ClinicalTrials.gov PRS
Protocol Registration and Results System

ID: Droxidopa NOH302 Clinical Study of Droxidopa in Patients With Neurogenic Orthostatic Hypotension (NOH) NCT00633880

Protocol Registration and Results Preview

Clinical Study of Droxidopa in Patients With Neurogenic Orthostatic Hypotension (NOH) (NOH302)

This study has been completed.

Sponsor:
Chelsea Therapeutics

Collaborators:
Chiltern International Inc.

Information provided by (Responsible Party):
Chelsea Therapeutics

ClinicalTrials.gov Identifier:
NCT00633880

First received: March 5, 2008
Last updated: April 22, 2014
Last verified: April 2014

Purpose

The purpose of this study is to see whether droxidopa is effective 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
Symptomatic Neurogenic Orthostatic Hypotension (NOH) Non-diabetic Neuropathy Primary Autonomic Failure Dopamine Beta Hydroxylase Deficiency	Drug: Placebo Drug: Droxidopa	Phase 3

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

Official Title: Phase III, Multi-Center, Study to Assess the Clinical Effect of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Neuropathy and Symptomatic NOH

Further study details as provided by Chelsea Therapeutics:

Primary Outcome Measure:

- Change in Dizziness/ Lightheadedness/ Feeling Faint/ or Feeling Like You Might Blackout (OHSA Item 1) [Time Frame: 14 days] [Designated as safety issue: No]
  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)

Close

Secondary Outcome Measures:

- Change in Fatigue (OHSA Item 4) [Time Frame: 14 days] [Designated as safety issue: No]
  OHSA item 4 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) .

- Change in Weakness (OHSA Item 3) [Time Frame: 14 days] [Designated as safety issue: No]
  OHSA item 3 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) .

- Change in Vision (OHSA Item 2) [Time Frame: 14 days] [Designated as safety issue: Yes]
  OHSA item 2 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) .

- Change in Concentration (OHSA Item 5) [Time Frame: 14 days] [Designated as safety issue: No]
  OHSA item 5 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) .

- Change in Head/Neck Discomfort (OHSA Item 6) [Time Frame: 14 days] [Designated as safety issue: No]
  OHSA item 6 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) .

- Change in Ability to Conduct Activities of Daily Living Score (OHDAS Composite 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 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) .

- Change in Orthostatic Hypotension Symptom Assessment Score (OHSA Composite) [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 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) .

- Change in Orthostatic Hypotension Symptom Scores Excluding Dizziness (OHSA Composite Items 2-6) [Time Frame: 14 days] [Designated as safety issue: No]
  OHSA composite scale (items 2-6) is the average of five OHSA items: 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 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) .

- 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) .

Enrollment: 181
Study Start Date: January 2008
Study Completion Date: September 2009
Primary Completion Date: August 2009

Arms	Assigned Interventions
Experimental: Droxidopa Double-blind	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: • L-DOPS • L-threo-DOPS • Northera
Placebo Comparator: Placebo Double-blind	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: • Placebo

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
PATIENT INCLUSION CRITERIA:

- Male or female and aged 18 years or over;
- Clinical diagnosis of orthostatic hypotension associated with Primary Autonomic Failure (PD, MSA and PAF), Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Autonomic Neuropathies;
- A documented fall in systolic blood pressure of at least 20 mmHg, or in diastolic blood pressure of at least 10 mmHg, within 3 minutes after standing;
- 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.

MAIN PATIENT EXCLUSION CRITERIA:

- Taking ephedrine or midodrine; Patients taking ephedrine or midodrine may enroll after a minimum 7 day washout period;
- Taking anti-hypertensive medication;
- Have a history of more than moderate alcohol consumption;
- Women who are pregnant or lactating;
- Have a history of closed angle glaucoma;
- Have 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;
- In the investigator's opinion, have any other significant systemic, hepatic, cardiac or renal illness;
- Have diabetes mellitus or insipidus;
- Have a known or suspected malignancy;
- Have 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;
- Have a serum creatinine level > 130 µmol/L;

Contacts and Locations

Locations

United States, Alabama

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

United States, Arizona

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Litchfield Park, Arizona, United States, 85340

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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

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United States, Colorado

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University of Cincinnati
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Markham, Ontario, Canada, L6B1C9
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Canada, Quebec
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Investigators

Principal Investigator:	Horacio Kaufmann, MD	New York University Medical Center
Principal Investigator:	Christopher J Mathias, MD	Imperial School of Medicine
Principal Investigator:	Roy Freeman, MD	Harvard Medicine School
Principal Investigator:	Phillip A Low, MD	Mayo Foundation

