)
3. Collect, review, and dispense study drug

6.3.23. Visit 14 – Week 182/End of Treatment/Early Termination after Week 26 through Week 182

Subjects who complete the 182-week treatment period, or terminate the study early after Week 26 will complete all End of Treatment visit procedures.

1. Review concomitant medications
2. Pregnancy test (in women of childbearing potential only)
3. AE assessment (AEs, SAEs, AESIs)
4. Collect and review study drug

6.3.24. Telephone Contact 8 – Week 184/Follow-up

The Follow-up visit must be completed within 2 weeks (+/- 7 days) from the date of the last dose for all subjects who complete the 182-week treatment period or terminate the study early at any point during the study. The following procedures will be performed at the Follow-up visit.

1. Review concomitant medications
2. AE assessment (AEs, SAEs, AESIs)

6.4. Description of Study Assessments

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

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

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

6.4.1. Demographic and Baseline Assessments

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

The data will be confirmed with information captured in Study 0170.

6.4.2. [redacted]

[redacted]

6.4.3. Safety Assessments

6.4.3.1. Columbia-Suicide Severity Rating Scale

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation). The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The C-SSRS Since Last Visit Version will be used for all visits. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the instrument is provided in Appendix 1.

6.4.3.2. Adverse Events

Study 0171 AEs will be reviewed and recorded from date of first dose of study drug through the end of follow-up. Adverse events may be observed by the site study personnel or spontaneously reported by the subject or subject's caregiver. In addition, ongoing AEs from preceding Study 0170 will be followed in this study.

Adverse events that start after signing of Study 0171 informed consent, but before the first dose of study drug is taken on Day 2, are to be captured in Study 0170 database. Adverse events started in Study 0170 but which worsen in severity or seriousness during Study 0171 should be reported as a new adverse event.

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

6.4.3.3. Medication and Medical History

A complete medical history will be taken during Study 0170 and will include evaluation of past and present cardiovascular, respiratory, GI, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, or any other diseases or disorders. Medical conditions will be recorded for 2 years prior to screening visit, along with the date of diagnosis, and any other relevant medical history that has an impact to the subject.

Medical events or conditions that arise or worsen in severity or frequency after date of first dose of study drug will be recorded as an AE in Study 0171.

6.4.3.4. Physical Examination

An abbreviated physical examination will be performed by an appropriately qualified individual (e.g., physician, nurse practitioner, physician's assistant, or equivalent, under the supervision of a physician) and will include examination of the following: general appearance; skin; head, ears, eyes, nose, and throat; neck; cardiovascular system; respiratory system; abdomen/ GI system; extremities; lymphatic system (lymph nodes); and nervous system. Physical examinations, at the discretion of the Investigator, can be abbreviated and symptomatic, largely focused on evaluation of AEs, if any, and any abnormalities identified.

6.4.3.5. Neurological Examination

Any abnormalities identified at Visit 1 will be recorded as neurological medical history. Any abnormalities or symptoms reported during treatment that arise or worsen in severity or frequency will be reported as AEs.

The examination will assess the following:

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

6.4.3.6. Vital Signs

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

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

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

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

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

6.4.3.7. Electrocardiograms

The 12-lead ECGs will be recorded in triplicate and separated by at least 1 minute for each replicate, according to the Schedule of Study Procedures (Table 1), after the subject has been resting at least 5 minutes in the seated or supine position before the first reading. Actual time of the assessment must be recorded for each iteration. The corrected QT interval using the Fridericia's formula (QTcF) will be used. The ECGs should be reviewed on the visit day at the site to allow for any appropriate action, if required.

6.4.3.8. Incidence of Falls Diary

Falls in subjects with symptomatic nOH are common and potentially catastrophic. They can lead to serious injuries including hip fractures or head trauma; furthermore, fear of falling can limit mobility and physical activity. Thus, incidence of patient-reported falls is being captured in a diary. Assessments will be performed as specified in the Schedule of Study Procedures (Table 1). An example of the diary is provided in Appendix 2.

6.4.3.9. Laboratory Tests

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

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

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

6.4.3.9.1. Hematology

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

6.4.3.9.2. Serum Chemistry

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

6.4.3.9.3. Urinalysis

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

6.4.3.9.4. Unscheduled Visit

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

6.5. Concomitant Medications

Subjects should not have changed dose, frequency, or type of prescribed medication for orthostatic hypotension within 7 days prior to Week 0.

