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Protocol Registration and Results System

ID: Droxidopa NOH303 | Open-Label Clinical Study of Droxidopa in Patients With Neurogenic Orthostatic Hypotension (NOH) | NCT00738062

Protocol Registration and Results Preview

Open-Label Clinical Study of Droxidopa in Patients With Neurogenic Orthostatic Hypotension (NOH) (NOH303)

This study has been completed.

Sponsor:
Chelsea Therapeutics

Information provided by (Responsible Party):
Chelsea Therapeutics

ClinicalTrials.gov Identifier:
NCT00738062

First received: August 19, 2008
Last updated: April 22, 2014
Last verified: April 2014

Purpose

The purpose of this study is to assess the durability of effect of Droxidopa in treating symptoms of neurogenic orthostatic hypotension in patients with Primary Autonomic Failure (Pure Autonomic Failure, Multiple System Atrophy, Parkinson's Disease), Non-diabetic neuropathy, or Beta Hydroxylase deficiency.

Condition	Intervention	Phase
Neurogenic Orthostatic Hypotension Non-Diabetic Autonomic Neuropathy Multiple System Atrophy Dopamine Beta Hydroxylase Deficiency	Drug: Droxidopa Drug: Placebo	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study

Official Title: An Open-label Study, to Assess the Long-term Safety and Clinical Benefit of Droxidopa in Subjects With PAF, Dopamine Beta

Close

Further study details as provided by Chelsea Therapeutics:

Primary Outcome Measure:

- Change in Orthostatic Hypotension Questionnaire Composite Score (OHQ) [Time Frame: 14 days] [Designated as safety issue: No]
  The OHQ is the average of two sub-scales, the Orthostatic Hypotension Symptom Assessment Scale (OHSA) and the Orthostatic Hypotension Daily Activities Scale (OHDAS). Each asks the patient to rate their symptoms or disease impact over the past week. The OHSA sub-scale is the average of six items: 1) Dizziness, lightheadedness, feeling faint or feeling like you might black out; 2) Problems with vision; 3) Weakness; 4) Fatigue; 5) Trouble concentrating; and 6) Head/neck discomfort. The OHDAS sub-scale is the average of

four items: 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. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug). All patients are on open-label droxidopa for 3 months prior to randomization.

Secondary Outcome Measures:

- Change in Orthostatic Hypotension Daily Activities (OHDAS) Score [Time Frame: 14 days] [Designated as safety issue: No]
  The OHDAS scale is the average of four items: 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. Each asks the patient to rate their disease impact over the past week. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. Change: score at end of randomization minus score at randomization. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug).

- Change in Orthostatic Hypotension Symptom Assessment (OHSA) Composite Score [Time Frame: 14 days] [Designated as safety issue: No]
  The OHSA scale is the average of six items: 1) Dizziness, lightheadedness, feeling faint or feeling like you might black out; 2) Problems with vision; 3) Weakness; 4) Fatigue; 5) Trouble concentrating; and 6) Head/neck discomfort. Each asks the patient to rate their symptoms over the past week. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. Change: score at end of randomization minus score at randomization. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug).

- Change in Systolic Blood Pressure (SBP) Measurements 3 Minutes Post Standing [Time Frame: 14 days] [Designated as safety issue: No]
  Change: standing systolic blood pressure at end of study minus standing systolic blood pressure at randomization. In this withdrawal design, a negative score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug). All patients are on open-label droxidopa for 3 months prior to randomization to either continued droxidopa or to placebo.

- Patient Reported Clinical Global Impression - Severity [Time Frame: 14 days] [Designated as safety issue: No]
  The CGI-S is a 7 point scale ranging from a score of 1 (no symptoms) to 7 (severe symptoms). Patients were grouped according to OH severity at the end of the randomization period as follows; - Normal-Borderline OH (CGI-S 1-2), - Mild-Moderate OH (CGI-S 3-4), - Marked OH-Most Ill with OH (CGI-S 5-7). .

