CLINICAL PROTOCOL

RESTORE: A clinical study of patients with symptomatic neuRogenic orthostatic hypotEnsion to assess Sustained effecTs Of dRoxidopa thErapy

Compound:	23651-95-8
Compound Name:	Droxidopa
Study Number:	**16306A**
US IND Number:	077248
Protocol Number:	NOH402
Version Number:	Amendment 6.0
Version Date:	18 March 2021
Phase:	4

SIGNATURE PAGE

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PROTOCOL SYNOPSIS

Title:

A clinical study of patients with symptomatic neurogenic orthostatic hypotension to assess sustained effects of droxidopa therapy

Indication:

Symptomatic neurogenic orthostatic hypotension (NOH) in patients with Primary Autonomic Failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) or Pure Autonomic Failure (PAF)], or Non-Diabetic Autonomic Neuropathy (NDAN) or Dopamine Beta Hydroxylase (DBH) deficiency.

Rationale:

Symptomatic NOH in patients is thought to be a consequence of norepinephrine (NE) neurotransmission dysfunction, leading to low systolic blood pressure (SBP) and cerebral hypoperfusion. Therapy with droxidopa results in increased levels of NE which should lead to improved SBP and cerebral perfusion thereby reducing the signs and symptoms of NOH.

Droxidopa was approved in the US for the treatment of orthostatic dizziness, light-headedness or the "feeling that you are about to black out" in patients with a clinical diagnosis of symptomatic NOH due to Parkinson's disease, multiple system atrophy, pure autonomic failure, non-diabetic autonomic neuropathy, or dopamine-β-hydroxylase deficiency. Effectiveness was established in short-term (≤ 2 week) studies; effectiveness longer than 2 weeks has not yet been demonstrated. This long-term study will evaluate the durability of the clinical benefit in NOH patients treated with droxidopa in a randomized withdrawal design (time to treatment intervention study).

Objectives:

Primary objective:

- To evaluate the time to treatment intervention in patients with PD, MSA, PAF, NDAN or DBH Deficiency who have been previously stabilized with droxidopa therapy for symptoms of NOH (dizziness, light-headedness, or feelings that they are about to black out)

Secondary objectives:

- 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
    - Clinicians' and patients' clinical global impression of severity (CGI-S)

- To evaluate the long-term safety and tolerability of droxidopa in patients with symptomatic NOH.

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, consisting of 5 periods (See Figure 1):

- 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

Study Country Locations:

United States

Study Duration:

The maximum duration of patient participation is 36 weeks.

Number of Patients/Sites:

Across approximately 125 study sites, a sufficient number of patients will be screened to randomize 240 patients into the Double-Blind Period (120 patients per treatment group).

Study Population:

Adult patients with symptomatic NOH associated with Primary Autonomic Failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) or Pure Autonomic Failure (PAF)] or Non-Diabetic Autonomic Neuropathy (NDAN) or Dopamine Beta Hydroxylase (DBH) deficiency.

Inclusion Criteria (All Patients):

1. 18 years or older and able to stand (with or without limited assistance)
2. Clinical diagnosis of symptomatic orthostatic hypotension associated with Primary Autonomic Failure (PD, MSA or PAF) or NDAN or DBH Deficiency
3. Score of at least 4 or greater on Orthostatic Hypotension Symptom Assessment (OHSA) Item #1 (measured at Screening [Visit 1] and the first Titration Visit [Visit 2a] prior to dosing)
4. A documented drop of at least 20 millimeters of mercury (mmHg) in SBP, within 3 minutes of standing. This can either be documented in the patient history or assessed during Screening prior to the first Titration Visit (Visit 2a)

5. Provide written informed consent to participate in the study and understand that they may withdraw their consent at any time without prejudice to their future medical care

Additional inclusion criteria for patients taking prescribed droxidopa prior to study entry:

Patients who are taking prescribed droxidopa therapy are eligible to participate in the study if they meet the other inclusion criteria (1-5 above) and also have been on a stable dose of prescribed droxidopa for at least 2 weeks prior to the Screening Visit (Visit 1). In addition, they must meet either of the following at the Screening Visit (Visit 1):

6. The patient's Visit 1 OHSA Item #1 score is ≥ 7 **AND** the prescribed dose is ≤ 300 mg three times daily (TID); OR
7. The patient's Visit 1 OHSA Item #1 score is ≤6 **AND** worsens by ≥ 2 units when retested after washing out of droxidopa for at least 3 days

Exclusion Criteria (All Patients):

1. In the investigator's opinion, the patient is not able to understand or cooperate with study procedures.
2. Known or suspected alcohol or substance use disorder within the past 12 months (DSM-5 criteria)
3. Women who are pregnant or breastfeeding
4. Women of childbearing potential (WOCP) who are not using at least one method of contraception with their partner
5. Sustained supine hypertension greater than or equal to 180 mmHg systolic or 110 mmHg diastolic. Sustained is defined as the average of 3 observations each at least 10 minutes apart with the patient having been supine and at rest for at least 5 minutes prior to each measurement.
6. Untreated closed angle glaucoma
7. Diagnosis of hypertension that requires treatment with antihypertensive medications (short-acting antihypertensives to treat nocturnal supine hypertension are allowed in this study)
8. Any significant uncontrolled cardiac arrhythmia
9. History of myocardial infarction or stroke within the past 2 years
10. Current unstable angina
11. Congestive heart failure (NYHA Class 3 or 4)
12. Diabetic autonomic neuropathy
13. History of cancer within the past 2 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma or cervical cancer *in situ*

14. Gastrointestinal condition that may affect the absorption of Investigational Medicinal Product (e.g., ulcerative colitis, gastric bypass)
15. Any major surgical procedure within 30 days prior to the first Titration Visit (Visit 2a)
16. Currently receiving any investigational drug or have received an investigational drug within 28 days prior to the first Titration Visit (Visit 2a)
17. Any condition or laboratory test result, which in the Investigator's judgment, might result in an increased risk to the patient, or would affect their participation in the study
18. The Investigator has the discretion to exclude a patient if, for any reason, they feel the patient is not a good candidate for the study or will not be able to follow study procedures
19. In the Investigator's opinion, the patient has increased risk of intracranial hemorrhage. For example: history of brain aneurysm or current use of anticoagulants in the drug classes of Coumarins, Factor Xa Inhibitors, and Direct Thrombin Inhibitors

End of Titration Criteria:

At the end of the Titration Period (Visit 3), patients must have an Acute Dizziness score that is ≥ 2 units lower (improved) than the Visit 2a OHSA Item #1 score. Patients who do not meet this criterion will be withdrawn from the study.

Randomization Criteria:

At the end of the Open-Label Period (Visit 6), patients must have an OHSA Item #1 score that is ≥ 2 units lower (improved) than the Visit 2a score. Patients who do not meet this criterion will be withdrawn from the study.

Treatment Intervention Criteria (Double-Blind Treatment Period):

At each visit during the Double-Blind Period (Visits 7-12), patients will be evaluated for the following criteria:

1. OHSA Item #1 ≥ 2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the investigator; OR
2. OHSA Item #1 ≥ 2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
3. OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
4. Patient stops IMP or withdraws from study for patient-reported lack of efficacy

If a patient meets any of these criteria for treatment intervention during the Double-Blind Period, the patient will be withdrawn from the study.

Investigational Medicinal Product and Formulation:

Droxidopa (also known as L-threo-3,4-dihydroxyphenylserine, or L-DOPS) in 100, 200, and 300 mg capsules

Placebo capsules (to match droxidopa 100, 200, and 300 mg capsules)

Dosage and Administration:

During the Titration Period (Visits 2a-2f) and Open-Label Period (Visits 3-5), patients will receive 100, 200, 300, 400, 500, or 600 mg 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 Open-Label Period. No dose changes are allowed after Visit 5.

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). No dose changes are permitted during the Double-Blind Period.

Statistical Analysis:

Sample Size Determination:

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 favor of droxidopa, a 240-subject sample size would be expected to result in 48 events, providing ~51% power to detect a difference between droxidopa and placebo. A blinded review conducted in July 2020 indicated that the event rate may be higher than originally assumed and, if accurate, 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.

Primary Efficacy Endpoint:

Time-to-intervention. Need for intervention is defined as meeting **ANY** of the following criteria during the Double-Blind Period:

- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the investigator; OR

- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
- Patient stops 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. Patients who withdraw without meeting criteria for treatment intervention will be censored at the time of withdrawal; patients who do not meet criteria for treatment intervention at the end of the Double-Blind Period (Visit 12) will be censored at the time of study completion.

The primary endpoint will be summarized using Kaplan-Meier method. The primary analysis is the log-rank test to compare the two treatment groups. In addition, the Cox regression model will be used to estimate the hazard ratio. Furthermore, the following sensitivity analyses using the same approach will be conducted:

- Time-to-intervention defined as the criteria specified above; or OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the last visit of the Double-Blind Period (Visit 12).
- Cox regression analysis of time to intervention based on various definitions above.

Secondary Endpoints: The Key Secondary Endpoint

Time to all cause discontinuation is the key secondary endpoint.

A gate keeping strategy will be applied in the testing of this key secondary endpoint. That is, the Log-rank test of this secondary endpoint will be performed at the nominal alpha level of 2-sided 0.05 only if the primary endpoint reaches statistical significance in the primary analysis. This strategy ensures the overall type 1 error rate is preserved.

Other Secondary Endpoints:

Efficacy measures of droxidopa versus placebo:

- Mean change in OHSA Item #1 score from Randomization (Visit 6) to all post-Randomization visits
- Mean change in Orthostatic Hypotension Questionnaire (OHQ) composite score from Randomization (Visit 6) to all post-Randomization visits (Visits 7-12)
- Clinician-rated CGI-S at all post-Randomization visits (Visits 7-12)
- Patient-rated CGI-S at all post-Randomization visits (Visits 7-12)
- Proportion of patients who need intervention over the 12-week Double-Blind Treatment period

Adverse events, vital signs, and clinical safety laboratory assessments will be observed throughout the entire study. Safety parameters from the open-label portions of the study (Titration Period and Open-Label Period) and the Double-Blind Period will be reported separately.

Study Procedures:

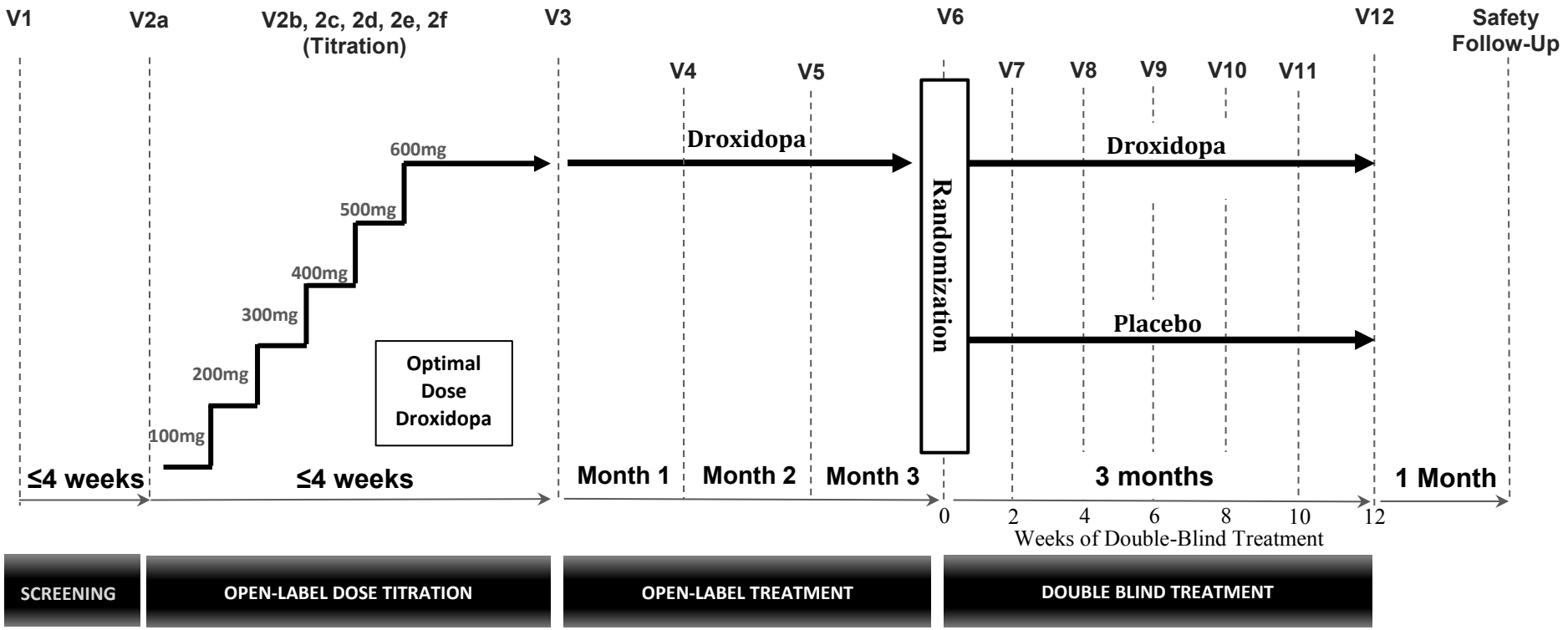
Refer to the Study Schedule/Flowchart (Table 1) on the following page for a summarization of the procedures and assessments conducted during this study.

