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

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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

SPONSOR:

Theravance Biopharma Ireland Limited

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

TD-9855, Study 0171 Statistical Analysis Plan

A Phase 3, 182-week, Open-Label, Safety and Tolerability Study of TD-9855 in Treating Symptomatic Neurogenic Orthostatic Hypotension (snOH) in Subjects with Primary Autonomic Failure

Plan Version: 13 January 2022

Author: [redacted]

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Reviewer: [redacted]

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	term
AE	adverse event
ATC	Anatomic Therapeutic Chemical
BP	blood pressure
BMI	body mass index
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
HR	heart rate
MedDRA	Medical Dictionary for Regulatory Activities
SD	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
VAS	visual analogue scale
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This document describes the plan for the summarization and analysis of clinical data collected in Study 0171 for TD-9855, which was terminated early by the sponsor with 110 subjects enrolled.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

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

[redacted]

3.2. Endpoints

3.2.1. Primary 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 medications
- AEs
- Subject compliance to study treatment
- Incidence of falls
- Columbia Suicide Severity Rating Scale (C-SSRS)

[redacted]

4. STUDY DESIGN

4.1. Summary of Study Design

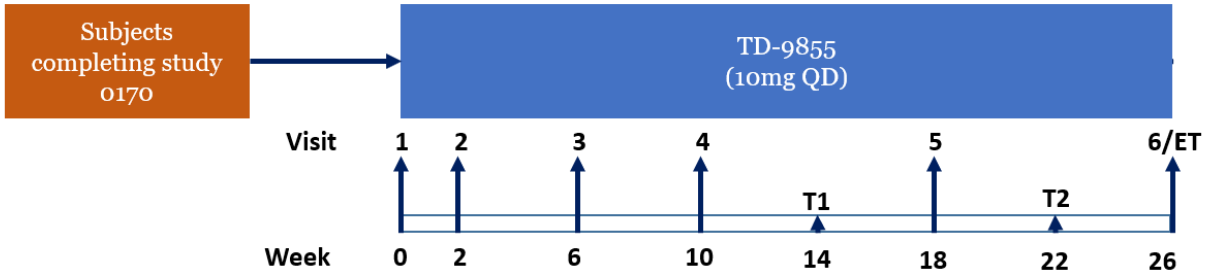
This is a phase 3, multicenter, open-label study to evaluate the safety and tolerability of TD-9855 in subjects with primary autonomic failures (MSA, PD, and PAF) and symptomatic neurogenic orthostatic hypotension (snOH) over 182 weeks.

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

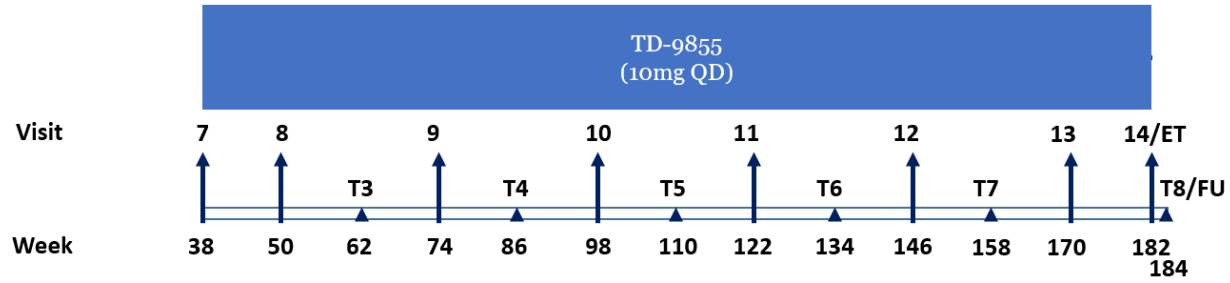
Eligible subjects will receive a single dose of [redacted] TD-9855 [redacted] for 182 weeks.

A schematic representation of study visits is shown below:

Visits 1 to 6



Visits 7 to Telephone 8



Subjects may discontinue at any time. The stopping criteria include meeting at least one of the following conditions:

- 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° 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, respiratory rate, 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.

The clinical assessments to be conducted are outlined in Section 4.5.