More Information

Click here for more information about the sponsor

NOH Study Website

Responsible Party: Chelsea Therapeutics

Study ID Numbers: Droxidopa NOH302

Health Authority: United States: Food and Drug Administration
Canada: Health Canada
United Kingdom: Medicines and Healthcare Products Regulatory Agency
Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
Australia: Department of Health and Ageing Therapeutic Goods Administration

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Study Results

Participant Flow

Recruitment Details	
Pre-Assignment Details	

Arm/Group Title	Open Label Titration	Droxidopa	Placebo	Total (Not public)
Arm/Group Description	All patients titrated to their optimal dose of droxidopa during an initial open label phase for 7-14 days	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 Titration**				
Started	181	0	0	181
Completed	101	0	0	101
Not Completed	80	0	0	80
Reason Not Completed				
Lack of Efficacy	1	0	0	1
Adverse Event	13	0	0	13
Treatment Failure	55	0	0	55
Protocol Violation	6	0	0	6
Physician Decision	1	0	0	1
Withdrawal by Subject	4	0	0	4
(Not Public)	Not Completed = 80 Total from all reasons = 80	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	
Period Title: **Randomized Double Blind**				
Started	0 NOTE : The number of participants to start a	50 NOTE : The number of participants to start a	51 NOTE : The number of participants to start a	101

	Period is not equal to the number who completed previous Period.	Period is not equal to the number who completed previous Period.	Period is not equal to the number who completed previous Period.	
Completed	0	50	51	101
Not Completed	0	0	0	0

Baseline Characteristics

Arm/Group Title	Not Randomized	Droxidopa	Placebo	Total
▼ Arm/Group Description	Entered open-label droxidopa dose titration, but did not randomize	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	80	50	51	**181**
▼ Baseline Analysis Population Description [Not specified]				
Age, Continuous Mean (Standard Deviation) Units: years	69.5 (9.74)	63.1 (13.76)	66.6 (11.25)	66.9 (11.62)
Gender, Male/Female Measure Type: Number Units: participants				
Female	35	20	19	74
Male	45	30	32	107
Race (NIH/OMB) Measure Type: Number Units: participants				
American Indian or Alaska Native	0	0	1	1
Asian	0	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	80	49	49	178
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	53	25	32	110
Canada	8	9	2	19
United Kingdom	5	3	2	10
Poland	5	10	8	23
Australia	8	2	6	16
New Zealand	1	1	1	3
Primary Clinical Diagnosis Measure Type: Number Units: participants				
Parkinson's Disease	38	21	23	82
Multiple System Atrophy	21	17	13	51
Pure Autonomic Failure	18	8	10	36
Dopamine Beta-Hydroxylase Deficiency	0	0	1	1
Non-Diabetic Autonomic Neuropathy	2	2	3	7
Other	1	2	1	4

Outcome Measures

1. Primary 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Missing data were imputed using the last observation carry forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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	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

	times per day	per day
Number of Participants Analyzed	50	51
Mean (Standard Deviation) Units: units on a scale	1.3 (2.75)	1.9 (3.16)

▼ 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	0.509
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors. As the primary endpoint was not positive, statistical analysis was not performed on secondary endpoints.
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

2. Secondary Outcome

Title:	Change in Fatigue (OHSA Item 4)
▼ Description:	OHSA item 4 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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
Number of Participants Analyzed	50	51
Mean (Standard Deviation) Units: units on a scale	0.7 (2.61)	1.5 (2.72)

3. Secondary Outcome

Title:	Change in Weakness (OHSA Item 3)
▼ Description:	OHSA item 3 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times

	times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	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	50	51
Mean (Standard Deviation) Units: units on a scale	0.3 (2.88)	1.2 (2.70)

4. Secondary Outcome

Title:	Change in Vision (OHSA Item 2)
▼ Description:	OHSA item 2 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) .
Time Frame:	14 days
Safety Issue?	Yes

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times

	times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	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	50	51
Mean (Standard Deviation) Units: units on a scale	1.1 (2.79)	0.8 (2.24)

5. Secondary Outcome

Title:	Change in Concentration (OHSA Item 5)
▼ Description:	OHSA item 5 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times

	times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	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	50	51
Mean (Standard Deviation) Units: units on a scale	0.1 (2.74)	0.9 (2.67)

