Neurol Ther (2022) 11:459–469
https://doi.org/10.1007/s40120-021-00317-5

BRIEF REPORT

Durability of the Clinical Benefit of Droxidopa for Neurogenic Orthostatic Hypotension During 12 Weeks of Open-Label Treatment

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Received: June 21, 2021 / Accepted: December 21, 2021 / Published online: February 2, 2022

ABSTRACT

Introduction: Droxidopa is approved to treat neurogenic orthostatic hypotension (nOH) symptoms in patients with autonomic failure based on short-term clinical trial data. Additional data on the long-term efficacy of droxidopa are needed. We have evaluated the 12-week efficacy and tolerability of droxidopa in patients with nOH in an open-label period of an ongoing phase 4 study .

Methods: Patients received 12 weeks of open-label treatment with an individually optimized droxidopa dose (100–600 mg, 3 times daily) as identified during a preceding titration period. Patient-reported outcomes included the Orthostatic Hypotension Symptom Assessment (OHSA), Orthostatic Hypotension Daily Activity Scale (OHDAS), and clinician- and patient-rated Clinical Global Impression–Severity (CGI-S) scales. Supine blood pressure (BP) and adverse events (AEs) were recorded.

Results: Data from 114 patients enrolled into the 12-week open-label period were available for analyses. After 12 weeks of droxidopa treatment, patients reported significant ($P < 0.0001$) improvements from baseline in OHSA and OHDAS composite and individual item scores and on clinician and patient CGI-S scores. Mean ± SD supine systolic and diastolic BP at week 12 increased by 15.5 ± 22.9 and 7.8 ± 11.7 mmHg from baseline, respectively ($P < 0.0001$ for both). The most frequently reported AEs were falls (17%), headache (13%), and dizziness (9%); one (0.9%) patient reported an AE of supine hypertension.

Conclusion: During 12 weeks of open-label treatment, droxidopa was associated with significant improvement from baseline in nOH symptoms and activities of daily living. No clinically important changes in supine hypertension or AEs of concern were observed. These results support the efficacy of droxidopa beyond 2 weeks of treatment.

Trial Registration: NCT02586623.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-021-00317-5.

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Keywords: Droxidopa; Durability; Efficacy; Neurogenic orthostatic hypotension; Safety; Treatment

Key Summary Points

Droxidopa is approved for the treatment of orthostatic dizziness/lightheadedness, or the "feeling that you are about to black out," in adult patients with symptomatic neurogenic orthostatic hypotension (nOH).

This open-label study investigated the 12-week clinical benefit of droxidopa for the treatment of nOH symptoms.

Droxidopa treatment was associated with significant patient-reported reductions in nOH symptoms, including dizziness/lightheadedness, which are the cardinal symptoms of nOH, and their effects on daily activities from baseline.

Droxiopda was generally well tolerated with a safety profile similar to that found in previous studies of droxidopa.

INTRODUCTION

Neurogenic orthostatic hypotension (nOH) occurs in patients with autonomic dysfunction [1]. Patients with nOH commonly report symptoms such as dizziness, lightheadedness, presyncope, and syncope [2] that may increase the risk of falls, negatively affect ability to perform daily activities, and decrease quality of life [3]. Droxidopa is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adults with symptomatic nOH with Parkinson disease (PD), multiple system atrophy, pure autonomic failure, dopamine β-hydroxylase deficiency, or nondiabetic autonomic neuropathy [4]. The approval of droxidopa in 2014 under the accelerated approval program by the US Food and Drug Administration was based on pivotal data showing rapid improvements in nOH symptoms (i.e., after 1 week of treatment) [5–8]. Although additional data supporting the long-term durability of treatment effects with droxidopa have been reported [9, 10], confirmatory evidence of longer-term efficacy in patients with various underlying neurologic conditions is important. Therefore, further characterization of the long-term clinical benefits of droxidopa for the treatment of symptomatic nOH is being assessed in an ongoing phase 4 clinical study (NCT02586623) [11]. Herein we report the results from the 12-week, open-label portion for the first 114 patients included in this trial.

METHODS

Study Design

This phase 4 study comprises five periods: screening (≤ 4 weeks), open-label titration (≤ 4 weeks), open-label treatment (12 weeks), double-blind treatment (12 weeks), and safety follow-up (30 days). The current analyses include evaluation of the patients who entered the 12-week, open-label treatment period no later than 22 August 2018.