4.2. Study Drugs

The study drug will be TD-9855 supplied as a [redacted] tablet in 35-count high-density polyethylene bottles.

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

Use of rescue medication during the study was discouraged, but midodrine was nonetheless provided as rescue medication, with the following restrictions:

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

4.3. Sample Size Considerations

[redacted]

4.4. Randomization

Not applicable.

4.5. Clinical Assessments

Table 2: 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

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**
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 3: 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.

5. TIMING OF PLANNED ANALYSES

The primary analysis was to occur when all subjects had completed the [redacted] and the database had been cleaned and locked. A final analysis was to be conducted when all subjects had completed the study through Week 184.

The study was terminated early by the sponsor and a single analysis of all data obtained is to be conducted instead, after the database has been cleaned to the extent possible and locked.

6. CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

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

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

Analyses and tabulations will be prepared using [redacted]

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

6.1. Analysis Sets

6.1.1. Enrolled Analysis Set

The enrolled analysis set comprises all subjects who were enrolled into this study.

6.1.2. Safety Analysis Set

The safety analysis set comprises all enrolled subjects who received at least 1 dose of TD-9855 in this study.

6.1.3. Examination of Subgroups

The following subgroups were to be examined:

1. Disease type: MSA, PD, and PAF
2. Sex: Male and Female
3. Age category: < 65 years and ≥ 65 years
4. Smoking status: Never, Former, Current

But because the feeder study (Study 0170) was terminated early by the sponsor, the overall sample size is too small to warrant safety summaries by subgroup.

6.2. Baseline Definition

In general, assessments obtained at Study 0170 Visit 9, which coincides with Study 0171 Visit 1, will serve as the baseline assessment for Study 0171. Subjects will start taking Study 0171 study drug on the day after Visit 1. If the start of Study 0171 dosing is delayed, however, the latest assessment obtained before the first Study 0171 dose will be used, even if obtained after Visit 1.

6.3. Derived and Transformed Data

6.3.1. Study Day

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

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

There is no Study Day 0. For analysis, Day 1 is defined as the day of the first study drug dose. The preceding day is Day -1.

6.3.2. Age

Only year of birth is captured in the clinical database. Hence, for analysis purposes, each subject's age at enrollment into Study 0171 is not derived but set to their age in integer years as reported by the site.

6.3.3. Change from Baseline

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

6.3.4. BMI (Body Mass Index)

BMI is calculated as:

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

BMI will be calculated using height as collected in Study 0169 or Study 0170 and weight as collected at Study 0170 Visit 9 (Day 154)/Study 0171 Visit 1 (Day -1).

6.3.5. Visit Windows

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

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

Table 4: Analysis Windows

	Analysis Window	
Nominal Visit	Start (days)	Stop (days)
Baseline	See Section 6.2.	
Week 2 (Day 14)	7	21
Week 6 (Day 42)	35	49
Week 10 (Day 70)	63	77
Week 14 (Day 98)	91	105
Week 18 (Day 126)	119	133
Week 22 (Day 154)	147	161
Week 26 (Day 182)	175	189

6.3.6. Multiple Assessments

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

- The record closest to the nominal time

If 2 records are equidistant or distance cannot be determined:

- The later record

If there are 2 or more records with the same date/time:

- The average (generally applies to assessments done in triplicate)

7. STUDY POPULATION

7.1. Enrollment by Investigator

Enrollment by geographic region (North America, Europe, Asia/Pacific, and Other), country, and investigator will be summarized.

7.2. Subject Disposition and Completion Status

The subject disposition summary will include the counts and percentages of subjects who:

- Completed study treatment
- Discontinued study treatment early, overall and by reason for not completing study treatment
- Completed the study
- Discontinued from the study early, overall and by reason for not completing the study

The subject disposition listing will include the date the informed consent form was signed, dates of first dose and last dose of study drug, primary reason for discontinuation of study treatment, and primary reason for study discontinuation. (If the treatment and study discontinuation reasons are the same for all subjects, as expected, a single column with the heading "Primary Reason for Discontinuation" may be shown.) A listing of premature discontinuation for reasons other than termination of the study by the sponsor will also be provided.

