Statistical Analysis Plan (SAP)

Sponsor:	H. Lundbeck A/S (Lundbeck)
Study title:	RESTORE: A clinical study of patients with symptomatic neuRogenic orthostatic hypotEnsion to assess Sustained effecTs Of dRoxidopa thErapy
Study number:	16306A
ICON ID:	0546/0093
SAP version:	Final 3.0 - 12 May 2022

	_____ Signature	_____ Date
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Signature Date

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REVISION HISTORY

Version/ Date	Version name	Section	Changes implemented
Version 1.0/ 11-Jul-2017	Initial approved version	N/A	N/A
Version 2.0/ 08-Dec-2017	Amendment 1 of the Final SAP	Section 5.1.9.1 Primary Efficacy Endpoints	Provided a detailed definition of "consecutive visits" and clarified how to classify patients who are missing the next or all OHSA Item 1 scores after having a worsening OHSA item 1 $\geqslant$ 2 units (and not meeting criteria 1, 3 or 4).
		Section 6.2.1.1 – Primary analysis	Removed the definition of time-to-intervention as already in section 5.1.9.1
Version 3.0/ 06 Apr-2022	Amendment 2 of the Final SAP	Throughout the document	Language edits. Removed listings to align with the needs for the CSR. Clarifications. Corrections.
		Section 3.3.2 – Planned sample size	Sample size update, incl rationale
		Section 4.3 – All Patients Treated Set (APTS)	Title of the section updated to Full analysis set (FAS)
		Section 4.4 – Per Protocol set (PP)	Removed the section, no PP analyses to be performed
		Section 4.5 – Clinical review of protocol violations and	Removed the section, no PP analyses to be performed

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		exclusions from analysis sets	
		Section 5.2.1 – Missing data analysis methods	Added modified BOCF
		Section 6.1.2 – Population membership and protocol deviations	Section removed as patients will not be excluded from any analyses
			New section 6.1.2 Protocol Deviations added
		Section 6.2.1.3 -	Removed PP analyses, removed competing risks analysis
		Section 6.2.3 – Analysis of other secondary endpoints	Added mBOCF Added ANCOVA Removed competing risks
		Section 6.3.4 – Physical examination	Removed section, to be included in datasets only
		Section 6.3.5 – 12-lead ECG	Removed section, to be included in datasets only
		Throughout the document	Language edits. Clarifications: For Safety Set Outputs “Droxidopa” treatment column will be presented instead of “Overall” column

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		Section 6.1.2	Protocol deviation outputs will be based on All-enrolled Set
		Section 6.2.3	Removed figure “A bar chart illustrating the need for treatment intervention and per criterion”

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1 LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
AP	Alkaline Phosphatase
AST	Aspartate Transaminase (SGOT)
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CGI-S	Clinical Global Impressions - Severity
CI	Confidence Interval
CSR	Clinical Study Report
DBH	Dopamine Beta Hydroxylase
DBL	Database Lock
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
FAS	Full Analysis Set
γGT	γ-glutamyl transferase
GCP	Good Clinical Practice
HR	Hazard Ratio
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
kg	Kilogram
LLN	Lower limit of the reference range
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mmHg	Millimetres of mercury
MSA	Multiple System Atrophy

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n	Number of non-missing observations
N	Number of patients in the population
NDAN	Non-Diabetic Autonomic Neuropathy
NOH	Neurogenic Orthostatic Hypotension
OH	Orthostatic Hypotension
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHQ	Orthostatic Hypotension Questionnaire
OHSA	Orthostatic Hypotension Symptom Assessment
PAF	Pure Autonomic Failure
PCS	Potentially Clinically Significant
PD	Parkinson's Disease
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TID	three times per day
TLFs	Tables, Listings and Figures
ULN	Upper limit of the reference range
WHO	World Health Organization

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2 INTRODUCTION

This statistical analysis plan (SAP) describes the detailed procedures for performing statistical analyses and for producing tables, listings, and figures (TLFs) for Study 16306A.

The SAP will be finalized before database lock (DBL).

This study consists of an Open-Label Titration Period, and Open-Label Treatment Period, and a Double-Blind Treatment Period. In the Double-Blind Treatment Period patients will be randomized (1:1) to either droxidopa or placebo using an Interactive Web Response System (IWRS). Unblinding is permissible after DBL or on an individual patient basis in case of emergency only. Emergency unblinding (via IWRS) should only be undertaken when it is essential to treat the patient safely and efficaciously.

3 STUDY OBJECTIVES, ENDPOINTS AND STUDY DESIGN

3.1 Objectives

The objectives of the study are to evaluate the clinical efficacy and safety of droxidopa versus placebo over a 12-week Double-Blind treatment period in patients with symptomatic neurogenic orthostatic hypotension (NOH) who have previously received up to 16 weeks of Open-Label treatment with an individually optimized dose of droxidopa (randomized-withdrawal design).

3.1.1 Primary objective

The primary objective is to evaluate the time to treatment intervention in patients with Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), non-diabetic autonomic neuropathy (NDAN) or dopamine beta hydroxylase (DBH) deficiency who have been previously stabilized with droxidopa therapy for symptoms of NOH (dizziness, light-headedness, or feeling that they are about to black out).

3.1.2 Secondary objectives

The secondary objectives are:

- To evaluate the long-term efficacy of droxidopa in patients with symptomatic NOH measured by:
  - Discontinuation for any reason (all-cause discontinuation)
  - Composite orthostatic hypotension questionnaire (OHQ) scores
  - Clinician- and patient-rated clinical global impression of severity (CGI-S) scores
- To evaluate the long-term safety and tolerability of droxidopa in patients with symptomatic NOH

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3.2 Endpoints

3.2.1 Primary efficacy endpoint

The primary efficacy endpoint is the “time-to-intervention”.

The need for intervention is defined as meeting ANY of the following events during the Double-Blind period:

- Orthostatic hypotension symptom assessment (OHSA) Item 1 ⩾2 units worsening from randomization (Visit 6) AND lack of efficacy as judged by the investigator; OR
- OHSA Item 1 ⩾2 units worsening from randomization (Visit 6) at 2 consecutive visits; OR
- OHSA Item 1 ⩾2 units worsening from randomization (Visit 6) at the visit before early discontinuation; OR
- Patient stops investigational medicinal product (IMP) or withdraws from study for patient-reported lack of efficacy

The timing of the need for intervention in the above criteria is defined as the first occurrence of a worsening of OHSA Item 1 by ⩾2 units, or when the patient stops taking IMP or withdraws due to a patient-reported lack of efficacy, whichever comes first.

Note: a patient that fulfils the criterion ‘Patient stops IMP or withdraws from study for patient-reported lack of efficacy’ has a final status ‘Discontinued’ on the ‘Subject Disposition’ Form in the eCRF.

3.2.2 Secondary endpoints

3.2.2.1 Key secondary endpoint

Time to all-cause discontinuation

3.2.2.2 Other secondary endpoints

- Efficacy measures of droxidopa versus placebo on the:
  - Mean change in OHSA item 1 score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
  - Mean change in OHQ composite score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
  - Clinician-rated CGI-S score at all post-randomization visits (Visits 7-12)
  - Patient-rated CGI-S score at all post-randomization visits (Visits 7-12)
  - Proportion of patients who need intervention over the 12-week Double-Blind treatment period
- Adverse events (AEs)
- Absolute values and changes from baseline in clinical safety laboratory tests and vital signs

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- Potentially clinically significant safety laboratory test values and vital signs