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				✓	✓	✓	✓	✓	

[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

Figure 1: Study Design



Note: Patients are anticipated to have up to 6 titration visits; the exact number of Titration Visits for a given patient will depend upon the number of Titration Visits required to reach their optimal dose.

Double-Blind Period is 3 months in duration. Week 0 of the Double-Blind Period begins with Randomization. Visits in the Double-Blind Period will occur at Weeks 2, 4, 6, 8, 10, and 12.

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APPENDICES

Appendix 1: Questionnaires

Appendix 1.1: Orthostatic Hypotension Questionnaire

Appendix 1.2: Clinical Global Impressions - Severity

TERMS AND ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase (SGPT)
AP	alkaline phosphatase
APTS	all patients treated set
AST	aspartate transaminase (SGOT)
BP	blood pressure
BUN	blood urea nitrogen
CGI-S	Clinical Global Impressions - Severity
CPK	creatine phosphokinase
CRA	clinical research associate
CNS	central nervous system
CRO	contract research organization
CSR	clinical study report
DBH	dopamine beta(β) hydroxylase
DBP	diastolic blood pressure
DDC	DOPA decarboxylase
DMC	data monitoring committee
DOPA	3,4-dihydroxyphenylalanine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPV-US	global pharmacovigilance – United States
HDPE	high-density polyethylene
HR	heart rate

Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IMP	investigational medicinal product
INN	international non-proprietary name
IRB/IEC	institutional review board/independent ethics committee
ITT	intent-to-treat
IWRS	interactive web response system
L-DOPS	L-threo-3,4-dihydroxyphenylserine (droxidopa)
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHPG	3-methoxy-4-hydroxy-phenylglycol
mmHg	millimeters of mercury
MSA	multiple system atrophy
NDAN	non-diabetic autonomic neuropathy
NE	norepinephrine
NOH	neurogenic orthostatic hypotension
NRIs	norepinephrine reuptake inhibitors
NYHA	New York Heart Association
OH	orthostatic hypotension
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHQ	Orthostatic Hypotension Questionnaire
OHSA	Orthostatic Hypotension Symptom Assessment
OST	orthostatic standing test
PAF	pure autonomic failure
PD	Parkinson’s disease

Abbreviation	Definition
PI	Package Insert
PK	pharmacokinetic
PPS	per protocol set
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SNRIs	serotonin–norepinephrine reuptake inhibitors
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TID	three times per day
TMF	trial master file
US	United States
WOCP	women of child-bearing potential

1. INTRODUCTION

1.1 Symptomatic Neurogenic Orthostatic Hypotension

Symptomatic neurogenic orthostatic hypotension (NOH) in patients is thought to be a consequence of norepinephrine neurotransmission dysfunction, leading to low systolic blood pressure (SBP) and cerebral hypoperfusion. SBP is transiently and minimally decreased in healthy individuals upon standing. Normal physiologic feedback mechanisms work through neurally-mediated pathways to maintain the standing blood pressure (BP), and thus maintain adequate cerebral perfusion. The compensatory mechanisms that regulate BP upon standing are dysfunctional in patients with symptomatic NOH, a condition that may lead to inadequate cerebral perfusion with accompanying symptoms of syncope, dizziness or lightheadedness, unsteadiness and blurred or impaired vision, among other symptoms. Symptomatic NOH may be a severely disabling condition which can seriously interfere with the quality of life of afflicted patients.

Many of the currently available therapeutic options provide some symptomatic relief in a subset of patients, but are relatively ineffective and are often accompanied by severe side effects that limit their usefulness. Support garments (e.g., tight-fitting leotards) may prove useful in some patients, but are difficult to don without family or nursing assistance, especially for older patients. Midodrine, fludrocortisone, methylphenidate, ephedrine, indomethacin and dihydroergotamine are some of the pharmacological interventions that have been used to treat orthostatic hypotension (OH), although, of these medications, only midodrine is specifically approved for this indication.

The only other medication approved for this indication is droxidopa. Therapy with droxidopa has been shown to result in increased levels of norepinephrine (NE) which leads to improved SBP and cerebral perfusion thereby reducing the signs and symptoms of symptomatic NOH. As of 2014, droxidopa has been approved in the United States (US) for the treatment of orthostatic dizziness, light-headedness or the "feeling that you are about to black out" in patients with a clinical diagnosis of symptomatic NOH due to Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), non-diabetic autonomic neuropathy (NDAN), or dopamine-β-hydroxylase (DBH) deficiency. Effectiveness was established in short-term studies and efficacy beyond two weeks has not yet been demonstrated. This long-term study will evaluate the durability of the clinical benefit in patients with symptomatic NOH treated with droxidopa.

1.2 Background

1.2.1 Droxidopa

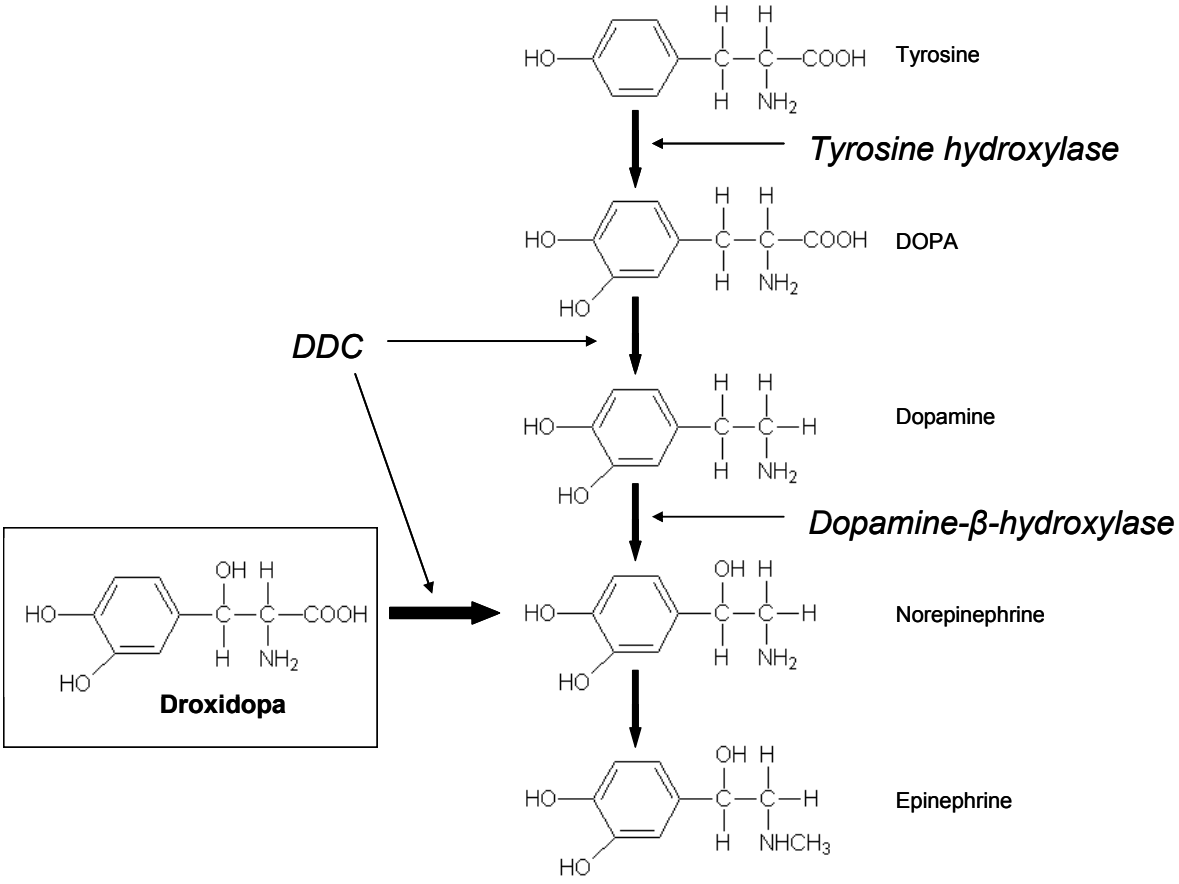
Droxidopa [also, known as L-threo-3,4-dihydroxyphenylserine, or L-DOPS] is the International Non-proprietary Name (INN) for a synthetic amino acid precursor of NE, which was originally developed by Sumitomo Dainippon Pharmaceuticals Co., Limited, Japan (SDP). It has been approved for use in Japan since 1989 and in the United States (US) since February 2014. Droxidopa has been shown to improve symptoms of orthostatic hypotension that result from a

variety of conditions including Shy-Drager syndrome (Multiple System Atrophy), Pure Autonomic Failure (PAF), and Parkinson's disease (PD). There are four stereoisomers of L-DOPS; however, only the L-threo-enantiomer (droxidopa) is biologically active.

1.2.2 Pharmacology

Droxidopa is decarboxylated by 3,4-dihydroxyphenylalanine (DOPA) decarboxylase (DDC), and is directly converted to NE (see Figure 1).

Figure 1: Biosynthesis of Norepinephrine from Droxidopa



The exact mechanism of action of droxidopa in the treatment of symptomatic NOH has not been precisely defined; however, its NE replenishing properties with concomitant recovery of decreased noradrenergic activity are considered to be of major importance.

1.2.3 Pre-clinical studies with Droxidopa

Numerous studies in animal models support central and peripheral mechanisms of action of droxidopa. Central nervous system (CNS) studies have shown the ability of droxidopa to increase the content of NE and 3-methoxy-4-hydroxy-phenylglycol (MHPG), the main metabolite of NE, in the brain of normal animals. Droxidopa also replenished the levels of NE in the brain of NE-

depleted animals. These results suggest that droxidopa acts as a NE precursor in the CNS. Droxidopa also increases the release of NE from nerve endings in experiments using brain synaptosomes and slices.

Studies of the peripheral action of droxidopa show that droxidopa increased heart rate (HR) and elevated BP. Inhibitors of DDC and α-adrenoceptors blocked this effect, which suggests that these changes can be attributed to peripheral conversion of droxidopa to NE rather than a direct action of droxidopa itself. Droxidopa inhibited the fall in BP associated with orthostatic changes, and accelerated the recovery from low BP in rats whose sympathetic nerves were chemically destroyed. The efficacy of droxidopa in OH is, therefore, thought to be the result of a compensatory increase in the overall BP or a possible improvement in the BP reflex process.

Further details of preclinical studies with droxidopa are provided in the Package Insert (PI).

1.2.4 Clinical studies with Droxidopa

To date, Lundbeck NA, Ltd. (Lundbeck; formerly Chelsea Therapeutics, Inc.) has completed three placebo-controlled Phase III studies and two long-term extension Phase III studies with droxidopa in patients with NOH. Lundbeck has also sponsored a fed/fast pharmacokinetic (PK) study with healthy volunteers (NOH101), a bioequivalence study in healthy volunteers (NOH104), a 24-hour BP monitoring study (NOH305) and a dedicated thorough QTc study (NOH102).

1.2.5 Efficacy Profile

To date, Lundbeck has completed three Phase III studies of droxidopa for the treatment of symptomatic NOH:

- A multi-center, double-blind, randomized, placebo-controlled, parallel-group, induction-design study using the OHQ composite score as the prospectively-defined primary outcome variable to assess the clinical effect of droxidopa in patients with symptomatic NOH and PD, MSA, PAF, DBH Deficiency, or NDAN (Study NOH301)

- A multi-center, double-blind, randomized, placebo-controlled, parallel-group, withdrawal-design study using the Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 (dizziness) as the prospectively-defined primary outcome variable and the OHQ composite score as a *post-hoc* analysis to assess the clinical effect of droxidopa in patients with symptomatic NOH and PD, MSA, PAF, DBH Deficiency, or NDAN and to study population PK/Pharmacodynamic parameters (Study NOH302)

- A multi-center, double-blind, randomized, parallel-group, placebo-controlled study to assess the clinical effect of droxidopa in the treatment of symptomatic NOH in patients with PD (Study NOH306)

Lundbeck has also completed two Phase III, multi-center long-term open-label extension studies with droxidopa in patients with symptomatic NOH and PD, MSA, PAF, DBH Deficiency, or NDAN (Studies NOH303 and NOH304).

In addition, numerous other studies have also shown droxidopa to be effective in the improvement of OH symptoms in PD patients (Birkmayer et al., 1983, Narabayashi et al., 1987, Yanagisawa et al., 1998), and in patients with PD or MSA (Sumitomo Pharmaceuticals Europe Limited CSR S10002, 2002).

The collective data from Lundbeck's clinical development program (further details of which are provided in the PI) demonstrate that treatment with droxidopa results in clinically meaningful improvements in the symptoms of NOH, including dizziness/light-headedness, vision, weakness, fatigue, trouble concentrating, head/neck discomfort, and their impact on patients' ability to perform daily activities that require standing or walking. Treatment with droxidopa also results in significant increases in standing BP in patients with NOH. These increases in BP were generally similar when standing compared to when supine.

Based on the results of Lundbeck's clinical program, droxidopa was approved in the US in 2014 for, "the treatment of orthostatic dizziness, light-headedness or the "feeling that you are about to black out" in patients with a clinical diagnosis of symptomatic NOH due to Parkinson's disease, multiple system atrophy, pure autonomic failure, non-diabetic autonomic neuropathy, or dopamine-β-hydroxylase deficiency." However, durable clinical benefits with chronic use beyond 2 weeks have not been demonstrated.

