ClinicalTrials.gov PRS
Protocol Registration and Results System

ID: Droxidopa NOH301 A Clinical Study for Patients With Neurogenic Orthostatic Hypotension (NOH) Using Droxidopa NCT00782340

Protocol Registration and Results Preview

A Clinical Study for Patients With Neurogenic Orthostatic Hypotension (NOH) Using Droxidopa (NOH301)

This study has been completed.

Sponsor:
Chelsea Therapeutics

Collaborators:
Chiltern International Inc.

Information provided by (Responsible Party):
Chelsea Therapeutics

ClinicalTrials.gov Identifier:
NCT00782340

First received: October 29, 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), 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 Orthostatic Hypotension Questionnaire Score (OHQ) [Time Frame: 7 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) Lightheadedness; 2) Dizziness; 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. For the change from randomization, negative numbers represent improvement from randomization in OHQ score.

Close

Secondary Outcome Measures:

- Change in Ability to Conduct Activities of Daily Living Score (OHDAS Composite Score) [Time Frame: 7 days] [Designated as safety issue: No]

  OHDAS composite scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus

score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.

- Change in Orthostatic Hypotension Symptom Assessment (OHSA Composite) Score [Time Frame: 7 days] [Designated as safety issue: No]
  OHSA composite scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.

- Change in Activities Involving Standing a Short Time (OHDAS Item 1) [Time Frame: 7 days] [Designated as safety issue: No]
  OHDAS Item 1 scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.

- Change in Activities Involving Walking a Short Time (OHDAS Item 3) [Time Frame: 7 days] [Designated as safety issue: No]
  OHDAS Item 3 scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.

- Change in Dizziness/ Lightheadedness/ Feeling Faint/ or Feeling Like You Might Blackout (OHSA Item 1) [Time Frame: 7 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. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.

- Patient-Reported Clinical Global Improvement - Severity Scores [Time Frame: 7 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-Reported Clinical Global Improvement - Severity Scores [Time Frame: 7 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).

- Change in Systolic Blood Pressure (SBP) Measurements 3 Minutes Post Standing [Time Frame: 7 days] [Designated as safety issue: No]
  Change: standing systolic blood pressure at end of study minus standing systolic blood pressure at randomization. A positive score indicates an improvement during the double-blind randomized phase relative to value at randomization.

Enrollment: 263
Study Start Date: September 2008
Study Completion Date: September 2010
Primary Completion Date: September 2010

Arms	Assigned Interventions
Active Comparator: 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	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 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	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
Inclusion Criteria:

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

Exclusion Criteria:

- Currently taking ephedrine or midodrine
- Patients taking ephedrine or midodrine must stop taking these drugs at least 2 days prior to their baseline visit (Visit 2).
- 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
- For WOCP a serum beta HCG pregnancy test must be conducted at screening, and a urine pregnancy test must be conducted at baseline and study termination; the results must be negative at screening and at baseline for the patient to receive study medication.
- 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 mmol/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
- Have participated in another clinical trial with an investigational agent (including named patient or compassionate use protocol) within 4 weeks before the start of the study
- Previous enrolment in the study.

Contacts and Locations

Locations

United States, Alabama

North Alabama Neuroscience

Huntsville, Alabama, United States, 35801

United States, Arizona

Mayo Clinic-Arizona

Scottsdale, Arizona, United States, 85340

United States, Arkansas

Arkansas Cardiology

Little Rock, Arkansas, United States, 72205

United States, California

University of California, Irvine
Irvine, California, United States, 92697

United States, Florida

Bradenton Neurology, Inc
Bradenton, Florida, United States, 34205

Suncoast Neuroscience Associates, Inc
St. Petersburg, Florida, United States, 33701

United States, Kansas

University of Kansas Medical Center
Kansas City, Kansas, United States, 66160

United States, Maryland

CNCS, NINDS,NIH
Bethesda, Maryland, United States, 20892

United States, Mississippi

Nerological Reserch Center at Hattiesburg
Hattiesburg, Mississippi, United States, 39401

United States, New York

North Shore Hospital
Manshasette, New York, United States, 11030

United States, Pennsylvania

Pennsylvania Hospital of the University of PA Health System- Department of Neurology
Philadelphia, Pennsylvania, United States, 19107

HAN Neurological Associates
Upland, Pennsylvania, United States, 19013

United States, Texas

Baylor College of Medicine
Houston, Texas, United States, 77030

United States, Washington

Evergreen Hospital Medical Center; Booth Gardner Parkinson's Care Center
Kirkland, Washington, United States, 98034