After a screening period, patients were given droxidopa titrated to an individually optimized dose (100–600 mg, 3 times daily [TID]). Patients initially received 100 mg TID of droxidopa, which was increased by 100-mg TID increments, with all dosing increases separated by ≥ 1 day. Titration was stopped when the patient reached the maximum allowed dose (600 mg TID) or sooner if the patient's supine systolic blood pressure (SBP) was ≥ 180 mmHg or diastolic blood pressure (DBP) was ≥ 110 mmHg 3 h after dosing (measured after 10 min of rest; head and torso elevated approximately 30° from horizontal; typically measured before midday) or if intolerable adverse effects related to the study drug were reported. If the titration was stopped because of elevated blood pressure (BP) or lack of tolerability, the patient's optimal dose was the highest dose at which neither of these events occurred. After the optimal dose of droxidopa was identified, patients received

12 weeks of open-label treatment. To enter the open-label treatment period, patients were required to show defined improvements in seated SBP (≥ 10 mmHg higher than pretreatment [baseline] value; typically measured before midday) and dizziness/lightheadedness symptoms (defined as ≥ 2-unit decrease from baseline in Item 1 of the Orthostatic Hypotension Symptom Assessment [OHSA]) [12]. At the end of the open-label period, patients with OHSA Item 1 scores ≥ 2 units lower than their baseline OHSA Item 1 score proceeded to randomization for the 12-week, double-blind treatment period.

Patients

Adults (aged ≥ 18 years) with a clinical diagnosis of symptomatic nOH associated with PD, multiple system atrophy, pure autonomic failure, nondiabetic autonomic neuropathy, or dopamine β-hydroxylase deficiency were eligible for this study. To be included, patients needed to be able to stand (with or without limited assistance), have symptoms of nOH with a pretreatment OHSA Item 1 (dizziness/lightheadedness) score ≥ 4, and a documented SBP drop ≥ 20 mmHg within 3 min of standing (either at any point in the patient's history or as assessed during screening). Patients with sustained supine hypertension, defined as SBP ≥ 180 mmHg or DBP ≥ 110 mmHg (average of 3 observations separated by ≥ 10 min; measured after ≥ 5 min of rest in the supine position with head and torso elevated approximately 30° from horizontal) were excluded. Patients with a diagnosis of hypertension that required treatment with antihypertensive medications were excluded, but those receiving treatment for nocturnal supine hypertension with short-acting antihypertensives were allowed.

Study Outcomes

At baseline (i.e., before the initiation of treatment) and during the 12 weeks of open-label treatment with droxidopa, OHSA, Orthostatic Hypotension Daily Activity Scale (OHDAS), and clinician- and patient-rated Clinical Global Impression–Severity (CGI-S) scale scores were measured [12, 13]. The OHSA is a patient-rated assessment of the severity of six nOH symptoms (dizziness/lightheadedness, vision problems, weakness, fatigue, trouble concentrating, head/neck discomfort) over the past week. The OHDAS is a patient-rated 4-item assessment of nOH symptom interference with activities involving standing or walking over the past week [12]. OHSA and OHDAS items are rated using a Likert scale from 0 (no symptoms/no interference) to 10 (worst possible symptoms/complete interference), with individual item and composite scores tabulated. The CGI-S evaluates the severity of patient illness and was scored by clinicians and patients using a rating scale from 1 (no symptoms) to 7 (severe symptoms) [13]. Supine BP (after 10 min of rest, with head and torso elevated approximately 30° from horizontal) was measured 3 h after dosing during each titration visit (measured at the study site or home [at the investigator's discretion] with investigator instruction on how to conduct measurement) and after each month of treatment with droxidopa. Adverse events (AEs) were collected throughout the study and summarized according to the Preferred Terms of the Medical Dictionary for Regulatory Activities.

Data Analysis

Continuous variables were summarized using descriptive statistics, including the number of observations; mean; standard deviation (SD); and minimum, median, and maximum values. The categorical values were summarized using number of observations and percentages. Other statistical tests were done using two-tailed tests to determine significance at a 5% level ($P < 0.05$), unless otherwise specified.