3.3 Study design

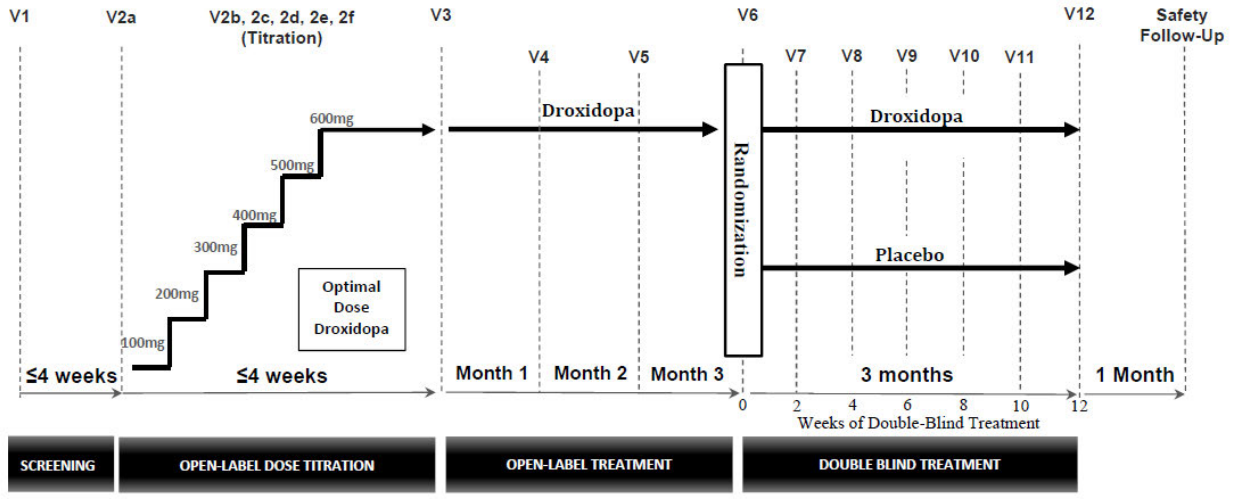
This is a multi-site, placebo-controlled, Double-Blind, randomized-withdrawal, time-to-intervention study with a duration of up to 36 weeks and consists of 5 periods:

- Screening period: up to 4 weeks duration
- Open-Label titration period (Titration Period): up to 4 weeks duration
- Open-Label treatment period (Open-Label Period): 12 weeks duration
- Double-Blind treatment period (Double-Blind Period): 12 weeks duration
- Safety follow-up period: 4 weeks duration

Adult patients with symptomatic NOH associated with primary autonomic failure (PD, MSA or PAF), NDAN or DBH deficiency will be enrolled. Across approximately 125 study sites in the United States, a sufficient number of patients will be screened to allow 240 patients (120 patients per treatment group) to be randomized in the Double-Blind Period.

The study design is presented in Figure 1.

Figure 1: Study Design



3.3.1 Assessments and study duration

The maximum duration of patient participation is 36 weeks.

All eligible patients will enter the Titration Period (Visit 2a). Patients are anticipated to have up to 6 titration visits. The exact number of titration visits for each patient will depend on the number of titration visits required to reach his/her optimal dose. At the end of the Titration Period (Visit 3), patients who have an acute dizziness score that is ⩾2 units lower (improved) than the Visit 2a

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OHSA item 1 score will enter the Open-Label Period. At the end of the Open-Label Period (Visit 6), patients who have an OHSA item 1 score that is ⩾2 units lower (improved) than the Visit 2a score will enter the Double-Blind Period and be randomized to receive either droxidopa or placebo. Week 0 of the Double-Blind Period begins with randomization (Visit 6). Visits in the Double-Blind Period will occur at Weeks 2, 4, 6, 8, 10 and 12 (Visits 7-12).

During the Titration Period (Visits 2a-2f) and the Open-Label Period (Visits 3-5), patients will receive 100, 200, 300, 400, 500 or 600 mg three times daily (TID) of droxidopa, orally. The droxidopa starting dose for all eligible patients in the Titration Period is 100 mg TID. Doses will be titrated in 100 mg TID increments until the optimal dose is achieved. Four dose changes are permitted within the first two months of the 3-month Open-Label Period. No dose changes are allowed between Visit 5 and Visit 6. Randomized patients will receive 100, 200, 300, 400, 500 or 600 mg TID of droxidopa or matching placebo (equal to their dose at the end of the Open-Label Period), orally at randomization (Visit 6) and during the Double-Blind Period (Visits 7-12). Dose changes are not permitted during the Double-Blind Period.

A detailed description of the procedures and assessments to be conducted during the study is provided in Sections 3.5 and 3.6 of the Protocol and summarized in the Study Schedule/Flowchart in Table 1 below.

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Table 1: Study Schedule/Flowchart

Study procedures	Screening	First Titration Visit	Dose Titration	Open-Label Treatment		End of Open-Label Treatment (Randomization)	Double-Blind Treatment	End of Treatment	Safety Follow-Up
	Visit 1	Visit 2a	Visits 2b...2f [f,g]	Visit 3	Visits 4-5	Visit 6	Visits 7-11 [h]	Visit 12 or Early Termination	Visit 13
Written informed consent	✓								
Review inclusion and exclusion criteria	✓	✓		✓		✓			
Demography	✓								
Medical history	✓								
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events (continuous monitoring)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓							✓	
Vital signs (BP, HR, RR, temp.) and weight	✓ [a, c]	✓ [a]		✓ [a]	✓ [b]	✓ [b]	✓ [b, i]	✓ [b]	
Orthostatic Standing Test	✓ [d]								
Seated, pre-dose BP			✓						
Supine BP							✓ [j]		
Supine, post-dose BP assessment		✓	✓						
Seated, post-dose BP assessment				✓					
Pregnancy test for WOCP [e]	✓					✓		✓	
12-lead ECG recording	✓								
Administer first daily dose of IMP on site		✓	✓	✓	✓	✓	✓	✓	
Dose titration evaluation			✓						
Clinical symptoms–OHQ (OHSA & OHDAS)	✓	✓			✓	✓	✓	✓	
Acute dizziness assessment				✓					
Patient-reported CGI-S		✓		✓	✓	✓	✓	✓	
Clinician-reported CGI-S		✓		✓	✓	✓	✓	✓	
Review Need For Intervention criteria							✓	✓	
Blood and urine samples (laboratory safety)	✓					✓		✓	
Randomization						✓			
IMP dispensed, as required		✓		✓	✓	✓	✓		
Capsule count/compliance check				✓	✓	✓	✓	✓	
IMP returned				✓	✓	✓	✓	✓	

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[a] Seated BP assessed during Vital Signs
[b] Supine BP assessed during Vital Signs
[c] Height recorded at Screening (V1) only
[d] Only required if OH not documented in patient history
[e] Local urine pregnancy test (on site dip-stick test; positive result to be verified by serum pregnancy test)
[f] Patients anticipated to have up to 6 titration visits
(g) Titration visits 2b-2f may be completed on site or via phone or video link
(h) Double-blind visits 7, 9 & 11, will be completed via phone or video link
(i) Visits 8 and 10 only
(j) Visits 7, 9 and 11 only

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3.3.2 Planned sample size

The sample size and power calculations are based on the analysis of time to intervention in the Double-Blind Period.

It is anticipated that event rates will be 0.15 for the droxidopa group and 0.25 for the placebo group 12 weeks post randomization. Assuming these event rates and a hazard ratio of 0.56 in favour of droxidopa, a sample size of 240 patients would be expected to result in 48 events, providing ~51% power to detect a difference between droxidopa and placebo. A blinded review of overall study events conducted in July 2020 indicated that the rate may be higher than originally assumed and, if maintained and the anticipated differential between droxidopa and placebo is an accurate assumption, will result in a substantially higher power than 51%. In addition, the study will contribute to the totality of results for the post-marketing requirement (PMR) evaluation, which justifies the reduced power given the circumstances.

3.4 Interim analysis

There will be no interim efficacy analysis. Accordingly, no formal stopping rules will be applied.

4 ANALYSIS POPULATIONS

4.1 All-enrolled set

All patients who were enrolled into the study (i.e. patients who entered the Open-Label titration period at Visit 2a).

Unless otherwise stated, data listings will be based on the all-enrolled set.

4.2 Safety set

The Safety set will consist of all patients who received at least one dose of IMP. This includes patients who received IMP during the Open-Label titration period. All safety analyses will be based on the Safety set unless otherwise specified.

Patients who did not receive the planned randomized treatment during the Double-Blind Period will be analysed according to the actual treatment received for >50% of the treatment duration of the randomized treatment period.

4.3 Full analysis set (FAS)

The FAS will be a modified intent-to-treat set, consisting of all randomized patients who took at least one dose of IMP in the Double-Blind period. Patients will be included in the analysis according to the treatment to which they were randomized.