- Clinician Recorded Clinical Global Impression - Severity [Time Frame: 14 days] [Designated as safety issue: No]
  The CGI-S is a 7 point scale ranging from a score of 1 (no symptoms) to 7 (severe symptoms). Patients were grouped according to OH severity at the end of the randomization period as follows; - Normal-Borderline OH (CGI-S 1-2), - Mild-Moderate OH (CGI-S 3-4), - Marked OH-Most Ill with OH (CGI-S 5-7).

- Patient Reported Clinical Global Impression - Improvement [Time Frame: 14 days] [Designated as safety issue: No]
  The CGI-I is a 7 point scale ranging from a score of 1 (very much improved) to 7 (very much worse), with no change in the middle, and assesses the improvement in relation to the baseline evaluation. Patients will be grouped according change in disease as follows; - Very Much Improved to Slightly Improved (CGI-I 1-3), - No Change (CGI-I 4), - Slightly Worse to Very Much Worse (CGI-I 5-7).

- Clinician Rated Clinical Global Impressions - Improvement [Time Frame: 14 days] [Designated as safety issue: No]
  The CGI-I is a 7 point scale ranging from a score of 1 (very much improved) to 7 (very much worse), with no change in the middle, and assesses the improvement in relation to the baseline evaluation. Patients will be grouped according change in disease as follows; - Very Much Improved to Slightly Improved (CGI-I 1-3), - No Change (CGI-I 4), - Slightly Worse to Very Much Worse (CGI-I 5-7).

Enrollment: 103
Study Start Date: January 2008
Study Completion Date: December 2010
Primary Completion Date: December 2010

Arms	Assigned Interventions
Active Comparator: Droxidopa Study medication	Drug: Droxidopa 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day Other Names: • Droxidopa
Placebo Comparator: Placebo Placebo	Drug: Placebo 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day Other Names: • Inactive drug (to look like Droxidopa)

Systolic blood pressure 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, and thus maintain adequate cerebral perfusion. The compensatory mechanisms that regulate blood pressure upon standing are dysfunctional in subjects with orthostatic hypotension (OH), 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.

The autonomic nervous system has a central role in the regulation of blood pressure. Primary Autonomic Failure is manifested in a variety of syndromes. Orthostatic hypotension is a usual presenting symptom. Primary Autonomic Failure may be the primary diagnosis, and classifications include pure autonomic failure (PAF), also called idiopathic orthostatic hypotension (Bradbury-Eggleston syndrome) autonomic failure with multiple system atrophy (Shy-Drager syndrome) and also Parkinson's disease. Regardless of the primary condition, autonomic dysfunction underlies orthostatic hypotension.

Orthostatic hypotension may be a severely disabling condition which can seriously interfere with the quality of life of afflicted subjects. Currently available therapeutic options provide some symptomatic relief in a subset of subjects, but are relatively ineffective and are often accompanied by severe side effects that limit their usefulness. Support garments (tight-fitting leotard) may prove useful in some subjects, but is difficult to don without family or nursing assistance, especially for older subjects. Midodrine, fludrocortisone, methylphenidate, ephedrine, indomethacin and dihydroergotamine are among some of the pharmacological interventions that have been used to treat orthostatic hypotension, although only midodrine is specifically approved for this indication. The limitations of these currently available therapeutic options, and the incapacitating nature and often progressive downhill course of disease, point to the need for an improved therapeutic alternative.

The current withdrawal design study will measure the efficacy of droxidopa on symptoms of neurogenic orthostatic hypotension in patients randomized to continued droxidopa treatment versus placebo, following 14 days of double-blind treatment.

Droxidopa

Droxidopa [also, known as L-threo-3,4-dihydroxyphenylserine, L-threo-DOPS, or L-DOPS] is the International non-proprietary name (INN) for a synthetic amino acid precursor of norepinephrine (NE), which was originally developed by Sumitomo Pharmaceuticals Co., Limited, Japan. It has been approved for use in Japan since 1989. 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, and Parkinson's disease. There are four stereoisomers of DOPS; however, only the L-threo-enantiomer (droxidopa) is biologically active.

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.