7.3. Protocol Deviations

A subject listing of all protocol deviations identified prior to database lock will be provided.

7.4. Medical History and Medical Conditions Present at Entry

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

7.5. Demographic and Baseline Clinical Characteristics

A summary of demographic and baseline characteristics will include the following: age (years), age category (< 65 years, ≥ 65 years), sex, race, ethnicity, weight (kg), height (cm), BMI (kg/m^2), and diagnosis of primary autonomic failure (Multiple System Atrophy, Parkinson's Disease, Pure Autonomic Failure). In addition, a summary of previous treatment during the Study 0170 randomized withdrawal period and a listing of previous treatment during the Study 0170 randomized withdrawal period and (if applicable) previous treatment during Study 0169 will be provided.

8. SAFETY AND TOLERABILITY

Safety and tolerability summaries include an overall summary of adverse events and summaries of drug exposure (duration of treatment), dosing information/compliance, concomitant medications, clinical laboratory results, vital signs, ECGs, incidence of falls/near-falls, C-SSRS responses, and [redacted]

8.1. Adverse Events

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

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of Study 0171 study drug up through 14 days after the date of last dose of study drug. AEs that begin more than 14 days after the date of last dose of study drug and AEs that begin during the period from obtaining informed consent to the start of administration of study drug will not be considered treatment-emergent and will be listed only.

The following AE summaries will be provided:

- TEAE overall summary
- TEAEs by preferred term
- TEAEs by system organ class and preferred term
- Moderate or severe TEAEs by system organ class and preferred term
- TEAEs by preferred term with frequency > 3% of safety analysis set subjects
- TEAEs by system organ class, preferred term, and severity
- Drug-related TEAEs by system organ class and preferred term
- Drug-related TEAEs by system organ class, preferred term, and severity
- Drug-related moderate or severe TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Drug-related serious TEAEs by system organ class and preferred term
- TEAEs resulting in on-study deaths
- TEAEs leading to premature study drug discontinuation
- TEAEs leading to temporary interruption of study drug
- TEAEs of special interest by system organ class and preferred term (Section 8.1.1)

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

The following AE listings will be provided:

- TEAEs
- AEs leading to premature study drug discontinuation
- AEs resulting in temporary interruption of study drug
- Serious adverse events
- Deaths
- Non-treatment-emergent adverse events

8.1.1. Adverse Events of Special Interest

An AE of special interest (AESI) is one of scientific and medical interest specific to understanding the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. The following are the AESIs defined for the study:

- Supine Hypertension
- Myocardial Infarction
- Cerebrovascular Accident
- Cardiac Arrhythmia
- Congestive Heart Failure
- Convulsion

The incidence of treatment-emergent AESIs will be summarized, overall (any AESI) and by system organ class and preferred term. A listing of AESIs will be provided.

8.2. Extent of Exposure and Treatment Compliance

Duration of study drug exposure (days) will be summarized. Duration of exposure to study drug is calculated as (date of last dose – date of first dose + 1).

Subjects will take their assigned study medication once daily.

Treatment compliance as a percentage of the expected total dose will be calculated as follows, using the information captured on the CRF page for "Study Drug Dispensing / Return":

$$100 \times \frac{\text{(number of tablets dispensed – number returned)}}{\text{(date of last dose – date of first dose + 1)}}$$

Treatment compliance as a percentage of expected total dose over the interval from first to last dose will be summarized as a continuous variable and using the following categories, after rounding to the nearest 0.1%:

- ≥ 120%
- ≥ 80% – < 120%
- < 80%

Study drug administration (date/time and study day) and drug accountability data will be listed.

8.3. Concomitant and Other Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODD, version 1Q 2021 C3). Medications entered on the case report form will be mapped to Anatomic Therapeutic Chemical (ATC) drug class and generic drug name. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and preferred name (ATC level 5, chemical substance).

Prior medications are medications taken before the first dose of study drug. Concomitant medications are medications taken after the first dose up through 14 days after the last dose, and include ongoing prior medications.