[redacted]

6.5.1. [redacted]

[redacted]

6.6. [redacted]

[redacted]

[redacted]

6.7. [redacted]

[redacted]

6.8. Discontinuation

6.8.1. 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:

- AE
- 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.

6.8.2. Subject Replacement

Subjects will not be replaced.

6.8.3. Study Discontinuation

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

Periodic review of unblinded data by an external IDMC (Section 8.7) may lead to the board's recommendation of pausing dosing or terminating the study. In the event of premature study termination, best efforts to guarantee appropriate safety follow-up of subjects who have already been enrolled will be made and institutional review boards (IRBs) and the regulatory authorities will be informed.

6.8.4. Dose Stopping Rules

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

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

6.9. Pregnancy

TD-9855 has been shown to be non-genotoxic in a standard battery of genotoxicity assays (in vitro Ames and chromosomal aberration assays and in vivo micronucleus assay in rat). TD-9855 demonstrated effects on neonatal mortality and decreased rates of pup growth in the pre- and postnatal study in rats. Based on the NOAEL in reproductive-toxicology studies in preclinical species, there exists a greater than 100x margin between exposure in preclinical species at NOAEL vs. exposure in male and female patients at 4 weeks post stopping administration of [redacted] TD-9855 dose. Thus, application of pregnancy prevention measures for 30 days post last dose of TD-9855 is sufficient to address the risk of substantial drug exposure in semen or maternal circulation.

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

If a subject becomes pregnant while taking TD-9855, or during the 1 month after the last dose of treatment, the pregnancy must be reported to the sponsor's medical monitor (or designee) immediately (within 24-hours) by following the procedures for SAE reporting as outlined in Section 7.4.2. Study drug must be discontinued for any pregnant subject still on study drug treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7. ADVERSE EVENTS

7.1. Definitions

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

7.1.1. Adverse Events (AE)

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

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

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.

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the date of first dose in Study 0171, is considered to be preexisting and should be documented in the medical history CRF.

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

7.1.2. Serious Adverse Event (SAE)

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

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

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

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. Deaths of unknown cause for which the Investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- "Occurring at any dose" does not imply that the subject is receiving study 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.

7.1.4. Adverse Event of Special Interest (AESI)

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

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

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

Theravance Biopharma Clinical Safety

[redacted]

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

Medical Monitor Contact Information:

[redacted]

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

Abnormal laboratory findings (such as 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 7.1.1 (Adverse Event) and 7.1.2 (Serious Adverse Event).

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

7.3. Assessment of Adverse Events

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

7.3.1. Severity

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

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

7.3.2. Causal Relationship to Study drug

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

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

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

- **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).
- **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 re-challenge. It should be emphasized that ineffective treatment

should not be considered as causally related in the context of adverse event reporting.

7.4. Adverse Event Reporting and Recording

7.4.1. Adverse Event Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and is mandated by regulatory agencies. Sponsor has established standard operating procedures in compliance with regulatory requirements worldwide to ensure appropriate reporting of safety information. All clinical trials sponsored by TBPH will be conducted in accordance with these procedures.

7.4.2. Adverse Event and Serious Adverse Event Recording

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

Description of event:

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

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

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

Outcome: The outcome of AEs will be recorded.

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

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

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

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

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

Theravance Biopharma Clinical Safety

[redacted]

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

Medical Monitor Contact Information:

[redacted]

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

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

7.5. Adverse Event Follow-up

A subject experiencing an AE 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. General Considerations

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

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range (IQR) [25% quartile, 75% quartile]), minimum, and maximum value unless otherwise stated.

Categorical data will be summarized using the counts and percentages.

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

Baseline is the last assessment (scheduled or unscheduled) obtained before start of study drug dosing, unless otherwise specified in the SAP.

Any changes to the protocol-specified analyses will be pre-specified in the Statistical Analysis Plan prior to data lock.

8.2. [redacted]

8.3. [redacted]

[redacted].

8.3.1. Examination of Subgroups

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

8.3.2. Major Protocol Analysis Deviations

Not applicable.