Droxidopa has been marketed in Japan since 1989. Data from clinical studies and post-marketing surveillance programs conducted in Japan show that the most commonly reported adverse drug reactions with droxidopa are increased blood pressure, nausea, and headache. In clinical studies, the prevalence and severity of droxidopa adverse effects appear to be similar to those reported by the placebo control arm.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Inclusion Criteria:

To be eligible for inclusion, each patient must fulfill the following criteria:

- Participated in Droxidopa Protocol 302;
- 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.

Exclusion Criteria:

Patients are not eligible for this study if they fulfill one or more of the following criteria:

- Currently taking ephedrine or midodrine;
- Patients taking ephedrine or midodrine must stop taking these drugs at least 2 days prior to their study entry visit (Visit 1).
- Currently taking anti-hypertensive medication;

  * The use of short-acting anti-hypertensive medications at bedtime is permitted.
- Currently taking tri-cyclic antidepressant medication or other norepinephrine re-uptake inhibitors;
- Have changed dose, frequency and or type of prescribed medication, within two weeks of study start (excluding ephedrine and midodrine);
- History of more than moderate alcohol consumption;
- History of known or suspected drug or substance abuse;
- Women of childbearing potential who are not using a medically accepted contraception;
  - Reproductive potential:
  - Female subjects should be either post-menopausal (amenorrhea for at least 12 consecutive months), surgically sterile, or women of child-bearing potential (WOCP) who are using or agree to use acceptable methods of contraception.
  - Acceptable contraceptives include intrauterine devices (IUDs), hormonal contraceptives (oral, depot, patch or injectable) and double barrier methods such as condoms or diaphragms with spermicidal gel or foam.
  - For WOCP a urine pregnancy test must be conducted at each study visit.
  - WOCP must be advised to use acceptable contraceptives throughout the study period and for 30 days after the last dose of investigational product.
  - If hormonal contraceptives are used they should be taken according to the package insert.
  - WOCP who are not currently sexually active must agree to use acceptable contraception, as defined above, if they decide to become sexually active during the period of the study and for 30 days after the last dose of investigational product.
- Sexually active males whose partner is a WOCP and who do not agree to use condoms for the duration of the study and for 30 days after the last dose;
- Women who are pregnant or breast feeding;
- Known or suspected hypersensitivity to the study medication or any of its ingredients;
- Pre-existing sustained severe hypertension (BP 180/110 mmHg in the sitting position);
- Have atrial fibrillation or, in the investigator's opinion, have any other significant cardiac arrhythmia;
- Any other significant systemic, hepatic, cardiac or renal illness;

- Diabetes mellitus or insipidus;
- Have a history of closed angle glaucoma;
- Have a known or suspected malignancy;
- Have a serum creatinine level > 130 umol/L;
- Patients with known gastrointestinal illness or other gastrointestinal disorder that may, in the investigator's opinion, affect the absorption of study drug;
- In the investigator's opinion, have clinically significant abnormalities on clinical examination or laboratory testing;
- In the investigator's opinion, are unable to adequately co-operate because of individual or family situation;
- In the investigator's opinion, are suffering from a mental disorder that interferes with the diagnosis and/or with the conduct of the study, e.g. schizophrenia, major depression, dementia;
- Are not able or willing to comply with the study requirements for the duration of the study.

Contacts and Locations

Locations

United States, Alabama

University of Alabama at Birmingham
Birmingham, Alabama, United States, 35233

United States, Arizona

Dedicated Clinical Research
Litchfield Park, Arizona, United States, 85340

Xenoscience Inc.
Phoenix, Arizona, United States, 85004

Sun Health Research Institute
Sun City, Arizona, United States, 85351

United States, California

The Parkinson's and Movement Disorders Institute
Fountain Valley, California, United States, 92708

Pacific Neuroscience Medical Group
Oxnard, California, United States, 93030

The Parkinson's Institute
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United States, Colorado

Electrophysiology Associates
Colorado Springs, Colorado, United States, 80910

United States, Florida

Parkinson's Disease & Movment Disorder Center
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University of Miami Miller School of Medicine