Canada, Alberta

University of Calgary
Calgary, Alberta, Canada, T2N 4N1

University of Alberta
Edmonton, Alberta, Canada, T5G 0B7

Canada, Manitoba

Movment Disorder Clinic Deer lodge Centre
Winnipeg, Manitoba, Canada, R3J 2H7

Canada, Nova Scotia

David B. King, - Private Clinic
Halifax, Nova Scotia, Canada, GB3J 3T1

Canada, Ontario

London Health Sciences Centre, UH
London, Ontario, Canada, N6A 5A5

UHNresearch
Toranto, Ontario, Canada, M5T 2S8

Canada, Quebec

IRCM
Montreal, Quebec, Canada, H2W 1 R7

Investigators

Principal Investigator:	Stephen Greer, MD	Arkansas Cardiology
Principal Investigator:	Alberto Vasquez, MD	Suncoast Neuroscience
Principal Investigator:	Richard Hull, MD	North Alabama Neuroscience
Principal Investigator:	Brent Goodman, MD	Mayo Clinic-Arizona
Principal Investigator:	Alvin McElveen, MD	Bradenton Neurology, Inc
Principal Investigator:	Mazen Dimachkie, MD	University of Kansas Medical Center

More Information

Sponsor's website

Study Website

Responsible Party: Chelsea Therapeutics

Study ID Numbers: Droxidopa NOH301

Health Authority: United States: Food and Drug 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 for up to 2 weeks during open-label dose titration.	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 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	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: 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	263	0	0	263
Completed	162	0	0	162
Not Completed	101	0	0	101
Reason Not Completed				
Adverse Event	12	0	0	12

Treatment failure	50	0	0	50
Protocol Violation	5	0	0	5
Withdrawal by Subject	5	0	0	5
Enrollment capped	16	0	0	16
Did not meet responder criteria	2	0	0	2
Lost to Follow-up	5	0	0	5
Randomized in error	6	0	0	6
(Not Public)	Not Completed = 101 Total from all reasons = 101	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 Period is not equal to the number who completed previous Period.	82 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	80 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	162
Completed	0	82	80	162
Not Completed	0	0	0	0

Baseline Characteristics

Arm/Group Title	Not Randomized	Droxidopa	Placebo	Total
Arm/Group Description	Patients entered open label droxidopa dose titration, but did not proceed into washout and randomization.	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 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	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: 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	101	82	80	**263**
Baseline Analysis Population Description [Not specified]				
Age, Continuous Mean (Standard Deviation) Units: years	64.6 (15.4)	57.4 (16.90)	55.7 (20.03)	59.6 (17.8)
Gender, Male/Female Measure Type: Number Units: participants				
Female	37	40	38	115
Male	64	42	42	148

Race (NIH/OMB) Measure Type: Number Units: participants				
American Indian or Alaska Native	0	0	0	0
Asian	0	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	2	0	1	3
White	99	82	78	259
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	48	33	32	113
Canada	3	0	4	7
Europe	50	49	44	143
Primary Clinical Diagnosis Measure Type: Number Units: participants				
Parkinson's Disease	45	35	31	111
Multiple System Atrophy	18	15	11	44
Pure Autonomic Failure	33	26	28	87
Non-Diabetic Autonomic Neuropathy	2	2	6	10
Other Diagnosis	3	4	4	11

Outcome Measures

1. Primary 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. For the change from randomization, negative numbers represent improvement from randomization in OHQ score.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Missing data are imputed using the last observation carried forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	80
Mean (Standard Deviation) Units: units on a scale	-1.83 (2.067)	-0.93 (1.691)

▼ 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	0.003
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors.
	Method	ANCOVA
	Comments	ANCOVA model that includes treatment as a

		factor and baseline OHQ composite score as a co-variate.

2. Secondary Outcome

Title:	Change in Ability to Conduct Activities of Daily Living Score (OHDAS Composite Score)
▼ Description:	OHDAS composite scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Missing data are imputed using the last observation carried forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	81	79
Mean (Standard Deviation) Units: units on a scale	-1.98 (2.310)	-0.92 (1.816)

▼ 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	0.003
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors.
	Method	ANCOVA
	Comments	ANCOVA model that includes treatment as a factor and baseline OHDAS composite score as a co-variate.

3. Secondary Outcome

Title:	Change in Orthostatic Hypotension Symptom Assessment (OHSA Composite) Score
▼ Description:	OHSA composite scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Missing data are imputed using the last observation carried forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	81	79
Mean (Standard Deviation) Units: units on a scale	-1.68 (2.125)	-0.95 (1.901)

▼ 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	0.010
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors.
	Method	ANCOVA
	Comments	ANCOVA model including a factor for randomized treatment along with the OHSA composite value at randomization as a covariate.