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5 STATISTICAL CONSIDERATIONS AND ANALYSIS

5.1 Derived variables

5.1.1 Period

- Titration Period - treatment started on or after first dose in the Titration Period (Visit 2a) and before first dose in the Open-Label period (Visit 3);
- Open-Label Period - treatment started on or after first dose in the Open-Label period (Visit 3) and before first dose in the Double-Blind period (Visit 6);
  Entire Open label portion includes Titration period and Open-Label period.
- Double-Blind Period - treatment started on or after first dose in the Double-Blind period (Visit 6).
- Follow-Up: After visit 12.

5.1.2 Baseline

- Baseline in the Titration Period - The Visit 2a date (initial dose of IMP) is considered Day 0 of the Titration Period. Baseline assessment for the Open-Label titration period is the assessment from visit 2a. If this value is missing, then the latest available value from the screening period will be used. Baseline in the Titration Period is also used for analysis of the entire open label portion (Titration and Open-Label Period combined).
- Baseline in the Open-Label Period – The Visit 3 date is considered Day 0 of the Open-Label Treatment Period. Baseline assessment for the Open-Label treatment period is the assessment from visit 3. If this value is missing, then the latest available value from the Open-Label titration period will be used.
- Baseline in the Double-Blind Period - The Visit 6 date (randomization) is considered Day 0 of the Double-Blind Period. Baseline assessment for the Double-Blind Period is the assessment from visit 6.
-

5.1.3 Definitions relative to study days

5.1.3.1 Study days for the Open-Label titration period (Visits 2a-3)

Visits within the Titration Period do not have fixed visit windows, although there should be a minimum of 1 day between each Titration Visit. The Visit 2a date (initial dose of IMP) is considered Day 0 of the Titration Period.

Therefore, study days for the Open-Label titration period will be calculated as: <visit/examination date> minus <date of Visit 2a>. Visit 3 is the last visit in the titration period and will be included in the calculations.

All assessments made prior to dosing at visit 3 will be part of the Open-Label titration period assessments.

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5.1.3.2 Study days for the Open-Label treatment period(Visits 3-6)

The windows for Visits 4-6 are anchored from the Visit 3 date, which is considered Day 0 of the Open-Label Period. If the patient is required to return for re-evaluation of the Open-Label entry criterion, the date of the repeat assessment (recorded as an Unscheduled Visit) will be considered Day 0 of the Open-Label Period.

Therefore, study days for the Open-Label treatment period will be calculated as: <visit/examination date> minus <date of Visit 3 or repeat assessment (if any)>.

For changes from baseline in efficacy or safety endpoints in the Open-Label treatment period, the last value obtained prior to the Open-Label titration period will be used as baseline value.

5.1.3.3 Study days for the Double-Blind treatment period (Visits 6-12)

The windows for Visits 7-12 are anchored from the Visit 6 date (randomization), which is considered Study Day 0 of the Double-Blind Period.

Therefore, study days for the Double-Blind treatment period will be calculated as: <visit/examination date> minus <date of Visit 6>.

For changes from baseline in efficacy or safety endpoints in the Double-Blind treatment period, the visit 6 value will be used as baseline value.

5.1.4 Age

Age at informed consent will be calculated in years as:
integer part of ([date of informed consent - date of birth + 1]/ 365.25)

5.1.5 Weight, height and BMI

Weight, recorded in pounds on the eCRF, will be converted to kilograms (1 pound = 0.45359 kg).
Height, recorded in inches on the eCRF, will be converted to centimeters (1 inch = 2.54 cm).

Body mass index (BMI) will be calculated as: weight (kg)/(height [m])^2

5.1.6 Temperature

Temperature, recorded in degree Fahrenheit on the eCRF, will be converted to degree Celsius: (degree Fahrenheit - 32) x (5/9)

5.1.7 Orthostatic hypotension

Orthostatic hypotension (OH) is defined as a fall in SBP $\geqslant$ 20 mmHg or in diastolic blood pressure (DBP) $\geqslant$ 10 mmHg between the supine and standing measurements.

5.1.8 Primary disease duration

Primary disease (PD, MSA, PAF, NDAN, or DBH deficiency) duration will be calculated in months as: (date of informed consent - date of primary clinical diagnosis of NOH + 1)/ 30.4375

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5.1.9 NOH duration

NOH duration will be calculated in months as:
(date of informed consent - date of diagnosis of NOH + 1)/ 30.4375

5.1.10 Definitions relative to IMP exposure and compliance

5.1.10.1 Exposure to IMP

Exposure to IMP (number of days) for the Open-Label titration period will be calculated between the Visits 2a-3 and will be defined in that period as:

(date of last dose of IMP – date of first dose of IMP)

Exposure to IMP (number of days) for the Open-Label treatment period will be calculated between the Visits 3-6 and will be defined in that period as:

(date of last dose of IMP – date of first dose of IMP)

Exposure to randomized IMP (number of days) for the Double-Blind treatment period will be calculated between the Visits 6-12 and will be defined in that period as:

(date of last dose of IMP – date of first dose of IMP) + 1

5.1.10.2 IMP compliance

At each visit at which IMP is dispensed, patients will be given sufficient IMP to last them until their next clinic visit.

Patients will be required to bring their IMP to all clinic visits, and compliance will be checked by capsule counts. The number of returned capsules will be counted by the Investigator or a designee and recorded in the eCRF. The compliance score (expressed in %) will also be recorded in the eCRF (Visits 3, 4, 5, 6, 8, 10 and 12).

In case of missing IMP compliance data for a patient at a clinic visit (due to IMP bottles missing/lost since last visit), the worst-case scenario will apply, i.e. the IMP compliance will be considered as 0% for that clinic visit.

At least 80% compliance will be defined as acceptable during the Open-Label and Double-Blind Treatment Periods.

5.1.11 Definitions relative to efficacy criteria

5.1.11.1 Primary efficacy endpoint

The primary efficacy endpoint is Time to intervention. Since it is predominantly based on the OHSA item 1 score, it is believed that the time-to-intervention endpoint requires corroboration to ensure that worsening OHSA item 1 scores represent a true event. The criteria below represent a balanced approach to identify true events requiring treatment intervention.

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During the Double-Blind treatment period, eligible patients will be withdrawn from the study if they require treatment intervention for their NOH symptoms, defined by meeting ANY of the following criteria:

- Criterion 1: OHSA item 1 ⩾2 units worsening from randomization and lack of efficacy as judged by the investigator; OR
- Criterion 2: OHSA item 1 ⩾2 units worsening from randomization at 2 consecutive visits; OR
- Criterion 3: OHSA item 1 ⩾2 units worsening from randomization at the visit before early discontinuation; OR
- Criterion 4: Patient stops IMP or withdraws from study for patient-reported lack of efficacy

A consecutive visit for OHSA item 1 will be defined as the next non-missing OHSA item 1 result, including the results from unscheduled visit. If a patient has all OHSA item 1 missing after having a worsening OHSA item 1 ⩾2 units (and not in Criterion 1, 3 and 4) then this patient is considered a treatment failure. See below an example for four patients who have an unscheduled visit between Visit 10 and 12. 'Yes' means that OHSA item 1 ⩾2 units worsening from randomization (and not in Criterion 1, 3 and 4). 'No' means that OHSA item 1 <2 units worsening from randomization. 'Missing' means that OHSA item 1 is missing for this patient for this particular visit.

Patient	Visit 7	Visit 8	Visit 9	Visit 10	Unsche-duled Visit	Visit 11	Visit 12	Outcome
001	Yes	No	Yes	No	Yes	No	No	This patient is not considered a treatment failure
002	No	Yes	missing	missing	Yes	No	No	This patient is considered a treatment failure at the unscheduled visit
003	No	No	No	Yes	No	Yes	No	This patient is not considered a treatment failure
004	Yes	missing	missing	missing	missing	missing	missing	This patient is considered a treatment failure at visit 7

The timing of the need for intervention in the above criteria is defined as the first occurrence of a worsening of OHSA item 1 by ⩾ 2 units, or when the patient stops taking IMP or withdraws due to a patient-reported lack of efficacy, whichever comes first.