Miami, Florida, United States, 33136

University of South Florida

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United States, Georgia

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Christchurch, New Zealand
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Investigators

Principal Investigator:	Horacio Kaufmann Kaufmann, MD	NYU School of Medicine
Principal Investigator:	Christopher J. Mathias, MD	Imperial School of Medicine

More Information
NOH Study Website

Responsible Party: Chelsea Therapeutics
Study ID Numbers: Droxidopa NOH303
Health Authority: United States: Food and Drug Administration

Study Results

Participant Flow

Recruitment Details	
Pre-Assignment Details	

Arm/Group Title	Open-Label Droxidopa	Double-blind Droxidopa	Double-blind Placebo	Total (Not public)
Arm/Group Description	3 months of open-label treatment with droxidopa (t.i.d., at optimal dose)	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	
Period Title: **Open Label Treatment**				
Started	103	0	0	103
Completed	75	0	0	75
Not Completed	28	0	0	28
Reason Not Completed				
Lack of Efficacy	5	0	0	5
Adverse Event	11	0	0	11
Protocol Violation	2	0	0	2
Withdrawal by Subject	9	0	0	9
Investigator Decision	1	0	0	1
(Not Public)	Not Completed = 28 Total from all reasons = 28	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	
Period Title: **2 Week Randomized Withdrawal**				
Started	0 [1] NOTE : The number of	38 NOTE : The number of	37 NOTE : The number of	75

	participants to start a Period is not equal to the number who completed previous Period.	participants to start a Period is not equal to the number who completed previous Period.	participants to start a Period is not equal to the number who completed previous Period.	
Completed	0	38	37	75
Not Completed	0	0	0	0

[1] Patients completing the open label titration phase were randomized to either Droxidopa or Placebo

Period Title: **Open-Label Extension**

Started	74 [1] NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	0 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	0 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	74
Completed	57	0	0	57
Not Completed	17	0	0	17
Reason Not Completed				
Adverse Event	5	0	0	5
Physician Decision	1	0	0	1
Lack of Efficacy	2	0	0	2
Withdrawal by Subject	6	0	0	6
Protocol Violation	1	0	0	1
Study Terminated	2	0	0	2
(Not Public)	Not Completed = 17 Total from all reasons = 17	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	

[1] One patient completed double blind randomization but did not enter the open label extension

Baseline Characteristics

Arm/Group Title	Open-Label Droxidopa	Double-blind Droxidopa	Double-blind Placebo	Total
Arm/Group Description	Only participated in 3 months of open-label treatment with droxidopa (t.i.d., at optimal dose)	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	
Overall Number of Baseline Participants	27	38	37	**102**
Baseline Analysis Population	Omits 1 patient who randomized into the study in error and did not receive study drug.			

Description				
Age, Continuous Mean (Standard Deviation) Units: years	61.9 (10.95)	68.2 (13.03)	66.2 (12.09)	65.8 (12.31)
Gender, Male/Female Measure Type: Number Units: participants				
Female	13	15	13	41
Male	14	23	24	61
Race (NIH/OMB) Measure Type: Number Units: participants				
American Indian or Alaska Native	0	0	1	1
Asian	0	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	27	37	36	100
More than one race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Region of Enrollment Measure Type: Number Units: participants				
United States	16	25	22	63
Canada	2	6	3	11
Australia	2	2	2	6
New Zealand	0	1	1	2
United Kingdom	0	1	3	4
Poland	7	3	6	16
Primary Clinical Diagnosis Measure Type: Number Units: participants				
Parkinson's Disease	10	20	18	48
Multiple System Atrophy	10	8	9	27
Pure Autonomic Failure	3	8	7	18
Dopamine Beta-Hydroxylase Deficiency	0	1	0	1
Non-Diabetic Autonomic Neuropathy	3	0	2	5