1.2.6 Safety Profile

The collective data from Lundbeck's clinical development program demonstrate that droxidopa is safe and well tolerated in patients with symptomatic NOH associated with primary autonomic failure (PD, MSA and PAF), DBH Deficiency, or NDAN. Data from this program indicates that droxidopa treatment is associated with a small increase in supine hypertension (SBP >180 mmHg), and an increase in the incidence of headaches, dizziness, and nausea. Data from the SDP-sponsored clinical studies conducted in Europe and the large safety database of patients treated in Japan, where droxidopa has been marketed for over 20 years, further support the safety of droxidopa. For further information on the safety of droxidopa, refer to the PI.

1.3 Study Rationale

Symptomatic NOH in patients is thought to be a consequence of NE neurotransmission dysfunction, leading to low SBP and cerebral hypoperfusion. Therapy with droxidopa results in increased levels of NE which leads to improved SBP and cerebral perfusion, thereby reducing the signs and symptoms of symptomatic NOH.

Droxidopa was approved in the US for the treatment of orthostatic dizziness, light-headedness or the "feeling that you are about to black out" in patients with a clinical diagnosis of symptomatic NOH due to PD, MSA, PAF, NDAN, or DBH deficiency. Effectiveness was established in short-term studies. This long-term study will evaluate the durability of the clinical benefit in patients with symptomatic NOH treated with droxidopa in a randomized withdrawal design (time to intervention study).

1.3.1 Selection of Droxidopa Dose and Schedule of Administration

Single rising doses of droxidopa (100, 300, 600, and 900 milligrams (mg)) have been shown to be well tolerated in healthy male Japanese and Caucasian volunteers. Droxidopa pharmacokinetics are roughly linear, but less than dose-proportional, for single doses between 100 and 2000 mg. The upper limit of individual doses for this study will not exceed 600 mg TID (1800 mg/day).

In Japan, the recommended dosing regimen for NOH-associated indications is to administer the daily maintenance dose of droxidopa in divided doses three times a day. Pharmacokinetic modeling based on Phase I data in healthy volunteers indicate no accumulation of droxidopa with multiple doses of 100 mg or 300 mg administered three times per day. Importantly, the reduced fluctuation in droxidopa plasma levels expected with three times a day dosing may help to maintain a therapeutic effect in NOH patients throughout the day, by maintaining a threshold NE level for beneficial pressor effects. Maintenance of plasma plateau drug levels is supported by divided daily doses, especially for a drug like droxidopa, which has a half-life of approximately 1.5 hours in humans. Increased dosing frequency is also supported by the findings of Kachi et al. (1988), who demonstrated decreased muscle sympathetic activity and reoccurrence of OH symptoms in a Shy-Drager patient 3 hours post-dosing of droxidopa despite concomitant peak NE levels, suggesting a shorter duration of action than what might be predicted from plasma NE concentrations. Lower peak plasma concentrations provided by split daily dosing should augment the drug's safety by reducing the incidence of any peak concentration-related side effects.

Lundbeck has conducted studies of droxidopa in more than 650 patients with pure autonomic failure (PAF) associated with symptomatic NOH and demonstrated that individually optimized doses from 100 to 600 mg TID are safe and effective for the treatment of symptomatic NOH associated dizziness or lightheadedness.

The present study will utilize an open-label dose titration, during which patients are titrated on droxidopa, based on efficacy and tolerability as assessed by OHSA Item #1, BP measurements and adverse events (AEs). The individual visits within the open-label dose titration period do not have fixed visit windows. Investigators should tailor the titration schedule based on individual patients' response to therapy and their own clinical judgment. Patients should be up-titrated until they reach 600mg TID or until a safety or tolerability concern prevent further up-titration. The entire dose-titration period will last for up to 4 weeks from the date of the initial titration visit (Visit 2a). The initial dose will be 100 mg TID, and increase in 100 mg TID steps to a maximum dose of 600 mg

TID. Once the optimized dose has been identified, patients will then enter a 12-week open-label dose treatment period, followed by a 12-week, double-blind, randomized withdrawal period on their individualized dose of investigational medicinal product (IMP). Doses are to be timed such that the first dose is taken upon waking and then taken approximately every 4 hours thereafter, with the final dose taken early enough (late afternoon) to minimize drug effects during night-time sleeping hours.

1.3.2 Selection of Primary Efficacy Endpoint

Time-to-intervention is the primary endpoint. 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.

During the Double-Blind Period, eligible patients will be randomized 1:1 to either their stable regimen of droxidopa or matching placebo. Patients will be withdrawn from the study if they require treatment intervention for their NOH symptoms, defined by meeting ANY of the following criteria:

1. OHSA Item #1 $\geq$ 2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
2. OHSA Item #1 $\geq$ 2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
3. OHSA Item #1 $\geq$ 2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
4. Patient stops IMP or withdraws from study for patient-reported lack of efficacy

Time-to-intervention measures clinically relevant deterioration of the patient's NOH symptoms. Importantly, patients are not required to remain on ineffective treatment. Patients will be withdrawn from the study if treatment fails.

The criteria for treatment intervention are predominantly based on the OHSA Item #1 score. This instrument has both strengths and limitations. One limitation is that it is has high variability. Conditions such as poor hydration and diarrhea can cause worsening of OHSA Item #1 scores independent of treatment effects. Therefore, the time-to-intervention endpoint requires corroboration to ensure that worsening OHSA Item #1 scores represents a true event. Investigator judgment is one way, but not the only way, to corroborate worsening of dizziness symptoms. Thus:

- If a patient has worsening OHSA Item #1 at any one visit and the investigator agrees that the worsening condition represents a treatment failure, then the patient is considered a treatment failure. If, however, the investigator does not consider the worsening OHSA Item #1 score at any one visit to be a true treatment failure, then the patient will continue

in the study. This gives the investigator the opportunity to ensure that non-pharmacologic care is optimized and any other medical conditions are treated appropriately.

- If the patient continues to have worsening OHSA Item #1 at the second consecutive clinic visit, then the patient is considered a treatment failure. This criterion is independent of investigator judgment.
- If the patient fails to return to the clinic after a visit with a worsened OHSA Item #1 score, the patient is considered a treatment failure by definition. This criterion is independent of investigator judgment.
- Also, a patient who stops study drug or withdraws from the study for patient-reported loss of efficacy is also a treatment failure. This criterion is also independent of investigator judgment.

Altogether, these criteria represent a balanced approach in an attempt to identify true events of treatment failure.

2. STUDY OBJECTIVES

The study is designed to evaluate the clinical efficacy and safety of droxidopa versus placebo over a 12-week double-blind treatment period in patients with symptomatic NOH who have previously received up to 16 weeks of open-label treatment with an individually optimized dose of droxidopa (randomized withdrawal design).

- Primary objective:
    - To evaluate the time to treatment intervention in patients with PD, MSA, PAF, NDAN or 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)

- Secondary objectives:
    - To evaluate the long-term efficacy of droxidopa in patients with symptomatic NOH measured by
        - Discontinuation for any reason (all cause discontinuation)
        - Composite OHQ scores
        - Clinicians' and patients' clinical global impression of severity (CGI-S)
        - To evaluate the long-term safety and tolerability of droxidopa in patients with symptomatic NOH.

3. STUDY METHODS

3.1 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, consisting 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

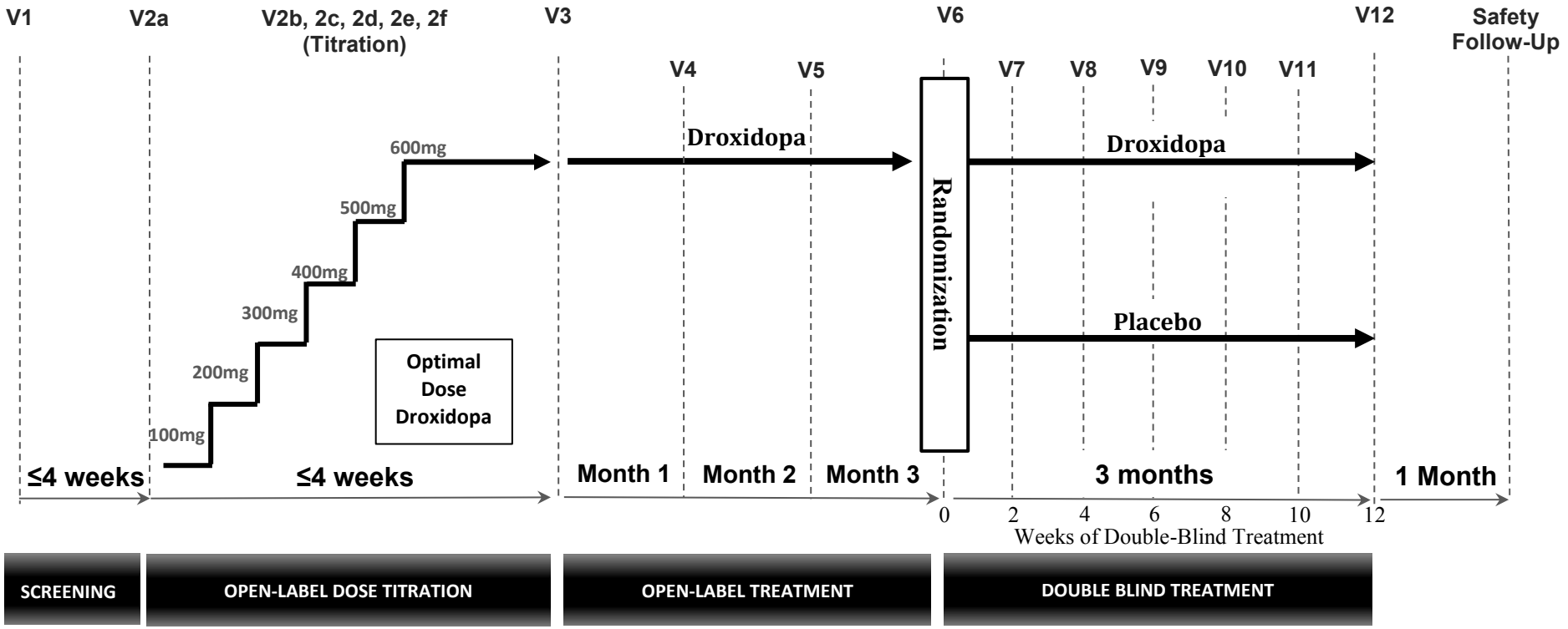
3.2 Sites

The study will be conducted in approximately 125 study sites in the United States.

3.3 Number of Patients and Assignment of Treatment Groups

A sufficient number of patients will be screened to allow 240 patients to be randomized into the double-blind period (120 patients per treatment group).

Figure 2: Study Design



Note: Patients are anticipated to have up to 6 titration visits; the exact number of Titration Visits for a given patient will depend upon the number of Titration Visits required to reach their optimal dose.

Double-Blind Period is 3 months in duration. Week 0 of the Double-Blind Period begins with Randomization. Visits in the Double-Blind Period will occur at Weeks 2, 4, 6, 8, 10, and 12.

3.4 Study Population

Adult patients with symptomatic NOH associated with primary autonomic failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) or Pure Autonomic Failure (PAF)] or Non-Diabetic Autonomic Neuropathy (NDAN) or Dopamine Beta Hydroxylase (DBH) deficiency.

3.4.1 Inclusion Criteria (All Patients)

1. 18 years or older and able to stand (with or without limited assistance)
2. Clinical diagnosis of symptomatic orthostatic hypotension associated with Primary Autonomic Failure (PD, MSA or PAF) or NDAN or DBH Deficiency
3. Score of at least 4 or greater on Orthostatic Hypotension Symptom Assessment (OHSA) Item #1 (measured at Screening [Visit 1] and the first Titration Visit [Visit 2a] prior to dosing)
4. A documented drop of at least 20 mmHg in SBP, within 3 minutes of standing. This can either be documented in the patient history or assessed during Screening prior to the first Titration Visit (Visit 2a)
5. Provide written informed consent to participate in the study and understand that they may withdraw their consent at any time without prejudice to their future medical care

3.4.1.1 Patients who are taking prescribed droxidopa therapy

Patients who are currently taking prescribed droxidopa therapy are eligible to participate in the study if they meet the other inclusion criteria (1-5 above) and also have been on a stable dose of prescribed droxidopa for at least 2 weeks prior to the Screening Visit (Visit 1). In addition, they must meet either of the following at the Screening Visit (Visit 1):

6. The patient's Visit 1 OHSA Item #1 score is ≥ 7 **AND** the prescribed dose is ≤ 300 mg three times daily (TID); OR
7. The patient's Visit 1 OHSA Item #1 score is ≤6 **AND** worsens by ≥ 2 units when retested after washing out of droxidopa for at least 3 days

These patients will be required to wash out of their current droxidopa treatment regimen for at least 3 days and will be required to go through the same titration procedures as all other patients in the study (see Section 3.5.1.1).