8.4. General Analyses

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

8.4.1. Demographics Characteristics and Other Baseline Characteristics

The demographics, baseline characteristics, medical history and safety will be summarized for all subject in the Safety set.

8.4.2. [redacted]

[redacted]

8.5. Safety Analyses

For all safety analyses, the safety set will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), corrected QT interval (QTcF) from standard safety digital ECGs and C-SSRS. Vital signs, ECGs and laboratory results will be summarized in terms of observed values and changes from baseline.

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

8.5.1. [redacted]

[redacted]

8.5.2. Adverse Event Data

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

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period.

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

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

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

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

8.5.3. Concomitant Medications

Medication names will be mapped according to the World Health Organization Drug Dictionary. Concomitant medications summaries will be provided, by drug class and preferred name. The summary of concomitant medications will comprise all medications taken during the treatment period, including ongoing medications at entry.

8.5.4. Laboratory Data

Laboratory data, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges will be summarized. 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.

8.5.5. Vital Signs Data

Vital Signs data will be summarized in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages within appropriately defined categories (Table 3).

Table 3: Outlier Threshold for Vital Signs

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

8.5.6. 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 (Table 4).

Table 4: Electrocardiogram Test Outlier Thresholds

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

Treatment emergent ECG abnormalities are defined as those not present at baseline, or those that worsened after treatment, e.g., borderline at baseline but were prolonged after treatment. QTcF {and QTcB} will also be summarized by the following categories, Normal (males <430, females <450), Borderline (males (≥430, <450); females (≥450, <470)) and Prolonged (males ≥450, females ≥470).

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

Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All recorded values for the ECG parameters will be presented in a by-subject listing.
A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

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

8.5.7. Analysis of Falls

Incidence of falls will be descriptively summarized using number of falls per subject, number and percentage of subjects with at least 1 fall since the previous study visit.

8.6. Missing Data Handling

[redacted]

8.7. [redacted]

[redacted]

9. STUDY ADMINISTRATION

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

9.1. Principal Investigator Responsibilities

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

The PI will ensure the following:

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

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the Investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and 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 CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

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

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

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

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

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

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

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

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

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

9.5. Document Retention

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

The Investigator must consult the Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the

responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6. Confidentiality

The Investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, the study sponsor's affiliated companies, the study sponsor's designated service providers, regulatory agencies, and the 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, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7. Access to Data and Documents

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

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

9.8. Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and 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. Metzler M, Duerr S et al (2013). Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. J Neurol;260(9): 2212-2219
2. Goldstein DS & Sharabi Y (2009). Neurogenic orthostatic hypotension: a pathophysiological approach. Circulation;119(1): 139-146
3. Lahrmann H, Cortelli P et al (2006). EFNS guidelines on the diagnosis and management of orthostatic hypotension. Eur J Neurol;13(9): 930-936
4. Goldstein DS et al (1997). Sympathetic cardioneuropathy in dysautonomias. N Eng J Med;336(10:696-702
5. Ehringer H & Hornykiewicz O (1998). Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Parkinsonism Related Disorders;4(2): 53-57
6. Braak H, Ghebremedhin E et al (2004). Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res;318(1): 121-134
7. Shibao C et al (2007). Norepinephrine transporter blockade with atomoxetine induces hypertension in patients with impaired autonomic function. Hypertension;50(1):47-53
8. Ramirez CE et al (2014). Efficacy of atomoxetine versus midodrine for the treatment of orthostatic hypotension in autonomic failure. Hypertension;64(6):1235-40

APPENDIX 1. EXAMPLES OF DISEASE INSTRUMENTS

Theravance Biopharma	Protocol: 0171		[redacted]
	Date of Assessment (DDMMMYYYY)	Time of Assessment (24-hour clock)	
		:	
Visit	Subject ID Number		Rater Initials
	1 7 1 -	-	

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

Protocol: 0171																	
Visit	Subject ID Number														Rater Initials		
	1	7	1	-						-							

SUICIDAL IDEATION

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

Since Last Visit

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

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

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

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

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

INTENSITY OF IDEATION

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

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

Most Severe

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

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

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

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

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

C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 3
THR173023_0171_C-SSRS SLV_English(US)_v1.0_2019_May_24

Protocol: 0171																	
Visit	Subject ID Number														Rater Initials		
	1	7	1	-						-							