Other	1	1	1	3

Outcome Measures

1. Primary Outcome

Title:	Change in Orthostatic Hypotension Questionnaire Composite Score (OHQ)
Description:	The OHQ is the average of two sub-scales, the Orthostatic Hypotension Symptom Assessment Scale (OHSA) and the Orthostatic Hypotension Daily Activities Scale (OHDAS). Each asks the patient to rate their symptoms or disease impact over the past week. The OHSA sub-scale is the average of six items: 1) Dizziness, lightheadedness, feeling faint or feeling like you might black out; 2) Problems with vision; 3) Weakness; 4) Fatigue; 5) Trouble concentrating; and 6) Head/neck discomfort. The OHDAS sub-scale is the average of four items: 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. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug). All patients are on open-label droxidopa for 3 months prior to randomization.
Time Frame:	14 days
Safety Issue?	No

Outcome Measure Data

Analysis Population Description

The analysis population was based on the ITT population of all patients randomized. Last observation carry forward was used for patients who prematurely discontinued the study.
One droxidopa patient was excluded from the analysis because OHQ values were not evaluable.

Arm/Group Title	Droxidopa	Placebo
Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	37	37
Mean (Standard Deviation) Units: units on a scale	0.57 (1.891)	0.90 (1.550)

Statistical Analysis 1

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.438
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHSA Item 1 value at randomization.

2. Secondary Outcome

Title:	Change in Orthostatic Hypotension Daily Activities (OHDAS) Score
▼ Description:	The OHDAS scale is the average of four items: 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. Each asks the patient to rate their disease impact over the past week. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. Change: score at end of randomization minus score at randomization. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug).
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

One droxidopa patient excluded from analysis because data were not evaluable.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	37	37
Mean (Standard Deviation) Units: units on a scale	0.53 (2.204)	0.71 (1.629)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.554
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHDAS Composite value at randomization.

3. Secondary Outcome

Title:	Change in Orthostatic Hypotension Symptom Assessment (OHSA) Composite Score
▼ Description:	The OHSA scale is the average of six items: 1) Dizziness, lightheadedness, feeling faint or feeling like you might black out; 2) Problems with vision; 3) Weakness; 4) Fatigue; 5) Trouble concentrating; and 6) Head/neck discomfort. Each asks the patient to rate their symptoms over the past week. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. Change: score at end of randomization minus score at randomization. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug).
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Mean (Standard Deviation)	0.59 (1.963)	1.10 (1.658)

Units: units on a scale		

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.198
	Comments	[Not specified]
	Method	Mantel Haenszel

	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHSA Composite value at baseline.

4. Secondary Outcome

Title:	Change in Systolic Blood Pressure (SBP) Measurements 3 Minutes Post Standing
▼ Description:	Change: standing systolic blood pressure at end of study minus standing systolic blood pressure at randomization. In this withdrawal design, a negative score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug). All patients are on open-label droxidopa for 3 months prior to randomization to either continued droxidopa or to placebo.
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Mean (Standard Deviation) Units: mmHg	-8.4 (26.63)	0.0 (18.51)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.286
	Comments	[Not specified]

	Method	Mantel Haenszel
	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHSA Item 1 value at randomization.

5. Secondary Outcome

Title:	Patient Reported Clinical Global Impression - Severity
▼ Description:	The CGI-S is a 7 point scale ranging from a score of 1 (no symptoms) to 7 (severe symptoms). Patients were grouped according to OH severity at the end of the randomization period as follows; • Normal-Borderline OH (CGI-S 1-2), • Mild-Moderate OH (CGI-S 3-4), • Marked OH-Most Ill with OH (CGI-S 5-7). .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description
[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Measure Type: Number Units: participants		
Normal-Borderline OH	13	12
Mild-Moderate OH	16	13
Marked OH-Most ill with OH	9	12

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.708
	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

6. Secondary Outcome

Title:	Clinician Recorded Clinical Global Impression - Severity
▼ Description:	The CGI-S is a 7 point scale ranging from a score of 1 (no symptoms) to 7 (severe symptoms). Patients were grouped according to OH severity at the end of the randomization period as follows; • Normal-Borderline OH (CGI-S 1-2), • Mild-Moderate OH (CGI-S 3-4), • Marked OH-Most Ill with OH (CGI-S 5-7).
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Measure Type: Number Units: participants		
Normal-Borderline OH	9	7
Mild-Moderate OH	16	15
Marked OH-Most ill with OH	13	15