To assess the impact of missing data on the primary analysis, the primary efficacy analysis was repeated excluding patients who had missing data for the primary endpoint. The primary efficacy variable was the mean change from randomization to the end of the study in disease activity assessed by the Orthostatic Hypotension Questionnaire (OHQ) composite score,

measured as the average of the OHSA composite and OHDAS composite scores.

Ethics

This study was approved by WIRB (Study 2015204), an institutional review board, and is being conducted in compliance with institutional review board, independent ethics committee, and International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and all local regulatory requirements and laws. Written informed consent from participating patients was obtained before any study-related procedure was performed.

RESULTS

Patients

The screening and titration phase included 304 and 176 patients, respectively. A total of 114 patients with a mean (SD) age of 68 (13.4) years were enrolled in the open-label treatment period by the cutoff date for analyses (Table 1; Fig. 1). There were more men (63%) than women (37%) in the study, and approximately half of the study population (52%) had a diagnosis of PD, with the remaining patients having a diagnosis of nondiabetic autonomic neuropathy (30%), pure autonomic failure (14%), or multiple system atrophy (4%).

The most common reasons for discontinuation were patient withdrawal ($n = 9$) and AEs ($n = 5$; Fig. 1). AEs leading to discontinuation were stridor, stomach cramps, dyskinesia, hypertension, and syncope reported between 1 and 83 days during the open-label period. One patient was excluded due to protocol deviation after 19 days of open-label treatment. Other reasons for discontinuation included reduced quality of life, site closure ($n = 3$), sponsor request for withdrawal due to heart attack, and meeting new exclusion criteria between 8 and 77 days during the open-label period. Among patients with a confirmed study withdrawal at the time of analyses ($n = 21$), the distribution of

Table 1 Patient demographics and baseline disease characteristics

Variable	Patients ($N = 114$)
Age, mean (SD), year	68 (13.4)
Sex, *n* (%)	
Men	72 (63.2)
Women	42 (36.8)
Race, *n* (%)	
White	105 (92.1)
Black/African American	5 (4.4)
Other	4 (3.5)
Diagnosis, *n* (%)[a]	
Parkinson disease	59 (52.2)
Nondiabetic autonomic neuropathy	34 (30.1)
Pure autonomic failure	16 (14.2)
Multiple system atrophy	4 (3.5)
OHSA scores, mean (SD)	
Composite	6.5 (1.6)
Dizziness/lightheadedness	7.0 (1.7)
Vision problems	4.9 (3.2)
Weakness	6.3 (2.5)
Fatigue	6.8 (2.4)
Trouble concentrating	6.0 (2.6)
Head/neck discomfort	5.3 (3.3)
OHDAS scores, mean (SD)[b]	
Composite	7.0 (1.8)
Standing, short time	6.1 (2.3)
Standing, long time	7.9 (2.0)
Walking, short time	6.0 (2.6)
Walking, long time	7.7 (2.3)
CGI-S scores, mean (SD)	
Clinician rated	4.7 (0.8)
Patient rated	4.6 (1.0)

Table 1 continued

Variable	Patients (N = 114)
Supine BP, mean (SD), mmHg	
Systolic	118 (21)
Diastolic	71 (12)

BP blood pressure, *CGI-S* Clinical Global Impression–Severity scale, *OHDAS* Orthostatic Hypotension Daily Activity Scale, *OHSA* Orthostatic Hypotension Symptom Assessment, *SD* standard deviation

[a]n = 113 patients (excluding 1 patient with diagnosis missing)

[b]n = 107–113 patients

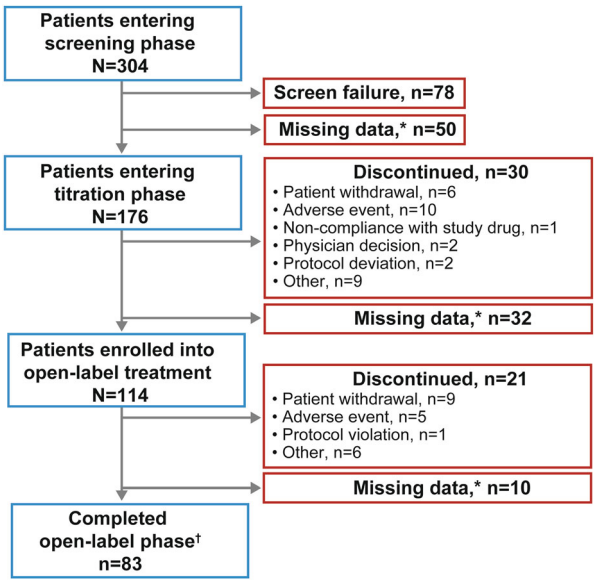


Fig. 1 Flow diagram of study disposition. Asterisk indicates that the dataset was not complete as of the cutoff date for analyses. Dagger indicates that the complete dataset was available as of the cutoff date for analyses