5.1.11.2 Secondary efficacy endpoints

5.1.11.3 Orthostatic Hypotension Questionnaire (OHQ)

The severity of NOH symptoms in patients is assessed using the Orthostatic Hypotension Questionnaire[1]. The questionnaire consists of two separate sections: an Orthostatic Hypotension

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Symptom Assessment (OHSA) scale and an Orthostatic Hypotension Daily Activity Scale (OHDAS) (see Appendix A).

The OHSA scale is designed to rate symptoms occurring specifically as a result of low blood pressure (BP), using an 11-point scale (0 to 10), with more severe symptoms scoring higher. A score of zero indicates that the symptom was not experienced. The scale assesses six symptoms: 1) dizziness/lightheadedness, 2) problems with vision, 3) weakness, 4) fatigue, 5) trouble concentrating, and 6) head/neck discomfort. Scores for each symptom and a composite score for all 6 symptoms are tabulated. The OHSA composite score is calculated as the average of the individual OHSA item score not rated zero at baseline.

The OHDAS is designed as a measure of quality of life. It uses an 11-point scale to assess whether OH "interfered" with 4 types of activities in the preceding week: 1) standing for a short time, 2) standing for a long time, 3) walking for a short time, and 4) walking for a long time. A score of zero means that in the preceding week, the activity was performed with no interference and a score of 10 means that OH completely interfered with the activity. As many of these patients have difficulty walking or standing for reasons not directly related to their OH (e.g., parkinsonism or somatic neuropathy), patients are able to check a box in the questionnaire stating that they could not perform the activity for reasons other than OH. Scores for each activity and a composite score for all 4 activities are tabulated. The OHDAS composite score is calculated as the average of the individual OHDAS item score not rated zero at baseline.

An overall OHQ composite score is calculated as the average of the OHSA and OHDAS composite scores.

The OHSA item 1 score and the OHQ composite score will be analysed at 2, 4, 6, 8, 10, and 12 weeks post-randomization (Visits 7-12) by comparing with scores at randomization (Visit 6).

5.1.11.4 Clinical Global Impression - Severity (CGI-S)

The CGI-S[2] is a one-item scale evaluating the severity of the patient's illness on a 7-point scale: 1=normal, no OH; 2=borderline OH; 3=mild OH; 4=moderate OH; 5=marked OH; 6=severe OH; 7=most extremely ill with OH (see Appendix B).

The clinician-reported CGI-S asks the clinician the question: "Considering your total clinical experience with this particular population, how severe is the patient's orthostatic hypotension (OH) at this time?". The patient-reported CGI-S asks the patient the question: "How severe is your orthostatic hypotension (OH) at this time?".

The clinical- and patient-rated CGI-S scores will be analysed at 2, 4, 6, 8, 10, and 12 weeks' post-randomization (Visits 7-12) by comparing with the scores at randomization (Visit 6).

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5.1.12 Definitions relative to safety parameters

To assess the long-term safety and tolerability of Droxidopa in patients with symptomatic NOH, adverse events, clinical safety laboratory assessments, vital signs, and physical examination were performed throughout the study.

5.1.12.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, ECGs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

All AEs, including pre-treatment AEs (those that start after the patient has signed the ICF and prior to the first dose of IMP) will be collected and recorded until 30 days after the last dose of IMP.

5.1.12.2 Serious Adverse Event (SAE)

An SAE is any AE that:

- results in death
- is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenial anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs defined above)

5.1.12.3 Duration of AEs

The duration of an AE will be calculated as the resolution date minus the date at which it first appeared plus 1.

In the case of an AE still continuing at the end of the study, the duration will be considered as unknown.

5.1.12.4 Relationship of AEs

The Investigator will assess the causal relationship between an AE and the IMP using the following definitions:

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- Probable: the AE has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely.
- Possible: the AE has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
- Not related: the AE has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

Adverse events will be considered causally related to the use of the IMP when the causality assessment is probable or possible, or if the relationship is not recorded.

5.1.12.5 Intensity of AEs

The Investigator will assess the intensity of AEs using the following definitions:

- Mild: the AE causes minimal discomfort and does not interfere in a significant manner with the subject's normal activities
- Moderate: the AE is sufficiently uncomfortable to produce some impairment of the subject's normal activities
- Severe: the AE is incapacitating, preventing the subject from participating in his or her normal activities.

5.2 Handling of missing data and/or invalid data and outliers

5.2.1 Missing data analysis methods

Exploratory analyses of the following secondary efficacy endpoints (quantitative variables) in the Double-Blind treatment period will be performed using the FAS using descriptive methods:

- OHSA item 1 score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
- OHQ composite score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
- Clinician-reported CGI-S score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
- Patient-reported CGI-S score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)

Missing change from randomization (Visit 6) to each post-randomization visit (Visits 7-12) will be imputed using LOCF, which is assumed to be a conservative approach in a randomized-withdrawal study, as the majority of the patients will be withdrawn when response is lost based on the OHSA item 1 score. Missing post-baseline data will be imputed using the last non-missing observation prior to calculating change from baseline.

In addition, due to the study design, missing data due to meeting the treatment intervention criteria are categorized as missing not at random (MNAR), and a modified baseline observation carried

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forward (BOCF) method will be applied, where missing data (due to any reason) will be imputed with the last available post-randomization OHSA Item 1 score. When no post-randomization score is available, the baseline value obtained before the start of treatment in the titration period (Visit 2a) will be used for imputations during the Double-Blind treatment period rather than the score at randomization (Visit 6), which is the baseline for the Double-Blind treatment period. The score at Visit 6 should not be missing, as OHSA Item 1 is part of the randomization criteria. However, in the unlikely event that it is missing, the score will be imputed with the last-obtained score from the Open-Label period. This method is assumed to provide a conservative estimate of the treatment difference.

5.2.2 Handling of missing or incomplete dates

5.2.2.1 Concomitant medications definition and handling of missing or incomplete dates

Medications will be assigned as being prior to the IMP or concomitant with IMP, based on the start and stop dates of the medication and the date of the first IMP dose (Visit 2a). If the medication stop date is before the date of the first dose of IMP, the medication will be assigned as being prior to IMP. Otherwise, the medication will be assigned as being concomitant with IMP. Concomitant medications that continued after first dose of IMP or that started after first dose of IMP will be tabulated separately and will be split into Open-Label period and Double-Blind period.

Prior medications – medications that stopped before visit 2a.

Concomitant medications during Titration period – medications that continued after first dose of IMP or that started after first dose of IMP.

Concomitant medication during Open Label period – medications that continued on or after visit 3 or started after visit 3.

Concomitant medication during Double-Blind Period – medications that continued after visit 6.

If the start date or stop date for a medication is missing or incomplete to the extent that it could be before or after the first IMP dose, then it will be assumed that the medication was started or stopped after the start of IMP (i.e. reported as a concomitant medication).

5.2.2.2 Definition of treatment-emergent AEs and handling of missing or incomplete dates

A treatment-emergent AE (TEAE) is defined as an AE occurring or worsening on or after the date of first IMP dose (Visit 2a). Events with an onset date or end date prior to the start of IMP will be classified as pre-treatment AEs.

If the onset date of an AE is partially or completely missing (such that it cannot be determined if the event onset was prior to the start of IMP), the AE will be assumed to be treatment-emergent, unless the AE stop date indicates otherwise (worst-case approach).

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Tabulations of AEs will be split into Titration Period, Open-Label period, and Double-Blind period.

For AEs listings, dates will be presented as they have been recorded (missing and partial dates will not be replaced).

5.2.3 Handling of Early Termination (ET) data

If, at any time during the study, a patient requests to withdraw from treatment or if a decision is made to withdraw the patient, including during the Double-Blind treatment period due to a need for intervention, the patient will be requested to return for an Early Termination Visit. Whenever practical, patients should be encouraged to remain on IMP until the completion of the early termination procedures. Such assessments are recorded on the 'Visit 12 - End of Treatment/Early Termination Visit' CRF pages.

5.2.3.1 Handling of ET data during the Titration Period

In patient listings and summary tabulations, the following time point will be presented to reflect this data:

- 'Visit 3/ET': If the ET Visit occurred during the Open-Label titration period, the ET Visit data will be labelled 'Visit 3/ET' and summarized separately from the other scheduled time points for that period.