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical	P-Value	0.873

Test of Hypothesis	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

7. Secondary Outcome

Title:	Patient Reported Clinical Global Impression - Improvement
▼ Description:	The CGI-I is a 7 point scale ranging from a score of 1 (very much improved) to 7 (very much worse), with no change in the middle, and assesses the improvement in relation to the baseline evaluation. Patients will be grouped according change in disease as follows; • Very Much Improved to Slightly Improved (CGI-I 1-3), • No Change (CGI-I 4), • Slightly Worse to Very Much Worse (CGI-I 5-7).
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Measure Type: Number Units: participants		
Very much - Slightly Improved	25	20
No Change	7	5
Slightly - Very much Worse	6	12

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.252
	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

8. Secondary Outcome

Title:	Clinician Rated Clinical Global Impressions - Improvement
▼ Description:	The CGI-I is a 7 point scale ranging from a score of 1 (very much improved) to 7 (very much worse), with no change in the middle, and assesses the improvement in relation to the baseline evaluation. Patients will be grouped according change in disease as follows; • Very Much Improved to Slightly Improved (CGI-I 1-3), • No Change (CGI-I 4), • Slightly Worse to Very Much Worse (CGI-I 5-7).
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data 

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Measure Type: Number Units: participants		

Very much - Slightly Improved	26	20
No Change	4	8
Slightly - Very much Worse	8	9

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.330
	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

9. Post-Hoc Outcome

Title:	Change in Dizziness/ Lightheadedness/ Feeling Faint/ or Feeling Like You Might Blackout (OHSA Item 1)
▼ Description:	OHSA item 1 scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. In this withdrawal design, a positive score indicates worsening during the double-blind randomized phase relative to value at randomization (on open-label drug). All patients were on open-label droxidopa for 3 months prior to randomization to either continued droxidopa or to placebo.
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Study medication Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Placebo Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day
Number of Participants Analyzed	38	37
Mean (Standard Deviation) Units: units on a scale	0.9 (2.39)	1.3 (2.21)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Droxidopa, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.251
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHSA Item 1 value at randomization.

Adverse Events

Time Frame	
Additional Description	
Source Vocabulary Name	[Not specified]
Assessment Type	[Not specified]

Arm/Group Title	Three Month Open-Label Droxidopa	Double-blind Droxidopa	Double-blind Placebo	Long-Term Follow-up	Total Droxidopa
Arm/Group Description	all patients who participated in 3 months of open-label treatment with droxidopa (t.i.d., at optimal dose)	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	Open-label treatment with droxidopa (t.i.d) following the double-blind randomization phase.	All Patients exposed to droxidopa

Serious Adverse Events

	Three Month Open-Label Droxidopa		Double-blind Droxidopa		Double-blind Placebo		Long-Term Follow-up		Total Droxidopa	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	12/102		1/38 (2.63%)		0/37 (0%)		16/74 (21.62%)		26/102 (25.49%)	

	(11.76%)								
Cardiac disorders									
Angina pectoris	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	2/102 (1.96%)	2
Atrial fibrillation	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Coronary artery disease	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Ear and labyrinth disorders									
Vertigo	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Gastrointestinal disorders									
Diverticulum	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
General disorders									
Sudden cardiac death	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Infections and infestations									
Pneumonia	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	2/74 (2.7%)	2	2/102 (1.96%)	2
Urinary tract infection	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	2/74 (2.7%)	2	2/102 (1.96%)	2
Injury, poisoning and procedural complications									
Cervical vertebral fracture	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Contusion	0/102 (0%)	0	1/38 (2.63%)	1	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Facial bones fracture	0/102 (0%)	0	1/38 (2.63%)	1	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Fall	0/102 (0%)	0	1/38 (2.63%)	1	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Hip fracture	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	2/74 (2.7%)	2	3/102 (2.94%)	3
Pelvic fracture	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Metabolism and nutrition disorders									
Dehydration	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Musculoskeletal and connective									