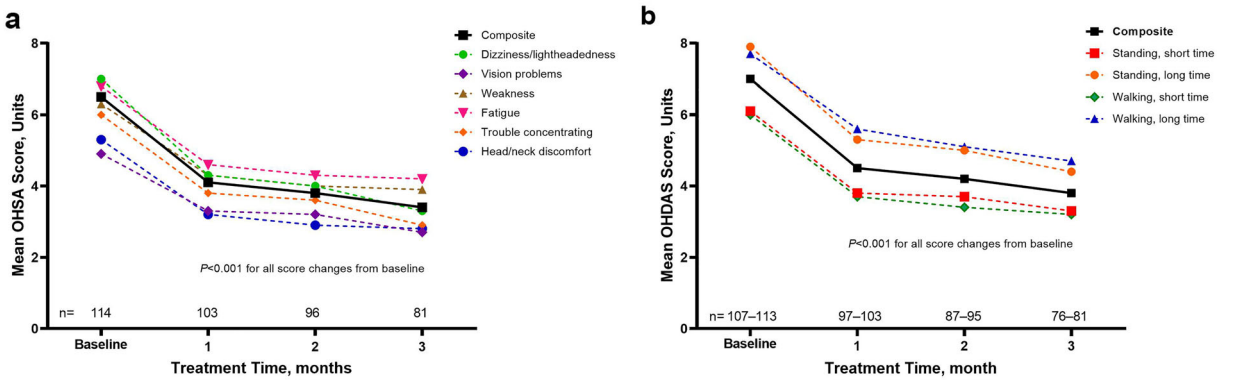
diagnoses (PD, 62%; nondiabetic autonomic neuropathy, 29%; pure autonomic failure, 5%; or multiple system atrophy, 5%) was generally similar to that of the enrolled population. Mean (SD) dose at the start of the open-label period was 493 (147) mg TID; 60% of patients received the maximum allowed dose of 600 mg droxidopa TID.

Outcomes

During the 12 weeks of open-label droxidopa treatment, patients reported significant improvement from baseline in nOH symptoms (i.e., reductions in OHSA composite and individual item scores; $P < 0.001$ for all; Fig. 2a, Table 2). Patients also indicated significantly less interference due to nOH in activities involving walking and standing (i.e., reductions in OHDAS composite and individual item scores; $P < 0.001$ for all; Fig. 2b, Table 2). Significant reductions from baseline scores in the mean composite and individual OHSA and OHDAS scores were observed after 1 month of treatment with droxidopa and were sustained throughout the open-label period. Consistent with the nOH-specific improvements reported, global benefits of treatment were also shown by similar onset (i.e., by 1 month) and sustainability of significant improvements in clinician- and patient-rated CGI-S scores from baseline ($P < 0.001$; Fig. 3).

Supine BP increased significantly from baseline when assessed after each month of open-label droxidopa treatment, with mean ± SD SBP increases of 15 ± 22.2 to 16 ± 25.2 mmHg and mean DBP increases of 7 ± 11.5 to 9 ± 12.3 mmHg (Fig. 4; $P < 0.001$ for all). During open-label droxidopa treatment, the incidence of supine SBP measurements > 160 and > 180 mmHg was low, with no patients having a supine SBP > 200 mmHg (Table 3).