3.4.2 Exclusion Criteria (All Patients)

1. In the Investigator's opinion, the patient is not able to understand or cooperate with study procedures.
2. Known or suspected alcohol or substance use disorder within the past 12 months (DSM-5 criteria)
3. Women who are pregnant or breastfeeding

4. Women of childbearing potential (WOCP) who are not using at least one method of contraception with their partner
5. Sustained supine hypertension greater than or equal to 180 mmHg systolic or 110 mmHg diastolic. Sustained is defined as the average of 3 observations each at least 10 minutes apart with the patient having been supine and at rest for at least 5 minutes prior to each measurement.
6. Untreated closed angle glaucoma
7. Diagnosis of hypertension that requires treatment with antihypertensive medications (short-acting antihypertensives to treat nocturnal supine hypertension are allowed in this study)
8. Any significant uncontrolled cardiac arrhythmia
9. History of myocardial infarction or stroke within the past 2 years
10. Current unstable angina
11. Congestive heart failure (NYHA Class 3 or 4)
12. Diabetic autonomic neuropathy
13. History of cancer within the past 2 years other than a successfully treated, non-metastatic cutaneous squamous cell or basal cell carcinoma or cervical cancer *in situ*
14. Gastrointestinal condition that may affect the absorption of Investigational Medicinal Product (e.g., ulcerative colitis, gastric bypass)
15. Any major surgical procedure within 30 days prior to the first Titration Visit (Visit 2a)
16. Currently receiving any investigational drug or have received an investigational drug within 28 days prior to the first Titration Visit (Visit 2a)
17. Any condition or laboratory test result, which in the Investigator's judgment, might result in an increased risk to the patient, or would affect their participation in the study
18. The Investigator has the discretion to exclude a patient if, for any reason, they feel the patient is not a good candidate for the study or will not be able to follow study procedures
19. In the Investigator’s opinion, the patient has increased risk of intracranial hemorrhage. For example: history of brain aneurysm or current use of anticoagulants in the drug classes of Coumarins, Factor Xa Inhibitors, and Direct Thrombin Inhibitors (see Prohibited Medications section 4.8.3)

3.4.3 End of Titration Criteria

At the end of the Titration Period (Visit 3), patients must have an Acute Dizziness score that is ≥ 2 units lower (improved) than the Visit 2a OHSA Item #1 score. Patients who do not meet this criterion will be withdrawn from the study.

3.4.4 Randomization Criterion

At the end of the Open-Label Period (Visit 6), patients must have an OHSA Item #1 score that is ≥ 2 units lower (improved) than the Visit 2a score. Patients who do not meet this criterion will be withdrawn from the study.

3.4.5 Treatment Intervention Criteria (Double-Blind Treatment Period)

At each visit during the Double-Blind Period (Visits 7-12), patients will be evaluated for the following criteria:

1. OHSA Item #1 ≥ 2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
2. OHSA Item #1 ≥ 2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
3. OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
4. Patient stops IMP or withdraws from study for patient-reported lack of efficacy

If a patient meets any of these criteria for treatment intervention during the Double-Blind Period, the patient will be withdrawn from the study.

3.5 Study Visit and Assessment Schedule

All study visits are to be conducted as out-patient visits. Titration Period visits 2b-2f and the Safety Follow-Up Visit (Visit 13) may be conducted via telephone or video link. Double-Blind Period visits 7, 9, and 11 will be conducted via telephone or video link. Written informed consent must be obtained before any study-specific procedures are undertaken.

3.5.1 Screening (Visit 1)

Screening assessments are to be conducted within 28 days of the patient's initial Titration Visit (Visit 2a) to allow the Investigator sufficient time to review laboratory results and determine if the patient is eligible for study participation.

The Investigator, or qualified designee, will conduct the following procedures at the visit and record the data in the eCRF provided:

- Conduct of informed consent procedures
- Assignment of patient identification number
- Review of inclusion and exclusion criteria
- Demography

- Medical history
- Review of concomitant medications
- Review of AEs
- Physical examination
- Vital signs (seated BP, HR, respiratory rate (RR), temperature), weight and height
- Orthostatic Standing Test (required only if OH is not documented in medical history)
- Pregnancy test for WOCP
- 12-lead electrocardiogram (ECG) recording
- Clinical Symptoms: OHQ
- Blood samples for hematology and biochemistry
- Urine sample for urinalysis

Screening laboratory test results and ECG reports must be reviewed and assessed by the Investigator or designee prior to the initial Titration Visit (Visit 2a).

3.5.1.1 Patients who are taking prescribed droxidopa therapy

Patients who are taking prescribed droxidopa therapy are eligible to participate in the study if they meet the additional inclusion criteria for this patient subgroup (see Section 3.4.1.1) in addition to all other inclusion / exclusion criteria. Discontinuation of prescribed droxidopa should not occur prior to signing the informed consent. It is permitted, based on the Investigator's judgment, for patients to continue their prescribed droxidopa therapy while eligibility is being assessed in the screening period. However, it is required that patients discontinue droxidopa for at least 3 days before entering the Open Label Dose Titration Period at Visit 2a.

Eligible patients will begin the Titration Period at 100 mg TID. Study procedures will be the same as patients who have not previously been prescribed droxidopa.

3.5.1.2 Re-Screening of patients

Patients who Screen Fail may be re-screened at a later date if, in the Investigator's opinion, circumstances have changed such that the patient may now be an appropriate candidate for the study. Approval by the Lundbeck Medical Monitor must be obtained for a patient to be re-screened. A patient will only be allowed to be re-screened once.

At the time of re-screening, the patient must sign a new Informed Consent Form (ICF) and will be assigned a new screening number. A re-screened patient must complete a full new Screening Visit (Visit 1), and all eligibility criteria must be re-assessed when re-screened.

The following information will also be recorded in the eCRF at the time of re-screening:

- That the patient has previously been screened for the study
- That re-screening has been authorized by the Lundbeck Medical Monitor
- The screening number that was assigned to the patient at the previous screening visit

For a re-screened patient, none of the data from the original Screening Visit, where the patient failed to enter the study, will be used in the statistical analysis.

3.5.2 Open-Label Dose Titration (Visits 2a-2f)

It is anticipated that patients will have up to 6 visits during the Titration Period (Visits 2a-2f); some patients may have as few as 2 visits. It is possible that a patient may have more than 6 visits during the Titration Period in order to properly ascertain their optimal dose of IMP. In these cases, subsequent visits would be considered as 2g, 2h, etc., and would be entered as Unscheduled visits in the eCRF. All open-label dose titration visits (except for Visit 2a) may be completed on site or via phone or video link.

Visits within the Titration Period do not have fixed visit windows, although there should be a minimum of 1 day between each Titration Visit. Patients should be titrated up until they reach 600mg TID or until they reach one of the Titration stopping criteria (see Section 3.5.2.3). Increases in dose must be at least 1 day apart. The entire dose-titration schedule is to be completed, and the patient's optimal dose reached, within the 4-week titration period, which begins with the initial Titration Visit (Visit 2a). At the end of the Titration Period, patients will proceed to Visit 3 where their End of Titration criteria will be assessed (see Section 3.5.3.1). If these criteria are met, they will proceed into the Open-Label Period.

Dose titration will begin with an initial dose of 100 mg TID open-label droxidopa and will not exceed 600 mg TID. All doses of IMP during the open-label dose titration period will be administered using 100 mg and 200 mg capsule strengths of droxidopa (no 300 mg capsules will be used during the Titration Period). Bottles of open-label IMP must be dispensed through the Interactive Web Response System (IWRS). Patients are to be given IMP only from bottles dispensed specifically for them through the IWRS.

3.5.2.1 Initial Open-Label Dose Titration Visit (Visit 2a)

The Investigator, or other qualified designee, will conduct the following procedures at the first dose titration visit (Visit 2a) and record the data in the eCRF provided:

- Clinical Symptoms: OHQ (prior to initiating dosing)
- Clinician- and Patient-recorded CGI-S (prior to initiating dosing)
- Review of inclusion and exclusion criteria (prior to initiating dosing)

- Vital signs (seated BP, HR, RR, temperature) and weight (prior to initiating dosing)
- Review of concomitant medications
- Review of AEs
- Use IWRS to dispense IMP for entire titration period
- Administer 100 mg dose of droxidopa and record time of administration
- Assessment of supine BP 3 hours (+/- 30 minutes) post-dose (as per section 3.6.1.1.1)
- Schedule the next visit and instruct patient on appropriate dosing schedule until the next visit

If the patient is found to be experiencing supine systolic blood pressure (SBP) greater than or equal to 180 mmHg or diastolic blood pressure (DBP) greater than or equal to 110 mmHg, when assessed ~3 hours after their initial dose of IMP, they will be withdrawn from the study.

3.5.2.2 Subsequent Open-Label Dose Titration (Visits 2b, 2c, 2d, 2e, 2f)

At each subsequent Titration Visit, it is anticipated that the patient's dose will be increased by 100 mg higher than the previously evaluated dose (up to a maximum of 600 mg TID). However, at the Investigator's discretion the patient's current dose may be maintained or reduced by 100 mg TID. The patient's first dose of IMP on the day of a Titration Visit should be administered in the clinic, regardless of the time of day for which the visit is scheduled. Visits 2b-2f may be completed on site or via phone or video link.

The Investigator, other qualified designee, will conduct the following procedures at each dose titration visit and record the data in the eCRF provided:

- Seated BP (prior to dosing)
- Time and dose of droxidopa taken on the day of the visit
- Review of concomitant medications
- Review of AEs
- Assessment of supine BP 3 hours (+/- 30 minutes) post-dose (as per section 3.6.1.1.1)
- Dose Titration Evaluation
- Schedule the next visit and instruct patient on appropriate dosing schedule until the next visit

If the visit is done via phone or video link, the patient (or their caregiver) will record the seated BP, time and dose of droxidopa and supine BP and report this information to the Investigator or qualified designee during the call, who will record this data in the eCRF provided.

If at any time during the study and / or the titration period a patient experiences sustained hypertension or if a patient becomes symptomatic for hypertension, the patient should be advised to immediately seek emergency medical attention and contact the investigator.

3.5.2.3 Titration Period Stopping Criteria

Patients will be titrated upwards until either one of the following stopping criteria is met:

1. The patient experiences supine SBP greater than or equal to 180 mmHg or DBP greater than or equal to 110 mmHg, when assessed ~3 hours after their initial dose of IMP;
2. The patient is unable to tolerate side effects considered by the Investigator to be related to the IMP.

If the initial supine BP measurement ~3 hours post-dose yields values greater than or equal to 180 mmHg SBP or 110 mmHg DBP, two additional supine measurements should be conducted which are at least 10 minutes apart and for each of which the patient has been supine for at least 5 minutes (see Section 3.6.1.1.1). If the average of these 3 supine measurements are either ≥180 mmHg systolic or ≥110 mmHg diastolic, the patient will be considered to have met stopping criterion #1.

A patient's optimal dose is defined as the highest dose at which they did not meet either of the titration stopping criteria. If a patient does not meet either of the stopping criteria at 600 mg, this will be considered their optimal dose.

Once the patient's optimal dose has been established, the patient should be scheduled to return to the clinic for Visit 3 and instructed to continue taking their optimal dose until Visit 3. This optimal dose will also be the dose assigned to the patient at the beginning of the Open-Label Period (Visit 3).

3.5.3 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 Open-Label Treatment. If the patient is required to return for a re-evaluation of the Open-Label entry criteria (see Section 3.5.3.1), the date of the re-evaluation will be considered Day 0 of Open-Label Treatment.

3.5.3.1 End of Titration / Initial Open-label Treatment Visit (Visit 3; Day 0)

At Visit 3, in order to successfully complete the Titration Period and enter the Open-Label Period, patients must demonstrate an Acute Dizziness score ≥ 2 units lower (improved) than the Visit 2a OHSA Item #1 score.

If a patient does not meet this criterion at Visit 3, they may, at the Investigator's discretion, continue to take their assigned dose of droxidopa and then return to the clinic for a second evaluation of their Acute Dizziness score within 7 days (and within 28 days of Visit 2a). This re-evaluation would be recorded as an Unscheduled Visit.

If the patient is found to meet this criterion at either Visit 3 or the repeat assessment, they may be enrolled into the Open-Label Period of the study as outlined below. If the patient fails to meet this criterion at both Visit 3 and the repeat evaluation, they are to be withdrawn from the study, and Early Termination procedures (see Section 3.5.7) should be conducted.

The patient is to take their first dose at Visit 3 from the IMP dispensed for the Titration Period. If the patient is required to return for a re-evaluation of the Open-Label entry criteria, they are to continue to take their assigned dose of droxidopa from the IMP dispensed for the Titration Period. Once a patient has been determined eligible to enter the Open-Label Period, the Investigator, or designee, will use the IWRS to dispense IMP for the Open-Label Period.

The Investigator, or qualified designee, will conduct the following procedures at the visit and record the data in the eCRF provided:

- Review of inclusion and exclusion criteria (prior to initiating dosing)
- Vital signs (seated BP, HR, RR, temperature) and weight (prior to initiating dosing)
- Clinician- and Patient-recorded CGI-S (prior to initiating dosing)
- IMP return and capsule count/compliance check from Titration period
- Record the time and dose of IMP taken on the day of the visit
- Review of AEs
- Review of concomitant medication
- Clinical Symptoms: Acute Dizziness 2 hours (+/- 15 minutes post-dose)
- Seated BP 2 hours (+/- 15 minutes post-dose)
- Record optimal dose as determined during titration period
- Use IWRS to dispense IMP, as required for next visit
- Schedule the next visit and instruct patient on appropriate dosing schedule until next visit

3.5.3.2 Open-Label Treatment Period (Visits 4 & 5; Day 28 [+/- 7days] & Day 56 [+/ 7days])

During the first 8 weeks of open-label treatment, the dose of droxidopa may be increased or decreased (by 100 mg TID increments) a maximum of four times at the Investigator's discretion. The dose should remain stable between visits 5 and 6; no dose changes are allowed after Visit 5.