The number and percentage of subjects receiving prior medications, the number and percentage receiving concomitant medications, and the number and percentage receiving prohibited concomitant medications will be summarized by medication class and standardized medication name (preferred name). If available, ATC level 4 will be used to determine the medication class. If ATC level 4 is not available, the next available level of ATC code (i.e., level 3, level 2, or level 1) will be used. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and preferred name) will be counted only once.

All medications will be listed.

On-treatment midodrine usage will be summarized by providing a categorical summary of number of uses and descriptive summaries (n, mean, SD, etc.) of usage rate (uses/month),

calculated as (number of uses)/(treatment period duration in days, divided by 28) and total dose (mg). For number of uses, counts and percentages will be provided for the following categories:

- 0
- 1
- 2
- 3
- 4
- 5
- 6 – 10
- 11 – 20
- > 20

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

8.4. Laboratory Data

Laboratory data hematology and serum chemistry summaries will include summary statistics for observed values and for changes from baseline at each postdose visit. In addition, changes from baseline for each visit relative to normal ranges (e.g., shifts from normal to abnormal high/low) will be summarized in shift tables for hematology and serum chemistry test results. (Urinalysis data will be listed only.)

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

8.5. Vital Signs

Vital sign (HR, systolic and diastolic BP, respiratory rate, and body temperature) values and their changes from baseline at each visit will be summarized. If baseline BP and HR were collected as a part of the orthostatic standing test at Visit 9 (Day 155) in Study 0170, the seated values will be used to calculate the change from baseline. The counts and percentages of subjects with vital signs in the following categories will be presented in a vital signs extreme values summary. Extreme values will be flagged in the listing.

Table 5: Vital Signs Thresholds

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

8.6. 12-Lead Safety ECGs

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

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

Investigator Assessment of ECGs

The investigator's assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Categorical ECG Summary

The number of subjects with absolute ECG values and changes from baseline in the ranges shown in Table 6 will be presented by visit.

Table 6: ECG Thresholds and Ranges

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

8.7. Incidence of Falls

The numbers and percentages of subjects with at least one fall during the interval beginning on Study Day 1 and ending on Day 189 (the end of the Week 26 analysis window) will be provided, together with the corresponding numbers and percentages of subjects with at least one fall or near-fall.

In addition, the following categorical summaries with counts and percentages will be provided for falls and falls + near-falls:

- None
- 1
- 2
- 3 or more

8.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation). The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The C-SSRS Since Last Visit Version will be used in this study.

The following 11 C-SSRS categories include 5 subtypes of suicidal ideation (1–5), 5 subtypes of suicidal behavior (6–10), and self-injurious behavior without suicidal intent. They all have binary responses (yes/no).

1. Wish to be Dead
2. Non-specific Active Suicidal Thoughts
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5. Active Suicidal Ideation with Specific Plan and Intent
6. Preparatory Acts or Behavior
7. Aborted Attempt
8. Interrupted Attempt
9. Actual Attempt (non-fatal)
10. Completed Suicide
11. Self-injurious Behavior Without Suicidal Intent

Frequency counts and percentages will be presented for subjects in each C-SSRS category, as well as subjects with any suicidal ideation (1–5), subjects with any suicidal behavior (6–10), and subjects with any suicidal ideation or behavior (1–10), by visit at which the items were collected.

[redacted]

9. REFERENCES

10. APPENDICES

[redacted]

[redacted]

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[redacted]

10.2. Handling of Missing Data

10.2.1. Adverse Events Severity and Relationship to Study Drug

AEs with severity not reported will be counted as severe, and AEs with relationship to study drug not reported will be counted as related.

10.2.2. Missing Start and Stop Dates for Adverse Events

Missing start date and times will be handled as follows:

- AE onset date completely missing:
  - If AE is not ongoing and AE onset date missing and AE end date missing, then impute AE onset as date/time of first dose.
  - Else if AE is not ongoing and AE onset date missing and AE end date not missing and date/time of first dose <= AE end date, then impute AE onset as date/time of first dose of study drug.
  - Else if AE is not ongoing and AE onset date missing and AE end date not missing and AE end date is BEFORE first dose of study drug, then impute AE onset as AE end date YEAR and MONTH with 01 as the day and 00:00 as time.
  - Else if AE IS ongoing and AE onset date missing, then impute AE onset as date/time of first study drug dose.
- AE onset date has year and month only:
  - If AE onset date has year and month only and they are the year and month of first dose of study drug, then impute AE onset as date/time of first dose:
  - Else if AE onset date has year and month only and date/time of first dose is not missing, then impute AE onset as AE onset year and month with 01 as the date and 00:00 as the time.
- AE onset date has year only:
  - If AE onset date has year only and it is year of first dose of study drug, then impute AE onset as date/time of first dose of study drug.
  - Else if AE onset date has year only and date of first study drug dose is not missing and year of AE onset is NOT the year of first dose of study drug, then impute AE onset as Jan. 1 of the AE onset year and 00:00 as the time.
- AE onset missing (where it was not handled by the above cases):

  - If AE onset date is missing, then impute AE onset as date/time of first study drug dose.

- AE onset has complete date but missing time:
  - If AE onset date is a date only and is same as date of first study drug dose, then impute AE onset as date/time of first study drug dose.
  - Else if AE onset date is a date only and is NOT = date of first study drug dose, then impute AE onset as AE onset date with 00:00 as the time.

Missing end date and times will be handled as follows:

- AE end date - completely missing:
  - If AE is not ongoing and both AE onset and AE end dates are missing, then impute AE end date as date/time of last study drug dose.
  - Else if AE is not ongoing and AE onset date not missing and AE end date missing AND AE onset date <= date/time of last dose, then impute AE end date as date/time of last study drug dose.
  - Else if AE is not ongoing and AE onset date is not missing and AE end date is missing and date of last dose is not missing and AE onset is AFTER date of last dose, then impute AE end date as the last day of the month of AE onset date, with 23:59 as time.
- AE end date = year and month only:
  - If AE is NOT ongoing and AE end date consists of year and month only, then impute AE end date as the last day of the month of AE end date month and year, with 23:59 as time.
- AE end date = year only:
  - If AE is NOT ongoing and AE end date consists of a year only, and year = year of AE onset and AE onset date <= date of last study drug dose, then impute AE end date as the date of last study drug dose.
  - Else if AE is NOT ongoing and AE end date consists of a year only, and year = year of AE onset and AE onset date > date of last study drug dose, then impute AE end date as the year and month of AE onset, with the last day of the month as the day, and 23:59 as the time.
- AE end date = complete date but no time:
  - If AE is NOT ongoing and AE end date consists of a complete date but no time, then impute AE end date = trim (AE end date) || "T23:59".

10.2.3. Missing Start and Stop Dates for Medications

To determine whether medications were used before dosing started and whether they were used after dosing started, missing or partial dates for medications will be imputed according to the following rule:

Missing medication start date/time:

- If only have a YEAR, impute as Jan. 1, at one minute after midnight.
- Else if only have YEAR and MONTH, impute as Day 1 of month, at one minute after midnight.
- Else if have a complete date, impute TIME as one minute after midnight.
- Else if completely missing, and ((end date is present and >= date of first dose) or (end date is missing and is marked as "ONGOING")), impute as date and time of first dose. If missing and end date/time is present and prior to date of first dose, then leave as missing.

Missing medication end date/time:

- If only have a YEAR and it is same as year of study completion, impute as date of study completion with time of 23:59.
- Else if only have a YEAR, impute as December 31 with time of 23:59.
- Else if only have YEAR and MONTH, then impute to last day of the month, with time of 23:59.
- Else if have a complete date but no time, impute time of 23:59.
- Else if end date/time completely missing and not flagged as Ongoing, impute as date of study completion with time of 23:59.

Otherwise missing, no imputation.

10.2.4. Laboratory Data

For laboratory data, a missing baseline value will be replaced with the last available assessment. A retest value will be used if the first test result is invalid, e.g., specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of "$< x$" (x is considered as the LOD). More specifically, $x-1$ is used for data summarization if the data are reported in the form "$< x$"; and $x.e$ where $e = d-1$ will be used for analysis if the data are reported in the form "$< x.d$".
- The LOD will be used for calculation of descriptive statistics if the data are reported in the form "$\leq x$" or "$\geq x$."