During titration, increases in supine BP showed stability and consistency over time, with the magnitudes of the mean increases (predosing vs. postdosing) across titration visits generally similar to those identified in monthly visits (SBP 12–17 mmHg, DBP 4–6 mmHg; Electronic Supplementary Material Fig. S1). One patient had a supine hypertension event during titration, with a supine BP of 186/107 mmHg (average of 3 measurements, measured 3 h after dosing) after receiving the first 400-mg dose of droxidopa. The patient entered into the open-



Item	Baseline	Month 1	Month 2	Month 3
SD				
Composite	1.6	2.2	2.3	2.1
Dizziness/ lightheadedness	1.7	2.5	2.5	2.1
Vision problems	3.2	2.7	2.9	2.5
Weakness	2.5	2.7	2.9	2.6
Fatigue	2.4	2.8	2.8	2.6
Trouble concentrating	2.6	3.0	2.9	2.6
Head/neck discomfort	3.3	2.9	2.7	2.7

Item	Baseline	Month 1	Month 2	Month 3
SD		N		
Composite	1.8	2.7	2.6	2.7
Standing, Short time	2.3	2.9	2.6	2.7
Standing, long time	2.0	2.8	2.8	2.9
Walking, Short time	2.6	2.9	2.7	2.7
Walking, long time	2.3	3.2	3.1	3.0

Fig. 2 Mean (SD) OHSA (**a**) and OHDAS (**b**) scores are shown, with the SD for each data point indicated in the tables beneath the figure panels. Note: Score reductions for OHSA and OHDAS indicate decreased symptom burden on a rating scale from 0 (no symptoms/no interference) to 10 (worst possible symptoms/complete interference). *OHDAS* Orthostatic Hypotension Daily Activity Scale, *OHSA* Orthostatic Hypotension Symptom Assessment, *SD* standard deviation

label treatment period with a droxidopa dose titrated to 300 mg TID.

An AE was reported by 64% (n = 73/114) of patients during open-label titration and/or open-label treatment periods; the most common AEs were falls (n = 19/114, 17%), headache (n = 15/114, 13%), dizziness (n = 10/114, 9%), and nausea (n = 8/114, 7%).

DISCUSSION

These analyses from the 12-week, open-label period of an ongoing phase 4 study showed that treatment with droxidopa is associated with significant improvements in the symptoms of nOH, effect of nOH symptoms on activities involving standing or walking, and the overall clinical presentation of patients. The symptomatic and functional improvements initially observed after 1 month of treatment were sustained up to 12 weeks of treatment (i.e., 3 months), supporting the long-term durability of droxidopa. The efficacy observed in the current study was slightly greater than that observed after droxidopa treatment of 1–2 weeks [7, 14], which is likely due to higher percentage of patients in the current study on the maximum dose and the longer duration of therapy. The efficacy we observed is consistent with that in other reports of long-term treatment with droxidopa. In a 1-year, open-label extension study, similar sustained improvements from baseline in nOH symptoms and their effect were observed from month 1 through month 12 [10]. Data from nonclinical trial populations also support the durability of benefits with long-term droxidopa treatment [9]. In a 6-month, open-label, prospective study of real-world use of droxidopa, patients reported sustained symptomatic improvement (i.e., significant decreases in dizziness/lightheadedness scores) from baseline, along with reductions in falls, and improved measures of function impairment and health-related quality of life throughout the study period [9].

Table 2 Mean OHSA and OHDAS at baseline and 3 months

Assessment	Baseline score (n = 114)	Month 3 score (n = 81)	Change from baseline score[a]	P value
OHSA				
Composite	6.5 (1.6)	3.4 (2.1)	− 3.3 (1.9); n = 81	< 0.0001
Dizziness/lightheadedness[b]	7.0 (1.7)	3.3 (2.1)	− 3.9 (2.2); n = 81	< 0.0001
Vision problems[c]	4.9 (3.2)	2.7 (2.5)	− 3.2 (2.5); n = 68	< 0.0001
Weakness[d]	6.3 (2.5)	3.9 (2.6)	− 2.8 (2.5); n = 79	< 0.0001
Fatigue[e]	6.8 (2.4)	4.2 (2.6)	− 3.1 (2.2); n = 77	< 0.0001
Trouble concentrating[f]	6.0 (2.6)	2.9 (2.6)	− 3.5 (2.3); n = 75	< 0.0001
Head/neck discomfort[g]	5.3 (3.3)	2.8 (2.7)	− 3.5 (2.8); n = 68	< 0.0001
OHDAS				
Composite	7.0 (1.8); n = 111	3.8 (2.7); n = 79	− 3.4 (2.4); n = 79	< 0.0001
Standing, short time[h]	6.1 (2.3); n = 112	3.3 (2.7); n = 80	− 3.1 (2.7); n = 76	< 0.0001
Standing, long time[i]	7.9 (2.0); n = 107	4.4 (2.9); n = 76	− 3.4 (2.8); n = 72	< 0.0001
Walking, short time[j]	6.0 (2.6); n = 113	3.2 (2.7); n = 81	− 3.2 (2.6); n = 78	< 0.0001
Walking, long time[k]	7.7 (2.3); n = 110	4.7 (3.0); n = 76	− 3.4 (2.5); n = 73	< 0.0001