The Investigator, or qualified designee, will conduct the following procedures at each visit and record the data in the eCRF provided:

- IMP return and capsule count/compliance check
- Clinical Symptoms: OHQ
- Clinician- and Patient-recorded CGI-S
- Vital signs (supine BP, HR, RR, temperature) and weight
- Review of AEs
- Review of concomitant medication
- Record the time and dose of IMP taken on the day of the visit
- Use IWRS to dispense IMP, as required for next visit
- Schedule the next visit and instruct patient on appropriate dosing schedule until next visit

3.5.3.3 End of Open-label Treatment Period / Randomization (Visit 6; Day 84 [+/- 7 days])

The Investigator, or qualified designee, will conduct the following procedures and record the data in the eCRF provided:

- Clinical Symptoms: OHQ (prior to first randomized dose)
- Review of inclusion and exclusion criteria (prior to first randomized dose)
- Clinician- and Patient-recorded CGI-S (prior to first randomized dose)
- Vital signs (supine BP, HR, RR, temperature) and weight (prior to first randomized dose)
- Pregnancy test for WOCP (prior to first randomized dose)
- IMP return and capsule count/compliance check
- Review of AEs
- Review of concomitant medication
- Blood samples for hematology and biochemistry
- Urine sample for urinalysis
- Randomize patient through the IWRS
- Use IWRS to dispense IMP
- Record the time and dose of IMP taken on the day of the visit
- Schedule the next visit and instruct patient on appropriate dosing schedule until next visit

If a patient has a score on OHSA Item # 1 that is not ≥ 2 units lower than their Baseline Score (at Visit 2a), they will not be eligible to continue into the Double-Blind Period and will be withdrawn from the study (see Section 3.4.4).

If a patient is deemed eligible to continue in the study, the Investigator, or their designee, after the completion of all procedures, will use the IWRS to randomize the patient to treatment with droxidopa or matching placebo (randomization is double-blind). The patient's daily dose will be the same as that at the end of the Open-Label Period. Patients will be dispensed their bottle(s) of IMP (droxidopa or matching placebo capsules) and will be counseled on how to take their IMP for the rest of that day and also for the duration of their double-blind treatment.

3.5.4 Double-Blind Study Visits (Visits 7-11)

No dose changes of IMP are permitted during the Double-Blind Period.

Visits 7, 9 and 11 will be completed via phone or video link; Visits 8 and 10 will be completed in-clinic.

The schedule for the visits in the Double-Blind portion of the study will be as follows (all visit windows are anchored from Visit 6, which is considered to be Day 0 of Randomization):

- Visit 7: Day 14 (+/- 3 days) – via phone or video link
- Visit 8: Day 28 (+/- 3 days) – clinic visit
- Visit 9: Day 42 (+/- 3 days) – via phone or video link
- Visit 10: Day 56 (+/- 3 days) – clinic visit
- Visit 11: Day 70 (+/- 3 days) – via phone or video link

3.5.4.1 Telephone / Video Link Double-Blind Study Visits (Visits 7, 9 & 11)

During the visits conducted via phone or video link during this period (Visits 7, 9 and 11), the patient or caregiver will record and report the information to the Investigator or qualified designee during the call or videoconference, who will record this data in the eCRF provided:

- Record the time and dose of IMP taken on the day of the visit
- Supine BP

During the call, the Investigator or qualified designee will conduct the following procedures and record the data in the eCRF provided:

- Review of AEs
- Review of concomitant medication
- Clinical Symptoms: OHQ

- Clinician- and Patient-recorded CGI-S
- Review "Need For Intervention" Criteria:
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
    - Patient stops IMP or withdraws from study for patient-reported lack of efficacy
- Schedule the next visit and instruct patient on appropriate dosing schedule until next visit

If a patient meets the criteria to be withdrawn due to a need for intervention during a phone / video link visit (Visits 7, 9 or 11), the patient should be brought in for an Early Termination Visit (see Section 3.5.7) as soon as possible.

3.5.4.2 On-Site Double-Blind Study Visits (Visits 8 & 10)

During the on-site visits during this period (Visits 8 and 10), the Investigator or other qualified designee, will conduct the following procedures at each dose titration visit and record the data in the eCRF provided:

- Record the time and dose of droxidopa taken on the day of the visit
- Review of AEs
- Review of concomitant medication
- Vital signs (supine BP, HR, RR, temperature) and weight
- Clinical Symptoms: OHQ
- Clinician- and Patient-recorded CGI-S
- Review "Need For Intervention" Criteria:
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR

- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
- Patient stops IMP or withdraws from study for patient-reported lack of efficacy

- IMP return and capsule count/compliance check
- Use IWRS to dispense IMP
- Schedule the next visit and instruct patient on appropriate dosing schedule until next visit

If a patient meets the criteria to be withdrawn due to a need for intervention while on-site at Visits 8 or 10, the Early Termination procedures should be completed during the visit as outlined in Section 3.5.7 below.

3.5.5 End of Treatment Visit (Visit 12; Day 84 [+/- 3 days] post Randomization)

Patients will return to the site for an End of Treatment (completion of Double-Blind Period) visit (Visit 12).

The Investigator, or qualified designee, will conduct the following procedures at each visit and record the data in the eCRF provided:

- Record the time and dose of IMP taken on the day of the visit
- Review of AEs
- Review of concomitant medication
- Clinical Symptoms: OHQ
- Clinician- and Patient-recorded CGI-S
- Review "Need For Intervention" Criteria:
  - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
  - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
  - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
  - Patient stops IMP or withdraws from study for patient-reported lack of efficacy
- Physical Exam
- Vital signs (supine BP, HR, RR) and weight.

- Pregnancy test for WOCP
- Blood samples for hematology and biochemistry
- Urine sample for urinalysis
- IMP return and capsule count/compliance check
- Schedule Follow-Up Visit (Visit 13)

If a patient meets the criteria for a need for intervention at this visit, the patient is to be considered withdrawn due to a need for intervention, and their disposition recorded as such. The Early Termination procedures should then be completed during the visit as outlined in Section 3.5.7 below.

3.5.6 Safety Follow-Up Visit (Visit 13)

Sites will contact the patient 30 days (+5 days) after their final visit (Visit 12 or Early Termination Visit) to record any new AEs and follow-up on any AEs that were ongoing at the end of their previous visit. This visit is to be conducted for all patients who have taken at least one dose of IMP; this visit is not required for patients who screen fail.

The follow-up visit may be conducted via phone or video link. In the event that the patient is unreachable, all reasonable efforts should be made and documented before considering the patient as unable to be contacted.

3.5.7 Early Termination Visit

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.

If a decision is made to withdraw the patient from the study while on site due to:

- a failure to meet criteria to enter the Open-Label Period at Visit 3
- a failure to meet criteria to enter the Double-Blind Period at Visit 6
- a need for intervention while on-site at Visits 8 or 10, OR
- for any other reason

the Early Termination procedures should be completed during that visit. The patient should not be brought back for an Early Termination Visit at a later date.

Whenever practical, patients should be encouraged to remain on IMP until the completion of the early termination procedures. This is particularly important for patients who withdraw from the study during the double-blind treatment period. As the primary efficacy endpoint is time

to intervention, it is critical that the date of withdrawal (which will be the date of the patient's last dose) due to a need for intervention during the double-blind period is accurately recorded.

The Investigator, or qualified designee, will conduct the following procedures and record the data in the eCRF provided:

- Record the time and dose of IMP taken on the day of the visit
- Record the reason for withdrawal
- Review of AEs
- Review of concomitant medication
- Clinical Symptoms: OHQ
- Clinician- and Patient-recorded CGI-S
- Review "Need For Intervention" Criteria:
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
    - OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
    - Patient stops IMP or withdraws from study for patient-reported lack of efficacy
- Physical Exam
- Vital signs (supine BP, HR, RR) and weight.
- Pregnancy test for WOCP
- Blood samples for hematology and biochemistry
- Urine sample for urinalysis
- IMP return and capsule count/compliance check
- Schedule Follow-Up Visit (Visit 13)

All patients who discontinue participation in the study are to have a Safety Follow-Up Visit (Visit 13) conducted 30 days (+5 days) after their final dose of IMP (see Section 3.5.6)**.**

3.5.8 Unscheduled Visit

A patient may return for an unscheduled visit at any time at the Investigator's discretion. The procedures conducted at the unscheduled visit may be limited, depending on the reason for the visit (for example, unscheduled visits for a repeat blood or urine sample, or for dispensing of new IMP to replace a lost bottle of IMP would only require those specific procedures relevant to the reason for the unscheduled visit to be done). If an Unscheduled Visit is conducted between Visits 3-5 of the Open-Label Period for the purpose of modifying a patient's dose of IMP, all procedures to be conducted during an Open-Label Treatment Visit (see Section 3.5.3.2) should be conducted.

3.5.9 Guidance regarding Covid-19

The protocol has always allowed the option of conducting Titration Visits 2b-2x remotely, via telephone or video chat. In addition, Visits 7, 9 and 11 are required to be conducted remotely, as per the protocol.

Due to the COVID-19 situation that developed in 2020, guidance was issued to all trial sites to temporarily allow all other study visits (except for Visits 1 and 2a) to be conducted remotely. This was done in the interest of patient safety as well to allow compliance with local and site regulations and guidance regarding COVID-19. This guidance also included procedures to allow IMP to be sent to patients via courier, if required, and allowed for Visit 6 and 12 lab samples to be collected at a later date if such visits could not be conducted on site. This guidance was placed into effect on 17 March 2020 and, as of the date of this version of the protocol, is still in effect. This guidance may be rescinded by Lundbeck at any time in the future, once it is determined to be no longer needed.

3.6 Study Procedures and Assessments

Table 1 summarizes the procedures and assessments conducted during this study.

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				✓	✓	✓	✓	✓	

[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

3.6.1 General Study Procedures and Considerations

3.6.1.1 Supine Blood Pressure Assessments

3.6.1.1.1 Titration Period

During the Titration Period, BP assessments are to be performed 3 hours (+/- 30 minutes) after dosing at each visit during the open-label titration period (Visits 2a-2f; Sections 3.5.2.1 & 3.5.2.2). The initial BP reading should be taken following a 10 minute period of rest in the supine position (head and torso elevated at approximately 30 degrees from horizontal). **If the initial measurements are greater than or equal to 180 mmHg SBP or 110 mmHg DBP**, two additional supine measurements should be conducted which are at least 10 minutes apart and for each of which the patient has been supine for at least 5 minutes prior to the reading.

These measurements will be conducted on site at Visit 2a. If further titration visits are to be conducted via phone or video link, the Investigator will instruct the patient and / or caregiver at Visit 2a on how to conduct this BP reading at home and how to report the results during the phone call or videoconference.

3.6.1.1.2 Open Label Period and Double-Blind Period

At Visits 4, 5, 6, 8, 10 and 12 (as well as during an Early Termination Visit): A supine BP reading will be taken as part of the Vital Signs, and does not need to be at any specified time following dosing. This BP reading should be taken following a 10 minute period of rest in the supine position (head and torso elevated at approximately 30 degrees from horizontal).

At Visits 7, 9 and 11, which are conducted via phone or video link, this supine BP reading will be conducted at home by the patient or caregiver. The Investigator will instruct the patient and / or caregiver on how to conduct this BP reading at home and how to report the results during the phone call or videoconference.

3.6.1.2 Seated Blood Pressure Assessments

A seated BP assessment is to be performed as part of the Vital Signs at the Screening Visit (Visit 1), at all Titration Period Visits (Visits 2a-2f) and at Visit 3. In addition, at Visit 3, a second seated BP is to be conducted 2 hours (+/- 15 minutes) post dose (see Section 3.5.3.1). These BP readings should be taken following a 5 minute period of rest with the patient in the seated position in a chair (head and torso elevated at approximately 90 degrees from horizontal, feet flat on the floor).

3.6.1.3 Orthostatic Standing Test

An Orthostatic Standing Test (OST) is to be conducted at the Screening Visit (Visit 1) if the patient does not have a documented history of OH. The patient will lie supine for at least 5 minutes (head and torso elevated at approximately 30° from horizontal). BP measurements will be taken

immediately prior to having the patient stand up, upon standing (minute 0) and after +3 minutes of standing. If the Investigator considers that a patient cannot, or is unlikely to be able to stand for 3 minutes, BP measurements should be taken as close to 3 minutes as possible.

To calculate the decrease in BP, the "immediately prior to standing" SBP measurement is used as the baseline. The decrease in SBP is the difference between the baseline measurement and the lowest SBP measurement at a time point within 3 minutes of standing (between "minute 0" and "minute +3").

3.6.1.4 Alcohol Consumption

Patients are to be instructed not to drink any alcohol in the 24 hours prior to any study visits, and not to exceed a moderate consumption level of alcohol at all other times during the study. Moderate consumption is defined as no more than 2 standard drinks per day, with a standard drink containing 0.6 ounces of alcohol (e.g., 12 ounces of 5% beer, 6 ounces of 12% wine, or 1.5 ounces of 80 proof spirits per day).