5.2.3.2 Handling of ET data during the Open-Label Period

Descriptive summary statistics based on absolute values and changes (relative to visit 2a) from baseline will be used to present the visits in the Open-Label treatment period (Visits 3-6) for the secondary efficacy endpoints (quantitative variables) using all available data.

For patients who withdrew during the Open-Label treatment period, the Early Termination visit will be reassigned for the OHSA item 1 score, the OHQ composite score, and both the clinician- and patient-reported CGI-S scores tabulation by visit using the actual visit/assessment dates and the following visit windows, based on baseline date (date of Visit 3 or repeat assessment on Day 0):

Visit	Visit Window
Baseline (Open-Label)	0 (no window)
Visit 4 (Day 28)	1 to 42
Visit 5 (Day 56)	43 to 70
Visit 6 (Day 84)	≥71

In summary tabulations, the ET data will be presented at the visit determined by the above rules. Within patient listings, this time point will be labeled as 'Visit 6/ET'. In the event that a patient's

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ET Visit is assigned (using the above rules) to a visit where he/she had attended (and thus, already had data), the data collected at the ET Visit will not be tabulated.

5.2.3.3 Handling of ET data during the Double-Blind Period

Descriptive summary statistics will be used to present the visits in the Double-Blind treatment period for the secondary efficacy endpoints (quantitative variables) using all available data between Visit 6 and Visit 12/Early Termination.

For patients who withdrew during the Double-Blind treatment period, the Early Termination visit will be reassigned for the OHSA item 1 score, the OHQ composite score, and both the clinician- and patient-reported CGI-S scores tabulation by visit using the actual visit/assessment dates and the following visit windows, based on baseline date (date of randomization on Day 0):

Visit	Visit Window
Baseline (Double-Blind)	0 (no window)
Visit 7 (Week 2)	1 to 21
Visit 8 (Week 4)	22 to 35
Visit 9 (Week 6)	36 to 49
Visit 10 (Week 8)	50 to 63
Visit 11 (Week 10)	64 to 77
Visit 12 (Week 12)	≥78

In summary tabulations, the ET data will be presented at the visit determined by the above rules. Within patient listings, this time point will be labeled as 'Visit 12/ET'. In the event that a patient's ET Visit is assigned (using the above rules) to a visit where he/she had attended (and thus, already had data), the data collected at the ET Visit will not be tabulated.

6 STATISTICAL PLAN AND METHODS

All data analyses and generation of TLFs will be performed using the SAS® software package version 9.4 or higher.

Descriptive statistical methods will be used to summarize the data, with statistical testing performed for the primary efficacy endpoint (time-to-intervention) and the key secondary endpoint (time to all-cause discontinuation). To control the overall type I error, statistical significance of the key secondary endpoint will be evaluated using hierarchical testing.

Analyses of the other secondary efficacy endpoints will be considered supportive and no

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confirmatory statistical testing will be performed. Nominal P-values will be calculated for presentation purpose.

Unless otherwise stated, all statistical testing will be two-sided using a significance (alpha) level of 0.05.

Continuous variables will, as a minimum, be summarized by number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), minimum (Minimum), median (Median), and maximum (Maximum). One additional decimal point for mean and median and 2 additional decimal points for SD will be used.

Categorical variables will be summarized using the number of non-missing observations (n) or the number of patients in the population (N), as applicable, and percentages (%). Percentages will be rounded to one decimal place. Two-sided 95% confidence intervals (CI) will be provided, when relevant.

Unless otherwise stated, the baseline in each study period as per section 5.1.2. The change from baseline value at each post-baseline assessment (scheduled and unscheduled assessments) will be calculated as post-baseline value minus the baseline value for each post-baseline time point. Unless otherwise stated, only scheduled assessment change from baseline values (including ET Visits windowed per Section 5.2.3) will be tabulated; however, all changes from baseline in safety assessment values will be included when listed.

The term “treatment group” refers to randomized treatment assignment for the Double-Blind Period. Summaries of efficacy and safety data will be presented in terms of randomized treatment group (Droxidopa and Placebo separately and overall) as well as for the Open-Label periods.

Unless otherwise stated, unscheduled/repeat visit results will be included in date/time chronological order in patient listings only. All listings will be sorted by study site, patient number, date/time and visit. For the Double-Blind Period, the treatment group (Droxidopa and Placebo) will be stated in each listing. Unless otherwise stated, data listings will be based on the All-Enrolled set.

Subgroup investigations will be performed to assess the potential impact of COVID-19 on the recruited patient population. The subgroup analyses will include demographics and baseline characteristics as well as efficacy subgroup analyses and/or sensitivity analyses stratified on the cut-off date (time-to-event) or adjusted for the cut-off date (ANCOVA). The cut-off date for these subgroup analyses will be 17 March 2020, which is the date when Lundbeck issued formal guidance to investigators on the COVID-19 pandemic. The cut-off date will be applied to the enrolment date, the randomization date and/or the withdrawal date, as further specified in sections 6.1 and 6.2. Comparisons between groups will be done based on visual inspections, if not otherwise stated.

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6.1 Background characteristics

6.1.1 Patient disposition

All patients who provided informed consent will be included in a summary of patient disposition. The number of patients screened, the number of screening failures, the frequency and percentage of patients enrolled, in enrolled and treated in the Open-Label period, in the Safety set randomized (by treatment group and overall), in the FAS (by treatment group and overall) will be summarized. The frequency and percentage of patients who completed/withdrew in the Titration Period, in the Open-Label Period, and in the Double-Blind Period (by treatment group and overall) will also be tabulated with the primary and all reasons for withdrawal. The reasons for screening failure will also be tabulated.

In addition, the number of enrolled, the number of randomized patients, and the main reason for withdrawal before and on/after 17 March 2020 will be included in the tabulations.

Patient disposition will be summarized by study periods (Titration Period, Open-Label Period, and the Double-Blind Period). Each study period summarizes (as appropriate) the number of patients screened, enrolled, randomized, completed, withdrawn, and the number of patients in each analysis sets. Withdrawal from the study will be summarized by primary reason and all reasons for withdrawal for each study period.

Patients withdrawn from the study will be listed, including last dose of IMP received prior to withdrawal and study period for withdrawal.

For all patients randomized, listings will be provided displaying screening number, randomization number, site ID, and treatment group, sorted by screening number. A similar list will be created sorted by randomization number, screening number, site ID, and treatment group.

6.1.2 Protocol Deviation

All major protocol deviations will be identified at the Classification Meeting prior to study unblinding using the following sources of information:

- Patient listings, based on data recorded on the eCRF
- Protocol Deviation Logs

The list of protocol deviations to be identified for the CSR is defined as:

- Failure to obtain informed consent (to be excluded from all analyses)
- ICF not dated correctly, not witnessed, wrong version signed, pages missing or no documentation that copy was provided to patient
- Patient does not meet one or more of the inclusion criteria
- Patient meets one or more of the exclusion criteria
- Non-compliance with randomization or other randomization error. Includes patient

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randomization when not meeting criteria for randomization

- Non-compliance with IMP (<80% or >120% of planned doses) during the Open-Label treatment period or the Double-Blind treatment period
- Disallowed medications, as per Sections 4.8.3 and 4.8.4 of the protocol
- Serious breach of GCP
- Patient/Investigator unblinded to treatment
- Incorrect treatment or dosing allocation
- Patient did not meet End of Titration criteria but entered the Open-Label treatment period
- Patient did not have an OHSA item 1 score meeting the randomization criterion (⩾2 units lower [improved] than the Visit 2a score) but was randomized

The number of patients with major protocol deviation will be summarized by treatment group (if applicable) and overall based on the All-enrolled Set.

All protocol deviations will be listed based on data recorded on the eCRF and/or protocol deviation Logs (from ICON Medical).

6.1.3 Demographic and baseline characteristics

Descriptive statistics of demographic variables (age, sex, ethnicity, race, baseline height, weight and BMI) and baseline characteristics including medical history past/ongoing at Screening, primary disease diagnosis (PD, MSA, PAF, NDAN, or DBH deficiency) and duration, NOH duration at the Screening visit and severity at the Screening and baseline visits (prior to initial dose titration) (OHSA item 1 score, OHSA, OHDAS, and OHQ composite scores), both clinician- and patient-reported CGI-S scores at baseline (prior to initial dose titration) will be presented for the Safety set and the FAS by treatment group . Demographics and baseline characteristics will also be presented by enrolment date into the study before versus on or after 17 March 2020, and by randomization date before versus on or after 17 March 2020 in order to assess the potential impact of the COVID-19 pandemic.