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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Protocol: 0171																
Visit	Subject ID Number													Rater Initials		
	1	7	1	-						-						

[redacted]

APPENDIX 2. INCIDENCE OF FALLS DIARY

MARIN Protocol 0171 - Fall Diary

Subject ID:______________________

Visit Dispensed:_________________ **Date Returned:**___________________

Instructions:

1) For each **Time of Day**, entry should be made at the end of that time period.
2) If you did not fall or have a near-fall, put a check mark in the **No Falls** or **No Near-Falls** box for that time of day.
3) If you had a fall or near-fall, record the number of **Falls** or **Near-Falls** in the appropriate box for that time of day.

Definitions:

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

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

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

If you recorded a **Fall** or **Near Fall** above, were you injured as a result? Please check one: No☐ or Yes☐

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

TO BE COMPLETED BY SITE PERSONNEL ONLY: I confirm that I have carefully reviewed all entries in this diary.

Signature of Reviewer: _________________ Date of Review: _________________

Reviewer Print Name: _________________ Reviewer Title: _________________

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APPENDIX 3. DOSING DIARY

Marin 0171 Dosing Diary

Subject ID:_____

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

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

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

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

TO BE COMPLETED BY SITE PERSONNEL ONLY:

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

Signature of Reviewer: _____ Date of Review: _____

Reviewer Print Name: _____ Reviewer Title: _____

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[redacted]

APPENDIX 5. [redacted]

[redacted]

APPENDIX 6. OVERVIEW OF DECENTRALIZATION PLAN

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

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

Rationale for Decentralized Platform:

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

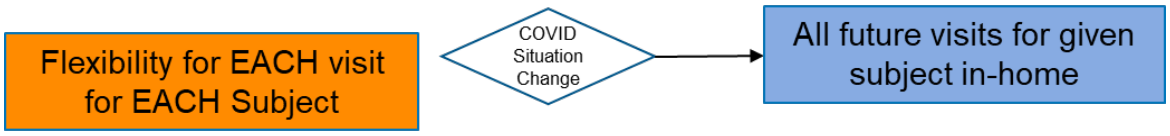
Selection of Visit Modality:

Given the challenges presented by the COVID-19 pandemic the trial utilizes an operational design featuring the ability to conduct protocol required visits as either in clinic or remote visits. Based upon discussion with the subject, the Investigator may conduct each study visit for a given subject either in clinic or remotely. The Investigator is recommended to conduct in clinic study visits consistent either with the standard of care for a subject outside of a clinical trial or at a minimum once per year for each subject.

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

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

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



Conduct of the Study and the Decentralized Platform:

All sites will follow the protocol Schedule of Procedures (see Table 1 and Table 2 of the protocol) for study visit scheduling and protocol required procedures (either in clinic or remote). Refer to the Study Procedures Manual for detailed instructions for conducting subject assessments in clinic and remotely. These instructions have been provided to ensure the method and conduct of each assessment is consistent across sites and subjects for both in clinic and remote visits.

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

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

Study operations support for remote visits:

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

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

B. A standardized HIPAA/GDPR compliant telemedicine platform will be provided so that site personnel can participate in remote visits that are conducted in the subject's home (or designated location), utilizing Home Health Providers.

C. A Home Health Provider (HHP) service has been employed.

D. Medically qualified and trained HHP staff employed will visit the subject's home (or designated location) and will work with Site Staff (SS) to conduct each remote study visit from the privacy of the subject's home or designated location (such as a caregiver's home).

E. During these remote visits, in coordination with Site Staff, the HHPs will use the Rater Station to facilitate collection of patient reported outcomes, will collect blood samples for safety labs and PK testing, will collect ECGs, and will measure the subject's vital signs.

F. All data collected during the remote visits will be transferred to the Investigator and the study site via established processes (either electronically or on paper).

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

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

Logistics Arrangements for Remote Visits:

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

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

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

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

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

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

Summary:

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

APPENDIX 7. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	0171
Protocol Title:	A Phase 3, 182-week, Open-Label, Safety and Tolerability Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension (symptomatic nOH) in Subjects with Primary Autonomic Failure
Version:	1.0 [redacted]
Version Date:	05 August 2020

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

Investigator's Name (print)

Investigator's Signature Date