3.6.1.5 Hydration

Patients should be well hydrated on entry to the study, and should be encouraged to remain well hydrated throughout the study period.

3.6.2 Efficacy Assessments

3.6.2.1 Orthostatic Hypotension Questionnaire (OHQ)

The OHQ was developed by clinicians who treat disorders of the autonomic nervous system, in consultation with a psychometrician and statistician (Kaufmann et al., 2011; 0 et al., 2005). **The questionnaire includes specific instructions that are read aloud to the patients before the questions are answered**, and is administered in two separate sections; a symptom assessment scale and a daily activity scale.

The Orthostatic Hypotension Symptom Assessment (OHSA) scale was designed to rate symptoms occurring specifically as a result of low BP, using an 11-point scale (zero 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 activity and a composite score for all 6 activities are tabulated.

The Orthostatic Hypotension Daily Activity Scale (OHDAS) was designed as a measure of quality of life. It uses an 11-point scale to assess whether OH "interfered" with 4 types of activities: 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 zero rating means that over the preceding week the activity was performed with no interference and a 10 rating 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 OHQ composite score is a mean of the OHSA composite and the OHDAS composite scores.

3.6.2.2 Acute Dizziness Assessment

At Visit 3, acute dizziness will be assessed by asking the patient to rate (on a scale from 0-10) the severity of their symptom of dizziness/lightheadedness/feeling faint/feeling like you might black out due to low blood pressure during the past 24 hours.

3.6.3 Safety Assessments

3.6.3.1 Adverse Events

All adverse events observed by the Investigator, elicited upon a non-leading question (such as "how do you feel?"), or reported spontaneously by the patient will be recorded, starting at the Screening Visit. The Investigator will assess the seriousness and the intensity of the adverse event and its relationship to the IMP. Refer to Section 5 for details on the definition of adverse events and the manner in which they are to be recorded and reported.

3.6.3.2 Blood Pressure Measurements

Blood pressure should be taken on the same arm every visit.

It is a recognized best practice that patients with symptomatic NOH are advised not to lay fully supine because of the associated risk of supine hypertension inherent with their condition (patients are advised to sleep in a semi-recumbent position). Accordingly, for the purpose of this study, supine BP measurements are not to be conducted in the fully horizontal position, but should be done with patients positioned with their head and torso elevated at approximately 30 degrees from horizontal (see Section 3.6.1.1).

Patients will be instructed by the Investigator or qualified designee how to take and report their BP for visits that take place via phone or video link (see Sections 3.6.1.1.1 and 3.6.1.1.2).

If at any time during the study and / or the titration period a patient experiences sustained hypertension or if a patient becomes symptomatic for hypertension, the patient should be advised to immediately seek emergency medical attention and contact the investigator.

3.6.3.3 Physical Examination

A physical examination will be conducted at the screening visit (Visit 1) and at the End of Treatment Visit (Visit 12) / Early Termination Visit. The physician conducting the physical exam must state whether or not any abnormal findings are of clinical significance.

3.6.3.4 ECG

A 12-lead ECG will be conducted at the Screening Visit (Visit 1). The Investigator, or a qualified designee, will be responsible for reviewing the results of this assessment, and must evaluate whether the results are normal or abnormal; the Investigator must also state whether or not any abnormal findings are of clinical significance.

3.6.3.5 Vital Signs and Weight

Vital signs (seated BP, HR, RR, temperature) and weight will be measured at the Screening Visit (Visit 1), the first visit of the Titration Period (Visit 2a) and Visit 3. At Visits 4-12 (and at the Early Termination Visit), the vital signs procedure will be modified to include a supine BP measurement (see Section 3.6.1.1.2) instead of a seated BP assessment. Height will be measured only at the Screening Visit (Visit 1). At Visit 3, a second, seated BP assessment will be taken ~2 hours post-dose (see Section 3.5.3.3).

3.6.3.6 Clinical Safety Laboratory Tests

All analytical tests will be performed by a central laboratory. Urine pregnancy test will be assessed at sites. Electronic copies of all results will be provided to the Investigator.

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

Hematology	**Hemoglobin**
	Erythrocyte Count
	Hematocrit
	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**
	Specific Gravity
	Protein
	Glucose
	Ketones
	Blood
	Bilirubin
	Leukocytes
	Nitrites
	Microscopic sediment examination, only if dipstick is abnormal

Female patients of childbearing potential will have a urine pregnancy test at the Screening Visit (Visit 1), End of Open-label Treatment / Randomization Visit (Visit 6) and End of Treatment Visit (Visit 12) or Early Termination Visit, as well as at any unscheduled visit if deemed appropriate by the Investigator. The test will be done via an onsite dipstick test. If the results of the urine test are positive, the results will be verified via a serum pregnancy test.

Patients with a positive result on microscopic urinalysis should be brought back for a urine culture.

Details of the procedures for blood and urine sample collection, handling and analysis are described in the laboratory manual provided by the central lab.

3.7 Study Endpoints

3.7.1 Efficacy Endpoints

3.7.1.1 Primary Efficacy Endpoints

Time to intervention. Need for intervention is defined as meeting A**NY** of the following events that occur in the Double-Blind Period:

- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) AND lack of efficacy as judged by the Investigator; OR
- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at 2 consecutive visits; OR
- OHSA Item #1 ≥2 unit worsening from Randomization (Visit 6) at the visit before early discontinuation; OR
- Patient stops 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, whichever comes first.

The primary efficacy analysis will include all randomized patients who received at least one dose of double-blind IMP (all patients treated set (APTS)) and will be analyzed by the log-Rank test to compare treatment on time to intervention during the double-blind period. Patients who withdraw without meeting criteria for treatment intervention will be censored at the time of withdrawal; patients who do not meet criteria for treatment intervention at the end of the Double-Blind Period (Visit 12) will be censored at the time of study completion.

3.7.1.2 Secondary Efficacy Endpoints

Efficacy of droxidopa versus placebo using patient- and clinician-rated endpoints on the APTS:

- Time to all cause discontinuation
- Mean change in OHSA item #1 score from Randomization (Visit 6; Week 0 of Double-blind Period) to all post randomization visits
- Mean change in OHQ composite score from Randomization (Visit 6; Week 0 of Double-blind Period) to all post randomization visits
- Clinician-rated CGI-S at all post randomization visits
- Patient-rated CGI-S at all post randomization visits
- Proportion of patients who need intervention over the 12 week double-blind period

3.7.2 Safety Endpoints

Adverse events, vital signs, and clinical safety laboratory assessments will be observed through the entire study. Safety parameters from the open-label portion of the study (Titration Period and Open-Label Period) and the Double-Blind Period will be reported separately.

3.8 Early Termination

An Early Termination occurs when an enrolled patient ceases participation in the study, regardless of the circumstances, prior to completion of the study. The Investigator must determine the primary reason for discontinuation or withdrawal. Patients withdrawing due to reasons other than a need for intervention will be censored at the time of withdrawal.

Withdrawal due to an AE (see Section 5.1 for the definition of an AE) should correspond to the AE recorded on the appropriate eCRF page.

When a patient is withdrawn due to a serious adverse event (SAE), the SAE must be reported in accordance with the reporting requirements defined below (see Section 5.4). A withdrawal due to an SAE must be reported immediately to Lundbeck or the site's Clinical Research Associate (CRA). The decision to withdraw a patient from treatment for safety reasons may be made by the Medical Monitor, Lundbeck, and/or the Investigator. In the event of discontinuation of treatment / withdrawal from treatment, the Investigator will complete Early Termination procedures for the specified patient, as outlined in Section 3.5.7.

If a subject becomes pregnant during the study, she will be withdrawn from study treatment immediately. The pregnancy must be reported as detailed in Section 5.2.

The patient may elect to withdraw from the study at any time and for any reason. **If the patient wishes to withdraw from treatment, they should return for a final, on-site visit, and the procedures outlined for an Early Termination Visit should be completed (see Section 3.5.7). Whenever practical, subjects should remain on IMP until the completion of the end of the Early Termination Visit.**

3.9 Study Termination

Premature termination of this clinical study may occur as a result of a regulatory authority decision, change in opinion of the institutional review board/independent ethics committee (IRB/IEC), drug safety concerns, or at the discretion of Lundbeck. In addition, Lundbeck retains the right to discontinue development of droxidopa at any time.

The Investigator reserves the right to terminate the study, at his/her participating study site, at any time, for any reasons. Should this be necessary, the procedures will be arranged on an individual site basis after review and consultation with Lundbeck. In terminating the study, Lundbeck, the

contract research organization (CRO), and the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY TREATMENTS

4.1 Allocation to Study Treatments

In the Double-Blind Period, each patient will be randomized to receive study treatment (droxidopa or matching placebo; 1:1 ratio) according to a computer generated randomization schedule administered through a central IWRS. Neither the Investigator nor the patient will know the identity of the treatment that the patient will receive; however, the study will not be blinded with respect to (expected) dose.

All bottles of IMP will be dispensed through the central IWRS.

4.2 Emergency Blind Breaking

In the case of an emergency where, in the opinion of the Investigator, discontinuation of IMP is not sufficient and the study treatment must be unblinded in order to evaluate a further course of action, the Investigator should make every effort to contact the Medical Monitor prior to unblinding. The Investigator requesting the unblinding should be able to confirm that the unblinding of the patient is necessary and directly impacts the patient's immediate medical management.

In the rare event that contact with the Medical Monitor and/or sponsor is not possible prior to unblinding, the Investigator reserves the right to unblind a patient in a true medical emergency, where patient safety is at immediate risk. All instances of emergency unblinding must be reported to the Medical Monitor within 24 hours. Upon breaking the blind, the patient must be withdrawn from the study, but should be followed up for safety purposes.

The procedures described below will be followed in the event a request for emergency unblinding is received.

The Medical Monitor will discuss the request with the Investigator and record the following information:

- Protocol Number
- Site Number
- Patient Number and Initials
- Reasons for Unblinding
- Current Interventions

The Medical Monitor may contact the sponsor to discuss the request for emergency unblinding. The sponsor representative/Study Medical Monitor will follow up with the Investigator to communicate the decision regarding the request for unblinding.

The Investigator will perform the emergency unblinding in accordance with the applicable procedure described in the IWRS procedures documentation.

4.3 IMP Supplies

IMP will be provided to the study site as open-label 100- and 200-mg capsules for the Titration Period, as open-label 100- 200-, and 300 mg capsules for the Open-Label Period, and as double-blind 100-, 200-, and 300-mg capsules and matching placebo for the Double-Blind Period. IMP is to be stored at room temperature (20°C-25°C).

Patients must bring their IMP (including empty bottles) with them to each study visit, and must return all unfinished IMP to the Investigator at the end of each study period. Inventory control of all IMP must be rigorously maintained throughout the duration of the study until final accountability procedures have been performed by the CRA, at which time the IMP may be destroyed on-site or returned to Lundbeck or the sponsor's designee (see Section 4.6). Any discrepancies noted between Drug Dispensing Records and the drug inventory must be reported to the sponsor.

4.4 Manufacturing, Formulation, Packaging and Labeling of IMP

4.4.1 Formulation Details

Each active IMP capsule will contain 100 mg, 200 mg, or 300 mg droxidopa.

Matching placebo capsules will contain the same ingredients as the active IMP capsules, except that droxidopa will be replaced by an equivalent quantity of mannitol.

4.4.2 Manufacturing, Packaging and Labeling Details

All IMP will be manufactured and packaged by Patheon, and will be labeled by Almac, and will be distributed in accordance with the principles of Good Manufacturing Practice, under the responsibility of Lundbeck. Patheon will provide sufficient test formulations and the respective certificates of analysis, and will keep reference samples of the medication.

IMP for the Titration, Open-Label and Double-Blind periods will be packaged and labeled to clearly identify the dose of the IMP. All double-blind IMP will be packaged and labeled according to a randomization schedule generated by the Lundbeck BioStatistics department or their designee. For the IMP provided for the Double-Blind Period, the labels will be blinded with respect to treatment identity (but not dose) and will contain at least the following information (where required):

- Patient identification number/space for inserting patient's initials
- Protocol number
- Bottle number
- Space for inserting Investigator name and phone number
- Number of capsules in container
- Capsule strength
- Directions for use
- Lot number
- Expiration date of capsules
- Denotation that the medication is "FOR CLINICAL TRIAL USE ONLY"
- Denotation to "Keep out of the reach of children"
- Storage conditions
- Space for inserting dispensing date
- Name of capsule manufacturer

IMP for the Titration and Open-Label periods will be labeled in the same manner, with the exception of being unblinded with respect to treatment identity (all IMP used during the Titration and Open-Label periods will be active droxidopa).

The wording on the labels will be in accordance with Good Manufacturing Practice (GMP) regarding labelling and national and/or local regulatory requirements.

4.5 Preparation, Administration and Dosing of Investigational Medicinal Product

4.5.1 Preparation

Droxidopa 100 mg capsules will be presented as hard, gelatin capsules (size: No. 3) with an opaque light blue cap and an opaque white body. Capsules will be imprinted with "Northera" and "100" for additional distinction of doses.