6.1.4 Medical condition

Summaries of medical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities® (MedDRA) Version 24.1 or higher. Concurrent medical conditions will be tabulated based on the Safety set (Open-Label period) and the FAS (Double-Blind Period).

6.1.5 Prior and concomitant medications and procedures

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2015 or later).

Prior and concomitant medications will be summarized according to WHO drug class and preferred term for each study period (Titration Period, Open-Label Period, and Double-Blind

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Period). This analysis will be based on the Safety set (Open-Label period) and the FAS (Double-Blind Period).

6.1.6 IMP exposure and compliance

6.1.6.1 IMP exposure

IMP exposure will be summarized for the Titration Period and the Open-Label Period (Safety Set), and by treatment group for the Double-Blind Period (FAS).

Exposure to IMP in the Open-Label Titration Period will be categorized by intervals (1-10 days, 11-20 days, ⩾21 days) and summarized using quantitative and categorical variables. The sum of patient days of IMP exposure will also be tabulated.

Exposure to IMP in the Open-Label Treatment Period will be categorized by intervals (1-30 days, 31-60 days, ⩾61 days) and summarized using quantitative and categorical variables. The sum of patient days of IMP exposure will also be tabulated.

The distribution of IMP dose administered (100, 200, 300, 400, 500, or 600 mg TID) will be tabulated upon entry into the Open-Label Treatment Period (Visit 3).

Exposure to IMP in the Double-Blind Treatment Period will be categorized by intervals (1-30 days, 31-60 days, ⩾61 days) and summarized by treatment group using quantitative and categorical variables. The sum of patient days of randomized IMP exposure will also be tabulated by treatment group.

The distribution of randomized IMP dose administered (100, 200, 300, 400, 500, or 600 mg TID) will be tabulated by treatment group upon entry into the Double-Blind Treatment Period (Visit 6).

6.1.6.2 IMP compliance

IMP compliance will be summarized for the Titration Period and the Open-Label Treatment Period (Safety Set), and by treatment group for the Double-Blind Treatment Period (FAS).

IMP compliance in the Open-Label Treatment Period will be categorized as <80% compliant, 80 to 120% compliant, or >120% compliant and summarized using quantitative and categorical variables, both by scheduled visit.

Compliance with randomized IMP will be categorized as <80% compliant, 80 to 120% compliant, or >120% compliant and summarized by treatment group using quantitative and categorical variables, by scheduled visit for the Double-Blind Treatment Period.

6.2 Efficacy analysis

6.2.1 Analysis of primary endpoint

6.2.1.1 Primary analysis

The primary efficacy analysis will be based on the FAS.

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The time-to-intervention is the primary endpoint and will be summarized using the Kaplan-Meier method[3].

The primary efficacy analysis is the Log-rank test to compare the two treatment groups on time to treatment intervention during the Double-Blind treatment period.

A Kaplan-Meier survival curve for time to treatment intervention in the 12 weeks post-randomization will be displayed by treatment group. The p-value of the Log-rank test comparing the treatment groups will be displayed in the survival curve.

Patients who withdrew or were lost to follow-up without meeting the criteria for treatment intervention will be censored at the time of withdrawal or last contact date; patients who did not meet the criteria for treatment intervention at the end of the Double-Blind Period (Visit 12) will be censored at the date of study completion.

6.2.1.2 Descriptive analyses

The number and percentage of patients who presented a need for treatment intervention, the number and percentage of patients still at risk for treatment intervention, and the number and percentage of censored patients will be tabulated. The treatment-intervention-free rate estimate and the corresponding two-sided 95% CI (using log-log methodology) will be presented at the upper limit of the visit window. The time window for the 12-week treatment-intervention-free rate is $\leqslant$84 + 3 days post-randomization. The median and quartiles time until treatment intervention will also be summarized with the corresponding 95% CIs.

6.2.1.3 Sensitivity analyses

A Cox proportional hazards model[4] will be used, including treatment as a factor and baseline OHSA item 1 score (prior to initial dose titration) as a covariate in order to compare the probability of need for treatment intervention between the two treatment groups. Treatment effect will be presented as a hazard ratio (HR) with the corresponding 95% Wald CI and p-value based on the Wald chi-square test.

Furthermore, both Kaplan-Meier and Cox regression analyses will also be performed as part of the following sensitivity analyses based on the FAS:

- Time to treatment intervention according to the treatment intervention criteria (Section 5.1.11.1) or OHSA item 1 $\geqslant$2 units worsening from randomization at the last visit of the Double-Blind Period (Visit 12)

See Appendix C for SAS code used to implement Kaplan-Meier method and Cox proportional hazards model.

To assess the potential impact of the COVID-19 pandemic, a sensitivity analysis will be performed based on the primary analysis model, but stratified by randomization date before or on/after 17 March 2020. In addition, a subgroup analysis based on the primary analysis model will be

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performed using the same cut-off for the randomization date subgroups.

6.2.2 Analysis of key secondary endpoint

Time to all-cause-discontinuation is the key secondary endpoint.

Analysis of the key secondary endpoint will be based on the FAS.

During the Double-Blind treatment period, the time to all-cause-discontinuation is defined as the time from randomization to withdrawal or last contact date.

Patients who did not withdraw at the end of the Double-Blind Period (Visit 12) will be censored at the date of study completion.

Sensitivity analyses of the potential impact of the COVID-19 pandemic will be performed the same way as described in Section 6.1.2.3.

6.2.2.1 Testing strategy for key secondary endpoint

A gate keeping strategy will be applied in the testing of the key secondary endpoint. The Log-rank test will be performed at the nominal alpha level of two-sided 0.05 and will be considered part of the testing strategy only if the primary efficacy endpoint reached the statistical significance in the primary analysis. This is to ensure that the overall type I error rate is preserved. The key secondary analysis will be performed similar to the primary efficacy analysis (Log-rank test of treatment difference, Kaplan-Meier plot, Cox regression analysis).

6.2.3 Analysis of other secondary endpoints

Analysis of all other secondary endpoints (described in Section 3.2.2.2) will be based on the FAS using observed cases, LOCF, and modified BOCF.

For exploratory purposes, Droxidopa will be compared to placebo. Nominal P-values will be calculated. Early Termination data will be utilized for data summarizations as specified in Section 5.2.3.3.

Summary tables including summary statistics by treatment group and visits and change from baseline summaries will be provided for:

- Analysis of OHSA item 1 score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
- Analysis of OHQ composite score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
- Analysis of clinician-reported CGI-S score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)
- Analysis of patient-reported CGI-S score from randomization (Visit 6) to all post-randomization visits (Visits 7-12)

For each of the secondary endpoint, graphical representations of the data distribution using plots

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of mean change from baseline (mean and 95% CI) will be provided over time by treatment group.

Additionally, the change from randomization to Week 12 in OHSA Item 1 score will be analysed using an analysis of covariance (ANCOVA) model that includes the treatment group, the pooled site (based on US state), and the OHSA Item 1 score at randomization. Additionally, the change from randomization (Visit 6) to all other visits (Visits 7-12) will be analysed using the same model. A sensitivity analysis will also be performed, including the change in OHSA Item 1 score from pre-treatment baseline (Visit 2a) to randomization (Visit 6) rather than having the OHSA Item 1 score at randomization as a covariate. In case of missing value at any post-randomization visit (Visits 7-12), the missing values will be imputed using LOCF as well as modified BOCF. Another sensitivity analysis will be performed with an indicator of randomization before or on/after 17 March 2020 included in the model to adjust for potential impact of the COVID-19 pandemic.

The number and proportion of patients who needed treatment intervention will be summarized by treatment group:

- over the 12-week Double-Blind treatment period (between Visit 6 and Visit 12/Early Termination)
- For each of the criteria[a] defining the need for treatment intervention

The need for treatment intervention during the 12-week Double-Blind treatment period will be compared between treatment groups using Chi-square test (of Fisher's exact test). A similar comparison between treatment groups will be performed for each of the criteria[a] defining the need for treatment intervention.