All scores are presented as the mean with the SD in parentheses

[a]Score reductions indicate decreased symptom burden on a rating scale from 0 (no symptoms/no interference) to 10 (worst possible symptoms/complete interference)

[b]Rates the severity of dizziness, lightheadedness, feeling faint, or feeling like you might black out on average over the past week

[c]Rates the severity of problems with vision (blurring, seeing spots, tunnel vision, etc.) on average over the past week

[d]Rates the severity of weakness on average over the past week

[e]Rates the severity of fatigue on average over the past week

[f]Rates the severity of trouble concentrating on average over the past week

[g]Rates the severity of head/neck discomfort on average over the past week

[h]Rates the impact of low blood pressure symptoms on activities that require standing for a short time

[i]Rates the impact of low blood pressure symptoms on activities that require standing for a long time

[j]Rates the impact of low blood pressure symptoms on activities that require walking for a short time

[k]Rates the impact of low blood pressure symptoms on activities that require walking for a long time

OHDAS Orthostatic Hypotension Daily Activity Scale, *OHSA* Orthostatic Hypotension Symptom Assessment, *SD* standard deviation

The current study included patients with symptomatic nOH due to a variety of autonomic failure diagnoses who were titrated to an individually optimized dose of droxidopa (i.e., stepwise increases of 100 mg TID from a starting dose of 100 mg TID). Titration of droxidopa to symptomatic response is necessary because the treatment response can vary among patients. Notably, in this study, 60% of patients were titrated to the maximum dose (600 mg TID). In other clinical trials of droxidopa, 600 mg TID was also the most commonly used dose, with approximately 40% of patients receiving 600 mg TID [5, 15]. When initiating treatment with droxidopa, clinicians should aim to safely and efficiently identify the dose of droxidopa that provides the individual patient optimal relief of nOH symptoms.

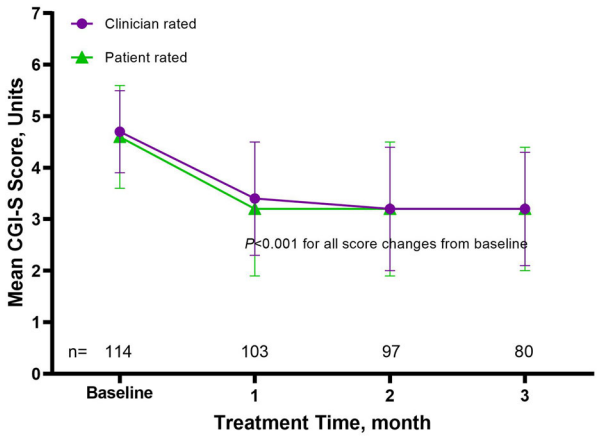


Fig. 3 Mean CGI-S* scores. *CGI-S* Clinical Global Impression–Severity scale. Note: Score reductions indicate decreased symptom burden on a rating scale from 1 (no symptoms) to 7 (severe symptoms)