tissue disorders									
Arthralgia	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Osteoarthritis	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Nervous system disorders									
Dementia	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Headache	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Hypoxic encephalopathy	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Loss of consciousness	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Syncope	1/102 (0.98%)	1	1/38 (2.63%)	1	0/37 (0%)	0	2/74 (2.7%)	2	4/102 (3.92%)	4
Psychiatric disorders									
Agitation	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Anxiety	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Confusional state	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Depression	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Hallucination	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Hallucination, visual	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Major depression	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Post-traumatic stress disorder	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Renal and urinary disorders									
Renal failure acute	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Respiratory, thoracic and mediastinal disorders									
Acute respiratory failure	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Bronchial haemorrhage	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Respiratory distress	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1

Surgical and medical procedures									
Malignant tumour excision	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1
Vascular disorders									
Deep vein thrombosis	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Orthostatic hypotension	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	1/102 (0.98%)	1
Venous thrombosis limb	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	0/74 (0%)	0	1/102 (0.98%)	1

▼ Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%

	Three Month Open-Label Droxidopa		Double-blind Droxidopa		Double-blind Placebo		Long-Term Follow-up		Total Droxidopa	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	37/102 (36.27%)		8/38 (21.05%)		4/37 (10.81%)		43/74 (58.11%)		62/102 (60.78%)	
General disorders										
Edema peripheral	0/102 (0%)	0	0/38 (0%)	0	0/37 (0%)	0	4/74 (5.41%)	5	4/102 (3.92%)	5
Infections and infestations										
Bacteriuria	2/102 (1.96%)	2	0/38 (0%)	0	0/37 (0%)	0	4/74 (5.41%)	4	5/102 (4.9%)	6
Upper respiratory tract infection	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	4/74 (5.41%)	4	5/102 (4.9%)	5
Urinary Tract Infection	9/102 (8.82%)	10	2/38 (5.26%)	2	0/37 (0%)	0	11/74 (14.86%)	18	17/102 (16.67%)	31
Injury, poisoning and procedural complications										

Fall	7/102 (6.86%)	8	0/38 (0%)	0	1/37 (2.7%)	1	16/74 (21.62%)	20	20/102 (19.61%)	29
Musculoskeletal and connective tissue disorders										
Back pain	4/102 (3.92%)	4	2/38 (5.26%)	2	0/37 (0%)	0	7/74 (9.46%)	8	11/102 (10.78%)	14
Muscle Spasms	2/102 (1.96%)	2	1/38 (2.63%)	1	0/37 (0%)	0	4/74 (5.41%)	4	7/102 (6.86%)	7
Neck Pain	3/102 (2.94%)	3	0/38 (0%)	0	0/37 (0%)	0	3/74 (4.05%)	3	6/102 (5.88%)	6
Nervous system disorders										
Dizziness	2/102 (1.96%)	2	1/38 (2.63%)	1	1/37 (2.7%)	1	5/74 (6.76%)	8	8/102 (7.84%)	12
Headache	5/102 (4.9%)	6	1/38 (2.63%)	1	2/37 (5.41%)	2	6/74 (8.11%)	6	13/102 (12.75%)	15
Somnolence	5/102 (4.9%)	5	0/38 (0%)	0	0/37 (0%)	0	1/74 (1.35%)	1	6/102 (5.88%)	6
Syncope	4/102 (3.92%)	5	1/38 (2.63%)	2	0/37 (0%)	0	7/74 (9.46%)	9	10/102 (9.8%)	17
Tremor	2/102 (1.96%)	2	0/38 (0%)	0	0/37 (0%)	0	4/74 (5.41%)	5	5/102 (4.9%)	7
Psychiatric disorders										
Insomnia	1/102 (0.98%)	1	0/38 (0%)	0	0/37 (0%)	0	4/74 (5.41%)	4	5/102 (4.9%)	5
Vascular disorders										
Orthostatic hypotension	3/102 (2.94%)	4	0/38 (0%)	0	0/37 (0%)	0	3/74 (4.05%)	3	6/102 (5.88%)	7

Limitations and Caveats

[Not Specified]

More Information

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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