Droxidopa 200 mg capsules will be presented as hard, gelatin capsules (size: No. 2) with an opaque light yellow cap and an opaque white body. Capsules will be imprinted with "Northera" and "200" for additional distinction of doses.

Droxidopa 300 mg capsules will be presented as hard, gelatin capsules (size: No. 1) with an opaque green cap and an opaque white body. Capsules will be imprinted with "Northera" and "300" for additional distinction of doses.

Placebo capsules will be identical in appearance to the droxidopa 100 mg, 200 mg, and 300 mg capsules.

The capsules for the Titration and Open-Label periods will be packaged in child-resistant high-density polyethylene (HDPE) bottles, each containing 90 capsules of either 100 mg or 200 mg droxidopa (Titration Period), or 100 mg, 200 mg, or 300 mg droxidopa (Open-Label Period). The capsules for the Double-Blind Period will also be packaged in child-resistant high-density polyethylene (HDPE) bottles, each containing 90 capsules of either 100 mg, 200 mg, or 300 mg droxidopa or matching placebo. IMP will be stored in a secure, locked area, which is only accessible to authorized study personnel.

4.5.2 Route of Administration and Dose Schedule

Each patient will take 1 to 3 capsules three times daily during the Titration Period, and 1-2 capsules three times daily during the Open Label Period and during the Double-Blind Period. Capsules will be taken orally with water (typically half a glass).

Doses are to be timed such that the first dose is taken upon waking and then taken approximately every 4 hours thereafter, with the final dose taken early enough (i.e., late afternoon) to minimize drug effects during night-time sleeping hours. However, **on days when a patient has a study visit, the first dose should not be taken until the patient has arrived at the site for their visit**.

The combinations of capsules that patients may receive are shown in Table 2.

Table 1: Capsule Combinations Per Dose

Medication for Open-Label Titration	TID Dose (mg)					
	100	**200**	**300**	**400**	**500**	**600**
# of Droxidopa 100 mg capsules	1		1		1	
# of Droxidopa 200 mg capsules		1	1	2	2	3

Medication for Open-Label Treatment and Double blind period*	TID Dose (mg)					
	100	**200**	**300**	**400**	**500**	**600**
# of Droxidopa 100 mg capsules	1					
# of Droxidopa 200 mg capsules		1		2	1	
# of Droxidopa 300 mg capsules			1		1	2

***** The medication for the double-blind period will include matching placebo treatments for each of the dose options.

4.5.3 Dose Increase / Dose Reduction

During the Titration Period, the dose of IMP will be up-titrated from 100 mg TID to 600 mg TID (see Section 3.5.2). It is anticipated that this will take up to 6 Titration visits, within the 4-week Titration Period.

During the initial 8 weeks of the Open-Label Period, the Investigator may elect to increase or decrease an individual patient's dose, in increments of 100 mg TID, a maximum of four times (see Section 3.5.3.2). The dose should remain stable during the last four weeks of the Open-Label Period (between Visits 5 and 6).

4.6 Drug Storage and Accountability

A central IWRS will be used to manage on-site IMP supplies. The Investigator or a qualified designee (e.g., pharmacist) will receive IMP supplies and keep records of their receipt, storage, and dispensing in accordance with current International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. A Drug Dispensing Log must be kept current and should contain, at a minimum, the following information:

- The identification/randomization number of the patient to whom the IMP was dispensed;
- The date(s) and quantity of IMP dispensed to the patient.

The inventory must be available for inspection by the study's CRA or Lundbeck. During the study, the Investigator or a qualified designee will liaise with the CRO to ensure that supplies of IMP are maintained.

Unused or partially used IMP may be destroyed by the Investigator only after authorization from the CRA (after verification with Lundbeck), provided such disposition does not expose humans to risk from the drug. The Investigator or their designee should maintain records of any such alternative disposition of the IMP. These records must show the identification and quantity of each unit that has been disposed, the method of destruction (taking into account the requirements of local law and the site's standard operating procedures [SOPs]), and the person who disposed of the IMP. Alternatively, Investigators may elect to return unused or partially used drug supplies to Lundbeck, or the sponsor's designee, instead of destroying them on-site.

4.7 Treatment Compliance

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

Patients will be required to bring their IMP to all in clinic visits, and compliance will be monitored by capsule counts. The number of returned capsules will be counted by the Investigator, or a designee, and recorded in the Drug Dispensing Log and eCRF. The study CRA will review the compliance documentation during routine monitoring visits.

At least 80% compliance will be defined as acceptable in this study during the Open-Label and Double-Blind periods. If a patient is found to be below 80% compliance during a treatment visit, the patient should be counseled on the proper dosing regimen and the counseling should be documented in the patient's chart. If a patient is found to be non-compliant at a second treatment visit, the Investigator is to discuss this issue with the Medical Monitor in order to determine the patient's eligibility to continue in the study. In the event of over-compliance (i.e., a patient who is found to be over 120% compliant with their IMP), the patient will be treated in the same manner as a patient with compliance below 80%.

4.8 Prior and Concomitant Medications

4.8.1 Concomitant Medications

No prescribed concomitant medication is to be taken without the knowledge of the Investigator. The Investigator may, at their discretion, prescribe any medication considered necessary for the patient's welfare that is not expected to interfere with the evaluation of the IMP.

All concomitant medications must be recorded in the eCRF. The generic name of the drug, dose, frequency of dose and the duration of treatment must be specified. In addition, any diagnostic, therapeutic or surgical procedure conducted during the study, that is not part of the study, should be recorded in the eCRF. The date, indication, description of procedure(s) and any clinical finding should be recorded.

All concomitant medications (including permitted medications given concomitantly for symptomatic NOH) should be maintained at stable doses during the study. Any proposed changes in a patient's treatment for symptomatic NOH considered necessary by the Investigator must be discussed with the Study Medical Monitor prior to implementation to determine its impact on the patient's participation in the study.

If patients are already on other concomitant medications, which based on investigator judgment, would be expected to have side effect of hypertension, (e.g, amphetamine, amphetamine-like drugs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine reuptake inhibitors (NRIs)), evaluate their continued use when introducing droxidopa.

4.8.2 Prior Medications

Prior medication includes all medications (including herbal treatments and vitamins) taken within 28 days prior the Screening Visit (Visit 1). All prior medications taken within 28 days of the Screening Visit must be recorded in the appropriate eCRF page.

4.8.3 Prohibited Medications

Administering droxidopa in combination with other agents that increase blood pressure (e.g, norepinephrine, ephedrine, midodrine, triptans) would be expected to increase the risk for supine hypertension. The following drugs must not be prescribed by the Investigator or taken by patients during the study:

- Vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine;
- Sumatriptan-like drugs, (for example, naratriptan, zolmitriptan, rizatriptan);
- Cyclopropane or halothane, or other halogen-containing inhalational anesthetics;
- Catecholamine-containing preparations (e.g. isoprenaline);

- Non-selective monoamine oxidase inhibitors (MAOIs) including linezolid;
- Ergotamine derivatives (except if anti-Parkinsonian medication);
- Drugs that have anti-hypertensive properties and, in the Investigator's opinion, significantly contribute to the patient's orthostatic hypotension; and
- Oral Anticoagulants in the drug classes of Coumarins: Coumadin (warfarin); Factor Xa Inhibitors: Xarelto (rivaroxaban), Eliquis (apixaban), Savaysa (edoxaban); and Direct Thrombin Inhibitors: Pradaxa (dabigatran etexilate mesylate)
- Any investigational medication.

Patients currently taking a prohibited medication at Screening may be enrolled into the study after a washout of at least 5 half-lives prior to first dose of IMP at Visit 2a. Patients taking midodrine at Screening are required to washout of this drug for at least 2 days prior to first dose of IMP at Visit 2a.

4.8.4 Allowed Medications

Concomitant treatment for symptomatic NOH (with the exception of vasoconstricting agents) will be permitted during the study. This includes fludrocortisone, which is permitted during the study. Medications for the treatment of PD will be permitted during the study. Fludrocortisone and medications for treatment of the patient's primary diagnosis should remain stable during the Double-Blind Period. Short-acting anti-hypertensive medications taken at bedtime to reduce the risk of nocturnal supine hypertension may be taken during the study.

The concomitant use of drugs that inhibit the re-uptake of NE at nerve terminals (e.g. tricyclic antidepressants) is permitted during the study. However, due to a potential interaction with droxidopa, patients are not allowed to either initiate treatment with NE re-uptake inhibitors or modify the dose of any such medications during the study (the combined action of both drugs can increase NE concentrations at the nerve terminal).

5. ADVERSE EVENTS

5.1 Definitions

5.1.1 Adverse Event Definitions

5.1.1.1 Adverse Events

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

An AE can therefore be any unfavorable and unintended sign (including 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 up until 30 days after the last dose of IMP.

Worsening of NOH is related to the primary endpoint in the Double-Blind Period. As such, "worsening of NOH" is not to be considered an AE in the Double-Blind Period of this study unless the worsening meets the criteria for an SAE (see Section 5.1.1.2).

5.1.1.2 Serious Adverse Events

A serious adverse event (SAE) – is any AE that:

- results in death
- is life-threatening (this refers to an event in which the subject 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 congenital 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)

SAE's are collected 30 days after the last dose of IMP.

Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the patient signed the ICF and that did not change in intensity are not SAEs.

A non-serious adverse event is any AE that does not meet the definition of an SAE.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

A suspected unexpected serious adverse reaction (SUSAR) is any AE that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the reference safety information) and related to an investigational product by either the Investigator or the sponsor.

An overdose is a dose taken by a patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) must, at a minimum be recorded as a non-serious adverse event.

5.1.2 Adverse Event Assessment Definitions

5.1.2.1 Assessment of Intensity

The Investigator must assess the intensity of the adverse event using the following definitions, and record it on the Adverse Event Form:

- 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.

5.1.2.2 Assessment of Causal Relationship

The Investigator must assess the causal relationship between the AE and the IMP using the following definitions, and record it on the Adverse Event Form (and on the Serious Adverse Event Report Form, if applicable):

- Probable: the AE has a strong temporal relationship to the IMP or recurs on rechallenge, 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).

An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

5.1.2.3 Assessment of Outcome

The Investigator must assess the outcome of the AE using the following definitions, and record it on the Adverse Event Form (and on the Serious Adverse Event Report Form, if applicable):

- Recovered: the subject has recovered completely, and no symptoms remain.
- Recovering: the subject's condition is improving, but symptoms still remain.

- Recovered with sequelae: the subject has recovered, but some symptoms remain (for example, the subject had a stroke and is functioning normally, but has some motor impairment).
- Not recovered: the subject's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- Death

5.2 Pregnancy

Although not necessarily considered an AE, a pregnancy in a patient in the study must be recorded on an Adverse Event Report Form, as well as on a Pregnancy Form, even if no adverse event associated with the pregnancy has occurred. Pregnancies must be reported to Lundbeck using the same expedited reporting timelines as those for SAEs.

An uncomplicated pregnancy should not be considered an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion (for example, hospitalization) must be indicated on the Serious Adverse Event Report Form. Examples of pregnancies to be reported as SAEs (medically important) are spontaneous abortions, stillbirths, and malformations.

The Investigator must follow up on the outcome of the pregnancy and report it on a Pregnancy Form. The follow-up must include information on the neonate at least up until the age of 1 month.

5.3 Recording Adverse Events

Adverse events (including pre-treatment AEs) must be recorded on an Adverse Event Form. The Investigator must provide information on the AE, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken; and outcome. If the AE is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of an adverse event, this must be recorded on the Adverse Event Intensity Log.

If the AE is serious, this must be indicated on the Adverse Event Form. Furthermore, the Investigator must fill out a Serious Adverse Event Report Form and report the SAE to Lundbeck, NA immediately (within 24 hours) after becoming aware of it (refer to section 5.4).

Adverse events, including clinically significant out-of-range clinical safety laboratory test values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

5.4 Reporting Serious Adverse Events

The Investigator must report SAEs to Lundbeck immediately (within 24 hours) after becoming aware of them by completing a Serious Adverse Event Form in the EDC system.

As much information as possible must be entered when initially completing the EDC form. If more information about the patient's condition becomes available at a later date, the Serious Adverse Event Form in the EDC system must be updated with the additional information.

If the investigator cannot report the SAE in the EDC System, then he or she must complete and sign the Serious Adverse Event Fallback Form and send to:

Global Pharmacovigilance – US (GPV-US)
Fax: +1 (847) 282-1003
e-mail: luinc_safety@lundbeck.com

The signed (original) Serious Adverse Event Fallback Form must be collected by the CRA and filed in the sponsor TMF.

Any Serious Adverse Event information provided on the Serious Adverse Event Fallback Form must be entered into the EDC system in a timely manner.

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local regulations.

It is the Investigator's responsibility to be familiar with local requirements regarding reporting SAEs to the IEC or IRB and to act accordingly.

Lundbeck will assess expectedness and inform the Investigators about suspected unexpected serious adverse reactions (SUSARs) via individual blinded CIOMS in accordance with local requirements.

5.5 Treatment and Follow-Up of Adverse Events

Patients with AEs must be treated in accordance with usual clinical practice at the discretion of the Investigator.

Non-serious AEs must be followed up until resolution or the follow-up assessment (Visit 13), whichever comes first. At the safety follow-up visit (Visit 13), information on new SAEs, if any, and stop dates for previously reported AEs must be recorded.