For quantitative variables, summary tables including summary statistics by scheduled visits and change from baseline will be provided for OHSA item 1 score, OHQ composite score, and both clinician- and patient-reported CGI-S scores in the Titration Period and Open-Label Treatment Period.

6.3 Safety analysis

All the safety analyses will be based on the Safety set.

Adverse events, vital signs, and clinical safety laboratory assessments will be performed throughout the study. Adverse events will be assessed for the Titration Period, the Open-Label Period, and for Double-Blind Period separately. Vital sign and clinical safety laboratory assessments will be assessed in two periods of the study: the entire Open-Label portion of the study (Titration Period and Open-Label Period) and the Double-Blind Period. The Titration and

[a] Criterion 1: OHSA item 1 ≥2 units worsening from randomization and lack of efficacy as judged by the investigator; Criterion 2: OHSA item 1 ≥2 units worsening from randomization at 2 consecutive visits; Criterion 3: OHSA item 1 ≥2 units worsening from randomization at the visit before early discontinuation; Criterion 4: Patient stops IMP or withdraws from study for patient-reported lack of efficacy.

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Open-Label Periods will be presented as appropriate in standard tabulations and listings. The absolute values and the changes from randomization to Week 12 in the Double-Blind Treatment Period will be summarized separately using standard tabulations and listings. The two treatment groups will be analysed separately during the Double-Blind Treatment Period. The analysis of safety endpoints during the Double-Blind Treatment Period will be based on the FAS. Patients who did not receive the planned randomized treatment during the Double-Blind Period will be analysed according to the actual treatment received for >50% of the treatment duration.

6.3.1 Adverse events

All AEs will be coded according to the MedDRA, Version 24.1 or higher.

The incidence of adverse events will be summarized for the Titration Period, the Open-Label Period, and for Double-Blind Period separately.

Summary presentations will be produced by treatment group (Double-Blind Period) and period (Titration Period, Open-Label Period and Double-Blind Period separately), for the number and percentage of patients in each of the following categories: at least one TEAE, TEAEs related to the IMP, severe TEAEs, TEAEs leading to IMP withdrawal, SAEs, SAEs related to the IMP and SAEs leading to IMP withdrawal.

Serious AEs and AEs that lead to IMP withdrawal will be listed.

Additional summaries will be produced for TEAEs (Titration Period, the Open-Label Period and Double-Blind Period separately) showing number and percentage of patients for:

- Incidence of TEAEs by treatment group (Double-Blind Period), SOC and PT
- Incidence of TEAEs related to the IMP by treatment group (Double-Blind Period), SOC and PT
- Incidence of TEAEs leading to IMP withdrawal by treatment group (Double-Blind Period), SOC and PT
- Incidence of SAEs by treatment group (Double-Blind Period), SOC and PT

The incidence of TEAEs by the maximum severity overall and by SOC and PT will be presented by treatment group (Double-Blind Period), and similarly for TEAEs related to IMP. TEAEs with an incidence $\geqslant$5% will be summarized.

All AEs will be listed by site/patient and will include verbatim and PT and SOC, onset and resolution date/time, study day of onset, the number of days since the last IMP dose prior to onset, duration, severity, seriousness, outcome, relationship to IMP, and action taken with IMP. The number of days since the last IMP dose prior to the AE onset will be calculated based on the difference in dates between the IMP dose and the onset date of the AE.

Pre-treatment AEs and TEAEs will be listed (Safety Set).

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6.3.2 Clinical safety laboratory tests

All analytical tests will be performed by ICON Central Laboratories. The laboratory's set of reference ranges will be listed. The Lundbeck's set of potentially clinically significant (PCS) criteria will be listed. Urine pregnancy test will be assessed at sites.

The following clinical safety laboratory tests will be performed at Screening (Visit 1), at the End of Open-Label Treatment/Randomization (Visit 6), and at the End of Treatment Visit (Visit 12/Early Termination), as well as at any unscheduled visit if deemed appropriate by the Investigator:

- Hematology:
  - Haemoglobin
  - Erythrocyte Count
  - Haematocrit
  - Total Leucocyte Count
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes
  - Thrombocyte Count
- Clinical Chemistry:
  - Total Bilirubin
  - Alkaline phosphatase (AP)
  - Alanine Aminotransferase (ALT)
  - Aspartate Aminotransferase (AST)
  - γ-glutamyl transferase (γGT)
  - Sodium
  - Potassium
  - Calcium (Total)
  - Bicarbonate
  - Chloride
  - Albumin
  - Glucose
  - Creatinine
  - Blood Urea Nitrogen (BUN)
  - Total Protein
- Urinalysis:
  - pH

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- Specific Gravity
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Leukocytes
- Nitrites
- Microscopic sediment examination, only if dipstick is abnormal

The clinical safety laboratory data will be reported in Standard International (SI) units.

Clinical safety laboratory parameters (haematology and clinical chemistry) will be summarized using descriptive statistics by scheduled visits by treatment group (Double-Blind Period) and Droxidopa (Open-Label portions). Change from baseline to each post-baseline visit will also be produced.

Urinalysis dipstick results will be summarized categorically by visit for each test and microscopy results will be summarized by visits according to the dipstick results by treatment group (Double-Blind Period) and Droxidopa (Open-Label portions).

Shift tables (haematology and clinical chemistry) will be presented as appropriate, showing the shift from baseline to post-baseline, categorized as below, within or above the reference range, presented by treatment group (Double-Blind Period) and Droxidopa (Open-Label portions).

The number and percentage of patients with PCS values will be summarised by parameter (haematology, clinical chemistry and urinalysis), visit, treatment group (Double-Blind Period) and Droxidopa (Open-Label portions). All available assessments will be included in the evaluation of PCS values (scheduled, reassessments, and unscheduled). See Appendix D for the Lundbeck PCS Criteria.

The number and percentage of patients with at least one post-baseline PCS value will be summarized by parameter (haematology, clinical chemistry), treatment group (Double-Blind Period) and Droxidopa (Open-Label portions). All available assessments will be included in the evaluation of PCS values (scheduled, reassessments, and unscheduled).

For patients with post-baseline PCS values, listings of all PCS laboratory values sorted by site/patient will be provided including all available values for the specific parameter, with flagging of PCS values. Listings will include out-of-range flags (“H” for a value higher than the upper limit of the reference ranges, “L” for a value lower than the lower limit of the laboratory reference ranges).

If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater

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than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

The clinical safety laboratory data will be based on the Safety Set.

6.3.3 Vital signs and weight

Vital signs (seated BP, heart rate, respiratory rate, temperature) and weight will be measured at Screening (Visit 1), at the first visit of the Titration Period (Visit 2a) and at Visit 3; at Visit 3, a second seated BP will be measured ~2 hours post-dose. At Visits 4-12 (and at the Early Termination Visit), supine BP will be measured instead of seated BP.

Vital signs will be summarized by visits by treatment group (Double-Blind Period) and Droxidopa (Open-Label portions). The change from baseline to each scheduled post-dose assessment will also be summarized.

The number and percentage of patients with PCS value will be summarized by parameter, visit, treatment group (Double-Blind Period) and Droxidopa (Open-Label portions). All available assessments will be included in the evaluation of PCS values (scheduled and unscheduled). See Appendix D for the Lundbeck PCS Criteria.

The number and percentage of patients with at least one post-dose PCS value will be summarized by parameter, treatment group (Double-Blind Period) and Droxidopa (Open-Label portions). All available assessments (scheduled and unscheduled) will be included in the evaluation of PCS values.

For patients with post-baseline PCS values, listings of all PCS values sorted by site/patient will be provided including all available values for the specific parameter, with flagging of PCS values.

The vital signs data will be based on the Safety Set.