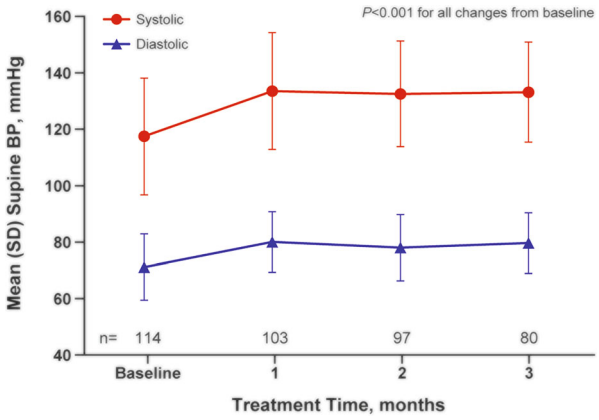


Fig. 4 Mean (SD) supine BP. *BP* Blood pressure

According to consensus recommendations, the goal of nOH treatment should be reduction of symptom burden and improvement of functionality, not the normalization of BP [2]. Droxidopa is a norepinephrine prodrug that increases norepinephrine levels and vasoconstriction [4]. In the clinical trials conducted to support the US approval of droxidopa, symptomatic improvements and orthostatic BP increase (mean increases after 1 week of treatment, SBP 12 mmHg, DBP 8 mmHg) were observed [5], and orthostatic BP increases have been shown to be sustained for up to 12 months of treatment [10]. Because the current phase 4 study was designed to further assess the durability of the clinical benefits of droxidopa (i.e., study of symptomatic improvement and its effects as measured by OHSA, OHDAS, and CGI-S outcomes), standing/orthostatic BPs were not evaluated.

Supine BPs were evaluated in this study because patients with nOH experience dysregulated autonomic BP control mechanisms as a consequence of autonomic failure pathophysiology, and the use of pressor agents may exacerbate or cause supine hypertension [16]. Not surprisingly, because droxidopa is a pressor agent that increases standing BP, increases in supine BPs from baseline that reached statistical significance were found in this study (mean changes, SBP 15–16 mmHg; DBP 7–9 mmHg). Importantly, mean supine SBP and DBP measurements remained $\leq$ 134 and $\leq$ 80 mmHg (respectively) during long-term treatment with droxidopa in this study, which is below the threshold for supine hypertension as defined in current consensus guidelines (SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg while supine) [16]. The incidence of supine hypertension SBP > 180 mmHg during the 12-week, open-label period was low (1%, 1/114) and generally similar to the rate

Table 3 Incidence of supine systolic blood pressure > 160, > 180, and > 200 mmHg by visit

Supine SBP	Baseline (n = 114)	Month 1 (n = 103)	Month 2 (n = 97)	Month 3 (n = 81)	Any time (n = 114)
> 160 mmHg	2 (2)	13 (13)	9 (9)	10 (12)	22 (19)
> 180 mmHg	0	1 (1)	0	0	1 (1)
> 200 mmHg	0	0	0	0	0

Values in table are the incidence (number of patients, n) with the percentage in parentheses
SBP Systolic blood pressure

reported at 3 months in a long-term, open-label extension study of droxidopa (4%, 3/79) [10]. During the titration period in which each patient's dose was identified based on tolerability and response, progressive increases in supine BP were not observed; however, because some patients were allowed to measure BP at home during titration, the accuracy of these data cannot be verified. Additionally, the most commonly reported AEs (i.e., falls, headaches, and dizziness) in the current study were consistent with those reported in other long-term studies of droxidopa [10, 15].

Although the results reported herein further support the long-term efficacy and safety profile of droxidopa for the treatment of nOH, the lack of a control group limits the ability to show the relationship between treatment with droxidopa and the outcomes observed. The subsequent double-blind, placebo-controlled period of the study will serve to address causality. However, the durability and stability of clinical outcomes in this study are consistent with data from a prospective study of real-world use of droxidopa, in which beneficial effects were maintained for up to 6 months (end of study), and from an open-label extension study of droxidopa, in which benefits were consistently maintained during 12 months of droxidopa treatment [9, 10].

Furthermore, regarding the discontinuations due to patient withdrawal ($n = 9$), the specific reasons for each discontinuation are unknown. Although it is possible that some resulted from lack of clinical effect, the stability of the reductions in OHSA, OHDAS, and CGI-S scores observed throughout the treatment period suggests that lack of efficacy was not the primary reason for study discontinuation. In a subanalyses of OHSA Item 1 scores in patients who discontinued ($n = 18$ with post-baseline data available), 67% (12/18) had improved scores from baseline in their last observed measurement.

CONCLUSIONS

In conclusion, the significant improvements in nOH symptoms and the effects of nOH symptoms on activities involving standing or walking after 12 weeks of treatment offer further evidence of the durability and sustained benefits of droxidopa for the treatment of nOH. Evaluations of safety including supine BPs, supine hypertension rates, and other AEs indicate no new signals of concern. The results of the double-blind, placebo-controlled period of this phase 4 study will provide more definitive information about the durability of benefits with droxidopa treatment for patients with symptomatic nOH.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Funding. The data reported here are from a clinical trial funded by Lundbeck. Lundbeck funded the Rapid Service Fee associated with the publication of this manuscript.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance was provided by Lisa Havran, PhD, Patrick Little, PhD, and Sonia Mohinta, PhD, employees of ICON (North Wales, PA, USA) and was supported by Lundbeck.