It is the responsibility of the Investigator to follow up on SAEs until the patient has recovered, stabilized, or recovered with sequelae, and to report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultations.

SAEs that are spontaneously reported by a patient to the Investigator after the follow-up assessment must be handled in the same manner as SAEs that occur during the study. These SAEs will be captured in the GPV database.

5.6 Warnings and Precautions

Patients will be informed in a language that is understandable to them, that the following clinically significant adverse reaction was reported in post-marketing data: neuroleptic malignant syndrome

(symptoms include hyperpyrexia, disturbance of consciousness, marked muscle rigidity, involuntary movements, and elevation of serum CPK). If these adverse reactions should occur, the Investigator should contact the medical monitor to discuss.

Other adverse reactions that have been reported with droxidopa can be found in the PI.

6. DATA ANALYSIS / STATISTICAL METHODS

Continuous variables will be summarized using descriptive statistics including the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical values will be summarized using number of observations and percentages.

All other statistical tests will be done at the two-sided, 5% significance level, unless otherwise specified. The assumptions underlying the statistical tests will be evaluated as appropriate and documented in the study report.

Unless otherwise specified, efficacy endpoints will be evaluated using the full analysis set (FAS). In order to control the overall type I error, statistical significance of the secondary endpoints (see Section 3.7.1.2) will be evaluated using a hierarchical testing procedure that will be described in the Statistical Analysis Plan (SAP).

A detailed description of all planned analyses will be provided in the SAP before the study is unblinded. Any deviations from the protocol or SAP will be documented in the study report.

6.1 Sample Size Determination

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 favor of droxidopa, a 240-subject sample size would be expected to result in 48 events, providing ~51% power to detect a difference between droxidopa and placebo. A blinded review conducted in July 2020 indicated that the event rate may be higher than originally assumed and, if accurate, 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.

6.2 Randomization

The study randomization schedule will be computer generated by the Lundbeck BioStatistics department or their designee, and provided to the IWRS programmers prior to the opening of site enrollment. Randomization will be on a one to one basis with no additional stratification factors.

Neither the Investigator nor the patient will know the identity of the treatment that the patient will receive; however, the study will not be blinded with respect to (expected) dose.

6.3 Study Treatments

Summaries of efficacy and safety data for this study will be presented in terms of randomized treatment group (i.e., droxidopa or placebo) as well as for all open-label periods of the study.

6.4 Analysis Population

6.4.1 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. All safety analyses will be based on the Safety Set unless otherwise specified.

6.4.2 All Patients Treated Set

The APTS will be a modified intent to treat (ITT) set, consisting of all randomized patients who take at least one dose of study drug in the double-blind period of the trial. Patients will be included in the analysis according to the treatment to which they were randomized.

6.4.3 Per Protocol Set

The per protocol set (PPS) will consist of patients in the FAS who do not have major protocol violations and are compliant with study treatment. Compliance will be defined as taking at least 80% of the planned study doses during the 12-week Double-Blind Period, from the date of Randomization (Visit 6) to the date of their final visit (Visit 12 or Early Termination Visit). In order to minimize the potential for bias, the review of protocol violations and assignment of patients to analysis sets will be performed prior to unblinding. Protocol violations will be defined in the SAP and will be listed by treatment group.

The primary efficacy analysis will be based on the APTS, although a secondary analysis will also be performed based upon the PP Set, to assess the sensitivity of the analysis to the choice of analysis population. Analysis of all other efficacy endpoints will be based upon the APTS. Selected secondary efficacy parameters may be evaluated using the PP Set. All safety analyses will be based on the Safety Set.

6.5 Data Summary

6.5.1 Summary of Efficacy Data

Details of the analysis of these endpoints, as well as exploratory endpoints, will be further described in the SAP.

6.5.1.1 Analysis of Primary Endpoint

The primary endpoint is time to treatment intervention defined in section 1.3.2. The event time is measured as the time from randomization to the time of occurrence of the earliest event, as defined in the treatment intervention criteria. Patients withdrawing and without need for intervention will be censored at the time of withdrawal; patients without need for intervention before the end of the study will be censored at the time of study completion.

The primary endpoint will be summarized using Kaplan-Meier method. The primary analysis is the Log-rank test to compare the two treatment groups. In addition, the cox regression model will be used to estimate the hazard ratio. Furthermore, the following sensitivity analysis using the same analysis approach will be conducted:

1 Time to treatment intervention according to the treatment intervention criteria (see Section 3.7.1.1) or OHSA Item #1 $\geq$ 2 unit worsening from randomization at the last visit of the study
2 Time to treatment intervention defined as discontinuation due to lack of efficacy as judged by the Investigator.
3 Cox regression analysis of time to treatment intervention based on various definitions above.

6.5.1.2 Analysis of Key Secondary Endpoint

A gate keeping strategy will be applied in the testing of the key secondary endpoint, time to all cause discontinuation. That is, the Log-rank test of this endpoint will be performed at the nominal alpha level of 2-sided 0.05 only if the primary endpoint reaches the statistical significance in the primary analysis. This strategy ensures the overall type 1 error rate is preserved.

6.5.1.3 Analysis of Other Secondary Endpoints

Proportion of patients with need for treatment intervention will be summarized by treatment groups and treatment difference will be tested using Chi-square test.

Descriptive statistics will be used to summarize mean change of OHSA item 1 score as well as OHQ composite score from randomization to each post randomization visit.

Categorical analysis will be used to summarize both clinician and patient reported CGI-S at each post-randomization visit.

6.5.2 Summary of Safety Data

The safety data will be presented in two separate periods of the study. The Titration Period and the 12 week Open-Label Period will be presented as appropriate in standard tabulations and listings. The changes from Randomization (Visit 6) to Week 12 of the Double-Blind Period (Visit

12) in the safety parameters will be summarized separately using standard tabulations and listings. Further details will be provided in the SAP.

Clinical laboratory tests will be summarized using descriptive statistics by visit and treatment group. Changes from randomization and shift tables will also be presented as appropriate. Vital signs will be summarized by treatment group using descriptive statistics and/or listed.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary. Treatment-emergent AEs will be summarized by system organ class, preferred term, and by treatment group. Severity of the AE and the relationship to IMP will also be summarized. Serious AEs and events leading to discontinuation of IMP will be summarized by body system, preferred term and treatment group.

6.6 Interim Analysis

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

An interim analysis of safety data will be prepared annually.

6.7 Replacement Policy

A sufficient number of patients will be screened to allow 240 patients to be randomized into the study and receive at least one dose of double-blind IMP (120 randomized to droxidopa and 120 randomized to placebo).

Patients who fail to qualify prior to receiving their first dose of IMP may be rescreened once, with approval of the Medical Monitor (see Section 3.5.1.2).

7. DATA MONITORING COMMITTEE

Safety data from this study will not be reviewed by an independent Data Monitoring Committee (DMC).

8. STUDY DOCUMENTATION, eCRF AND RECORD KEEPING

8.1 Investigator's Files and Retention of Study Data

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be separated into two categories: Investigator's study file and patient clinical source documents.

1. The Investigator's study file will contain the protocol and protocol amendments (if applicable), eCRF guidelines, eCRF query forms, IRB/IEC and governmental regulatory approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence.

2. Patient clinical source documents (which are usually defined by the project in advance to record key efficacy and/or safety parameters independent of the eCRF) may include patient and/or hospital clinical records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant's letters, screening and enrollment log, etc.

The patient's involvement in the study should be clearly documented in the study site's clinical records. Details should include the study protocol number, the patient's screening and randomization number, the patient's consent to take part in the study (including the date of consent), the dates of all study visits, details of any treatments withdrawn because of study participation, the dates of dispensing IMP, details of any AEs (including any SAEs), and changes in concomitant medications.

The documents in these two categories must be kept on file by the Investigator for at least 15 years after completion or termination of the study.

Study documents should not be destroyed without prior written agreement between Lundbeck and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, Lundbeck must be notified in advance.

If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the Investigator and Lundbeck to store these in a sealed container(s) outside the site. The sealed container(s) can therefore be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made for storing outside the site.

8.2 Electronic Case Report Forms

The Investigator is to record all data with respect to protocol procedures, drug administration, local laboratory data, safety data and efficacy ratings in the eCRF. The Investigator must sign the final eCRF pages to attest to the accuracy and completeness of all data.

8.3 Background Data

The Investigator will supply Lundbeck and the CRO, on request, with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have direct access to the completed study records, provided that patient confidentiality is protected.

8.4 Monitoring, Verification of Data, Audit, and Inspection

The Lundbeck monitor, or assigned CRA, will periodically visit each site that has enrolled patients into the study to discuss the progress of the study and review eCRFs and original source documents

with the study personnel, for accuracy of data recording, IMP accountability, and correspondence. Periodically, some/all of the facilities used in the study (e.g., laboratory, pharmacy) may be reviewed or inspected by Lundbeck, the IRB/IEC and/or regulatory authorities.

The Investigator is to ensure that the study participants are aware of and consent that personal information may be reviewed during the data verification process as part of monitoring/auditing by properly authorized agents of Lundbeck or subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent the applicable law permits and not publicly available. The audit or inspection may include, for example, a review of all source documentation, drug records, original medical notes, some or all of the facilities used in the study.

The Investigator must notify Lundbeck, without delay, of an announced inspection by a regulatory authority. During audits and inspections, the Investigator must permit direct access to all the source documents, including medical records and other documents pertinent to the study.

During audits and inspections, the auditors and inspectors may copy relevant parts of medical records. No personal identification apart from the screening or randomisation number will appear on these copies. Patient data will not be disclosed to unauthorised third parties, and patient confidentiality will be maintained at all times.

9. ADMINISTRATIVE PROCEDURES

9.1 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with Institutional Review Board/Independent Ethics Committee (IRB/IEC) and International Committee on Harmonization (ICH) GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the study participants.

This study will be conducted in general according to the Declaration of Helsinki and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a study, the Investigator/institution will have written and dated approval/favorable opinion from the IRB/IEC for the study protocol, written informed consent form, patient recruitment procedures (e.g., advertisements), and data collection instruments which will be completed by patients. Protocol amendments, consent form updates, and any amendments to the documents described before must be approved by the IRB/IEC prior to implementation unless such changes are necessary to address immediate safety concerns.

9.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, potential benefits and any potential hazards of the study. The informed consent procedure needs to be documented at

each study site. No study-related procedures, including washout of any medications, may be performed prior to obtaining written informed consent.

The Investigator must explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time and for any reason. Similarly, the Investigator or Lundbeck is free to withdraw the patient from the study at any time for safety reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained, according to current ICH GCP Guidelines.

A sample copy of the patient information sheet and consent form will be provided by the sponsor. These documents may, however, be subject to country specific changes and the IRB/IECs may ask for them to be altered. In this case, any modifications are to be approved by Lundbeck. A copy of the patient information sheet and consent form that is approved for this study by each IRB/IEC and Lundbeck will be kept by the CRO in the trial master file (TMF).

9.3 Confidentiality of Patient Information

All patients who provide written informed consent will be assigned a patient number. Subsequently, patients will be identified in the eCRFs only by their initials, date of birth, and their patient number (as allowed by local country regulations). Any information published as a result of the study will be such that it will not permit identification of any patient. The information from this study will be available within Lundbeck and may be shared with regulatory authorities. It may also be the subject of an audit by a regulatory agency, such as the Food and Drug Administration (FDA), within the local government. The patient's identity will remain protected except as required for legal or regulatory inquiries.

9.4 Protocol Compliance

Lundbeck has a "no-waiver" policy, which means that permission will not be given to deviate from the protocol. If deviations occur, the Investigator must inform the CRA and they must review, discuss, and document the implications of the deviation.

9.5 Conditions For Modification of the Protocol

Protocol modifications to an ongoing study that could potentially adversely affect the safety of participating patients, or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of patients treated or patient selection criteria must be made only after consultation with appropriate representatives of Lundbeck, the CRO, and the Investigator.

Protocol modifications will be prepared, and reviewed by Lundbeck, and reviewed and signed by the Investigator.

Any modifications to the protocol that are made after receipt of the IRB/IEC approval must be submitted by the Investigator to the IRB/IEC in accordance with local procedures and regulatory requirements, before the changes can be implemented. Modifications to the protocol that eliminate an apparent immediate hazard to patients do not require pre-approval by the IRB/IEC.

9.6 Clinical Study Report and Publications

9.6.1 Clinical Study Report

Upon completion of the study, a Clinical Study Report will be prepared by Lundbeck or the company's designee.

9.6.2 Data Ownership

The data collected in this study are the property of Lundbeck.

9.6.3 Publications

The results of this study will be submitted for publication.

The primary publication based on this study must be published before any secondary publications are submitted for publication.

Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).

INVESTIGATOR SIGNATURE

I, the undersigned, certify that I have reviewed and approve the protocol, the appropriate informed consent form, and other associated documents and agree to abide by their terms and to comply with current ICH GCP Guidelines. I fully understand that any changes initiated by the Investigator without prior agreement in writing from Lundbeck would constitute a deviation from the protocol.

…… ……..

Investigator Signature Date

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Investigator Name (Print)

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Address

10. REFERENCES

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11. APPENDICES

Appendix 1: Questionnaires

Appendix 1.1: Orthostatic Hypotension Questionnaire (OHQ)

Appendix 1.2: Clinical Global Impressions – Severity