6. Secondary Outcome

Title:	Change in Head/Neck Discomfort (OHSA Item 6)
▼ Description:	OHSA item 6 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	Double-blind Droxidopa: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three	Double-blind Placebo: 100 mg, oral, three times per day 200 mg, oral, three times per day 300 mg, oral, three times

	times per day 400 mg, oral, three times per day 500 mg, oral, three times per day 600 mg, oral, three times per day	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	50	51
Mean (Standard Deviation) Units: units on a scale	-0.1 (2.45)	1.2 (3.19)

7. Secondary Outcome

Title:	Change in Ability to Conduct Activities of Daily Living Score (OHDAS Composite 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 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

One placebo patient excluded from analysis because OHDAS values were not evaluable.

Arm/Group Title	Droxidopa	Placebo

▼ Arm/Group Description:	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
Number of Participants Analyzed	50	50
Mean (Standard Deviation) Units: units on a scale	-0.24 (2.35)	0.91 (2.50)

8. Secondary Outcome

Title:	Change in Orthostatic Hypotension Symptom Assessment Score (OHSA Composite)
▼ 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 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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
Number of Participants Analyzed	50	51
Mean (Standard Deviation) Units: units on a scale	0.6 (2.27)	1.35 (2.53)

9. Secondary Outcome

Title:	Change in Orthostatic Hypotension Symptom Scores Excluding Dizziness (OHSA Composite Items 2-6)
▼ Description:	OHSA composite scale (items 2-6) is the average of five OHSA items: 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 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

One placebo patient excluded from analysis per the SAP because all baseline values in the composite

were zero.
LOCF was used to impute values for patients who did not have an end of study visit.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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
Number of Participants Analyzed	50	50
Mean (Standard Deviation) Units: units on a scale	0.44 (2.29)	1.07 (2.25)

10. 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

three placebo patients excluded from the analysis due to missing standing blood pressure values at either randomization or end of study.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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
Number of Participants Analyzed	50	48
Mean (Standard Deviation) Units: mmHg	-7.6 (19.71)	-5.2 (26.83)

11. Post-Hoc Outcome

Title:	Change in Orthostatic Hypotension Questionnaire 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) .
Time Frame:	14 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

3 droxidopa patients and 2 placebo patients were excluded from the analysis due to missing randomization values.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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
Number of Participants Analyzed	47	49
Mean (Standard Deviation) Units: units on a scale	0.11 (2.176)	1.22 (2.390)

▼ 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	0.026
	Comments	[Not specified]
	Method	Wilcoxon (Mann-Whitney)

	Comments	[Not specified]

Adverse Events

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

Arm/Group Title	Droxidopa	Placebo	Open Label Phase
Arm/Group Description	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	All patient titrated on droxidopa during open-label phase

Serious Adverse Events

	Droxidopa		Placebo		Open Label Phase	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	0/50 (0%)		1/51 (1.96%)		4/181 (2.21%)	
Blood and lymphatic system disorders						
leukopenia	0/50 (0%)	0	0/51 (0%)	0	1/181 (0.55%)	1
Cardiac disorders						
Cardiac failure congestive	0/50 (0%)	0	0/51 (0%)	0	1/181 (0.55%)	1
Coronary artery disease	0/50 (0%)	0	0/51 (0%)	0	1/181 (0.55%)	1
Infections and infestations						
Pneumonia	0/50 (0%)	0	0/51 (0%)	0	1/181 (0.55%)	1
Urinary tract infection	0/50 (0%)	0	1/51 (1.96%)	1	0/181 (0%)	0
Psychiatric disorders						
Mental status change	0/50 (0%)	0	1/51 (1.96%)	1	0/181 (0%)	0
Vascular disorders						
Orthostatic hypotension	0/50 (0%)	0	0/51 (0%)	0	1/181 (0.55%)	1

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%					
	Droxidopa		**Placebo**		**Open Label Phase**	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	4/50 (8%)		11/51 (21.57%)		44/181 (24.31%)	
General disorders						
Fatigue	0/50 (0%)	0	1/51 (1.96%)	1	10/181 (5.52%)	10
Injury, poisoning and procedural complications						
Fall	1/50 (2%)	2	6/51 (11.76%)	7	9/181 (4.97%)	12
Nervous system disorders						
Dizziness	2/50 (4%)	2	1/51 (1.96%)	1	15/181 (8.29%)	18
Headache	2/50 (4%)	2	4/51 (7.84%)	4	20/181 (11.05%)	28

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.

Results Point of Contact

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