7 CHANGES FROM THE PLANNED ANALYSIS IN STUDY PROTOCOL

- Both clinician- and patient-reported CGI-S ratings will be analysed as quantitative variables instead of a categorical analysis. Quantitative analysis will be used to summarize both clinician- and patient-reported CGI-S scores at each scheduled visit as well as changes from baseline.
- The APTS has been renamed to FAS to avoid confusion (all patients were treated with droxidopa in the initial Open-Label part of the study).
- The per protocol analyses have been removed as they add no value to a late stage study.
- A modified BOCF has been introduced for imputation of missing data.
- The changes in the OHSA item 1 score during the Double-Blind treatment period will be explored using ANCOVA, with missing data imputed with LOCF as well as mBOCF.

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- Subgroup based on the cut-off date 17 March 2020 has been added to assess the potential impact of the COVID-19 pandemic.

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8 REFERENCES

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APPENDIX A - ORTHOSTATIC HYPOTENSION QUESTIONNAIRE (OHQ)

I. The Orthostatic Hypotension Symptom Assessment (OHSA)

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

1. **Dizziness, lightheadedness, feeling faint, or feeling like you might black out**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

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

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

3. **Weakness**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

4. **Fatigue**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

5. **Trouble concentrating**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

6. **Head/neck discomfort**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

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II. The Orthostatic Hypotension Daily Activity Scale (OHDAS)

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

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

1. Activities that require standing for a short time

CANNOT DO FOR OTHER REASONS ☐

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

2. Activities that require standing for a long time

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

3. Activities that require walking for a short time

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

4. Activities that require walking for a long time

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

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APPENDIX B - CLINICAL GLOBAL IMPRESSIONS - SEVERITY (CGI-S)

CLINICAL GLOBAL IMPRESSIONS - CLINICIAN

1) Severity of Illness

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

0 - Not assessed

1 - Normal, no OH

2 - Borderline OH

3 - Mild OH

4 - Moderate OH

5 - Marked OH

6 - Severe OH

7 - Among those patients most extremely ill with OH

CLINICAL GLOBAL IMPRESSIONS - PATIENT

1) Severity of Illness

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

0 - Not assessed

1 - Normal, no OH

2 - Borderline OH

3 - Mild OH

4 - Moderate OH

5 - Marked OH

6 - Severe OH

7 - Most extremely ill with OH

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APPENDIX C – ALGORITHMS/SAS REFERENCE CODES

- **Tables that require Kaplan-Meier estimates and log-rank test:**

```
PROC LIFETEST data=dataset timelist=(0 2 4 6 8 10 12) alpha=.05 outsurv=estim reduceout;
    TIME time*event(0);
    STRATA trt;
RUN;
```

Notes:

- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (0 = censored);
- Trt represents the treatment group;

- **Tables that require Cox proportional hazards model and 95% CIs of hazard ratios between treatments:**

```
PROC PHREG data=dataset;
    CLASS trt OHSA_1_score;
    MODEL time*event(0) = trt OHSA_1_score / ties=exact;
    CONTRAST 'a vs b' trt 1 -1 / estimate=exp;
RUN;
```

Notes:

- Trt represents the treatment group;
- OHSA_1_score represents the OHSA item #1 score (quantitative) prior to initial dosing at the first Titration Visit (Visit 2a);
- Time represents the time to event or time to censoring;
- Event represents the censoring indicator (0 = censored);
- Treatment order: 1 = Droxidopa, 2 = Placebo;

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APPENDIX D – LUNDBECK PCS CRITERIA

The Lundbeck PCS criteria are presented on the next page for clinical safety laboratory tests and vital signs.

The PCS criteria are either absolute, relative to the lower limit of the reference range (LLN) or the upper limit of the reference range (ULN), or relative to the baseline value.

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Lundbeck PCS Criteria for Clinical Safety Laboratory Tests

Laboratory Test	CDISC Term	Unit	PCS LOW	PCS HIGH
Haematology / Coagulation				
B-haemoglobin	HGB	g/dL	≤ 9.5 (women); ≤ 11.5 (men)	≥ 16.5 (women); ≥ 18.5 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women); ≤ 3.8 (men)	≥ 6.0 (women); ≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women); ≤ 0.37 (men)	≥ 0.50 (women); ≥ 0.55 (men)
B-MCV (mean cell volume)	MCV	fL	≤ 0.8 x LLN	≥ 1.2 x ULN
B-total leucocyte (white cell count)	WBC	x 10E9/L	≤ 2.8	≥ 16
B-neutrophils/leucocytes	NEUTLE	%	≤ 20	≥ 85
B-eosinophils/leucocytes	EOSLE	%		≥ 10
B-basophils/leucocytes	BASOLE	%		≥ 10
B-lymphocytes/leucocytes	LYMLE	%	≤ 10	≥ 75
B-monocytes/leucocytes	MONOLE	%		≥ 15
B-thrombocytes (platelet count)	PLAT	x 10E9/L	≤ 75	≥ 600
P-INR (prothrombin ratio)	INR	Ratio		≥ 2.0
B-prothrombin time	PT	Sec		≥ 18
Liver				
S-aspartate aminotransferase	AST	IU/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	IU/L		≥ 3 × ULN
S-bilirubin	BILI	µmol/L		≥ 34
S-bilirubin, direct	BILDIR	µmol/L		≥ 12
S-bilirubin, indirect	BILIND	µmol/L		≥ 22
S-alkaline phosphatase	ALP	IU/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	IU/L		≥ 200
S-alpha-glutathione S-transferase (alpha-GST)	GSTAL	µg/L		≥ 20
Kidney				
S-creatinine	CREAT	µmol/L		≥ 1.5 x ULN
B-urea nitrogen (BUN)	BUN	mmol/L		≥ 11
S-uric acid (urate)	URATE	µmol/L		≥ 510 (women); ≥ 630 (men)
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0
S-calcium	CA	mmol/L	≤ 1.8	≥ 3.0
S-chloride	CL	mmol/L	≤ 90	≥ 117
S-magnesium	MG	mmol/L	≤ 0.6	≥ 1.3
S-phosphate (phosphorus, (inorganic)	PHOS	mmol/L	≤ 0.65	≥ 1.95
S-bicarbonate	BICARB	mmol/L	≤ 12	≥ 38
Endocrine / Metabolic				
B-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.4	≥ 9.4
B-glucose, fasting	GLUC	mmol/L	≤ 3.0	≥ 6.0
S-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.9	≥ 11.1
S-glucose, fasting	GLUC	mmol/L	≤ 3.5	≥ 7.0
B-glycosylated haemoglobin, fasting	HBA1C	%		≥ 6.5
S-prolactin	PROLCTN	mIU/L		≥ 1350
S-thyrotropin/TSH	TSH	mIU/L	≤ 0.3	≥ 5.5

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Lundbeck PCS Criteria for Clinical Safety Laboratory Tests (continued)

Laboratory Test	CDISC Term	Unit	PCS LOW	PCS HIGH
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L		≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L		≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L		≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L		≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L		≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L		≥ 4.9
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	
S-HDL cholesterol, fasting	HDL	mmol/L	≤ 0.9	
Cardiac / Skeletal/Muscle				
S-creatine kinase (total)	CK	IU/L		≥ 400 (women); ≥ 750 (men)
S-creatine kinase MB isoenzyme	CKMB CKMBCK	µg/L %		≥ 8.5 or ≥ 3.5% of total CK
S-lactate dehydrogenase (total)	LDH	IU/L		≥ 750
S-troponin I	TROPONI	µg/L		≥ 1.5
S-troponin T	TROPONT	µg/L		≥ 0.4
Infection				
S-C-reactive protein	CRP	mg/L		≥ 25
S-globulin (total)	GLOBUL	g/L	≤ 15	≥ 55
Urine				
Urinary pH	PH		≤ 4	≥ 9

S=serum; B=whole blood; U=urine

Lundbeck PCS Criteria for Vital Signs, Weight/BMI, and Waist Circumference

Parameter	CDISC Term	Unit	PCS LOW	PCS HIGH
Waist circumference	WSTCIR	Cm	decrease ≥ 7%	increase ≥ 7%
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure[a]	OBP	mmHg	≤ -30	
Orthostatic pulse rate[a]	OPR	beats/min		≥ 20
Temperature[b]	TEMP	°C	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value

[a] For definition of orthostatic blood pressure and pulse rate, see text after Table 3

[b] Note, the diurnal variation may affect the temperature. Morning temperature is lower

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