4. Secondary Outcome

Title:	Change in Activities Involving Standing a Short Time (OHDAS Item 1)
▼ Description:	OHDAS Item 1 scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Missing data are imputed using the last observation carried forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	80
Mean (Standard Deviation) Units: units on a scale	-1.9 (2.75)	-0.8 (2.60)

▼ 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	0.003
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors.
	Method	Mantel Haenszel
	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHSA Item 1 value at baseline.

5. Secondary Outcome

Title:	Change in Activities Involving Walking a Short Time (OHDAS Item 3)
▼ Description:	OHDAS Item 3 scale range: 0 (none) -10 (worst), likert scale. Change: score at end of study minus score at randomization. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

Missing data are imputed using the last observation carried forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	80
Mean (Standard Deviation) Units: units on a scale	-1.7 (2.55)	-0.6 (2.37)

▼ 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	0.009
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors.
	Method	ANCOVA
	Comments	ANCOVA model including a factor for randomized treatment along with the OHSA composite value at randomization as a covariate.

6. Secondary 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. A negative score indicates an improvement during the double-blind randomized phase relative to value at randomization.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

Missing data are imputed using the last observation carried forward method.

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	80
Mean (Standard Deviation) Units: units on a scale	-2.4 (3.20)	-1.1 (2.58)

▼ 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	<0.001
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors.
	Method	Mantel Haenszel
	Comments	Mantel-Haenszel statistic comparing treatment groups based on rank statistics adjusted for the covariate OHSA Item 1 value at baseline.

7. Secondary Outcome

Title:	Patient-Reported Clinical Global Improvement - Severity Scores
▼ 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:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	80
Measure Type: Number Units: participants		
Normal-Borderline OH	23	16
Mild-Moderate OH	39	47
Marked OH-Most ill with OH	20	17

▼ 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	0.327
	Comments	Statistical analysis plan involved a hierarchical assessment of secondary endpoints to prevent inflation of type I errors. As the this endpoint was not positive, no additional statistical analyses will be performed on secondary endpoints.

	Method	Fisher Exact
	Comments	[Not specified]

8. Secondary Outcome

Title:	Clinician-Reported Clinical Global Improvement - Severity Scores
▼ 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:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	80
Measure Type: Number Units: participants		
Normal-Borderline OH	21	15
Mild-Moderate OH	39	44
Marked OH-Most ill with OH	22	21

9. 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. A positive score indicates an improvement during the double-blind randomized phase relative to value at randomization.
Time Frame:	7 days
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

[Not specified]

Arm/Group Title	Droxidopa	Placebo
▼ Arm/Group Description:	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 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	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: 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	82	79
Mean (Standard Deviation) Units: mmHg	11.2 (22.89)	3.9 (16.28)

Adverse Events

Time Frame	
Additional Description	One patient randomized to the droxidopa group in the randomized double blind phase was treated with placebo during this period and is included in the placebo group (actual treatment received) for the safety analyses.
Source Vocabulary Name	[Not specified]
Assessment Type	[Not specified] NOTE : An Assessment Type for Table Default has not been specified.

Arm/Group Title	Open-Label Titration	Droxidopa	Placebo
▼ Arm/Group Description	All patients treated with study drug during dose titration (7-14 days)	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 Droxidopa: 100 mg, oral, three times per day 200	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: 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	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

Serious Adverse Events

	Open-Label Titration		Droxidopa		Placebo	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	2/263 (0.76%)		0/81 (0%)		0/81 (0%)	
Gastrointestinal disorders						
Nausea	1/263 (0.38%)	1	0/81 (0%)	0	0/81 (0%)	0
Vomiting	1/263 (0.38%)	1	0/81 (0%)	0	0/81 (0%)	0
Infections and infestations						
Urinary Tract Infection	1/263 (0.38%)	1	0/81 (0%)	0	0/81 (0%)	0
Renal and urinary disorders						
Neurogenic bladder	1/263 (0.38%)	1	0/81 (0%)	0	0/81 (0%)	0
Ureteric obstruction	1/263 (0.38%)	1	0/81 (0%)	0	0/81 (0%)	0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%

	Open-Label Titration		Droxidopa		Placebo	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	38/263 (14.45%)		9/81 (11.11%)		1/81 (1.23%)	
Nervous system disorders						
Dizziness	17/263 (6.46%)	18	3/81 (3.7%)	3	1/81 (1.23%)	1
Headache	26/263 (9.89%)	34	6/81 (7.41%)	7	0/81 (0%)	0

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

Name/Official Title:	Chief Scientific Officer
Organization:	Chelsea Therapeutics Inc.
Phone:	704-973-4202
Email:	hewitt@chelsearx.com