Authorship. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors were involved in the conception of this research project. Additionally, Robert A. Hauser provided review of the statistical analyses. L. Arthur Hewitt was involved with the organization and execution of the research project and review of the statistical analyses. Annika Lindsten was also responsible for the design and execution of the statistical analyses. Stephen Gorny was involved with the organization and execution of the research project and review of the statistical analyses. All authors were involved in the

review of the manuscript and provided their final approval of the manuscript for publication.

Investigators. Horacio Kaufmann (New York University Medical Center, New York, NY 10016) and Christopher J. Mathias (Imperial School of Medicine, London, UK) are the principal investigators of this study.

Prior Presentation. Aspects of this work have been previously presented as posters at the 2019 American Neurological Association Annual Meeting, October 13–15, 2019, in St. Louis, MO, and at the International Symposium on the Autonomic Nervous System, November 6–9, 2019, in Clearwater, FL.

Disclosures. Robert A. Hauser is a consultant for Acadia Pharmaceuticals, Acorda Therapeutics, Adamas Pharmaceuticals, AlphaSights, Amneal Pharmaceuticals, ApoPharma, Aptis Partners, Clinical SCORE, CNS Ratings, Compass Group, Decision Resource Group, Dedham Group, Defined Health, Enterin, Ernst and Young, Extera Partners, Gerson Lehrman Group, Global Kinetics Corporation, Guidepoint Global, Health Advances, Impax Laboratories, Impel NeuroPharma, IntraMed Educational Group, IQVIA, International Stem Cell Corporation, Jazz Pharmaceuticals, Kashiv Pharma, L.E.K. Consulting, Lundbeck, Med-IQ, Medscape, Mitsubishi Tanabe Pharma America, Michael J. Fox Foundation, Morgan Lewis Neuro Challenge Foundation for Parkinson's, Neurocrea, Neurocrine Biosciences, Neurocrine Continental, Northwestern University, Orbees, Orion, Parkinson's Foundation, Partners Healthcare, Penn Technology Partnership, Perception OpCo, Prescott Medical Communications Group, Prilenia Therapeutics, Parkinson Study Group, Regenera Pharma, Scion NeuroStim, Seelos Therapeutics, Slingshot Insights, Sunovion Pharmaceuticals, Teva Pharmaceuticals, US World Meds, and WebMD. He has received research support from AbbVie, Acorda Therapeutics, AstraZeneca, Axovant Sciences, Biogen, Cavion, Enterin, Impax Laboratories, Intec Pharma, Jazz Pharmaceuticals, NeuroDerm, Michael J. Fox Foundation for Parkinson's Research, F. Hoffmann-La Roche, Dart NeuroScience, Prexton Therapeutics, Revance Therapeutics, and Sunovion Pharmaceuticals and grant support from the Parkinson's Foundation. Stuart H. Isaacson has served as a consultant and/or promotional speaker and has received honoraria for continuing medical education and research grants on behalf of AbbVie, Acadia, Acorda, Adamas, Addex, Affiris, Alexza, Allergan, Amarantus, Amneal, Aptinyx, Axial, Axovant, Benevolent, Biogen, Britannia, Cadent, Cala, Cerecor, Cerevel, Cipla, Eli Lilly, Enterin, GE Healthcare, Global Kinetics, Impax, Impel, Intec Pharma, Ipsen, Jazz, Kyowa, Lundbeck, Merz, Michael J. Fox Foundation, Mitsubishi Tanabe, Neuraly, Neurocrine, Neuroderm, Parkinson Study Group, Pharma Two B, Prilenia, Promentis, Revance, Roche, Sanofi, Sunovion, Sun Pharma, Supernus, Teva, Theravance, and UCB. Stephen Gorny, Steven Kymes, and Annika Lindsten are employees of Lundbeck and Antonella Favit and L. Arthur Hewitt were employees of Lundbeck at the time of this study; Antonelle Favit is currently an employee of Helius Medical Technologies, and L. Arthur Hewitt is currently an employee of Amneal Pharmaceuticals.

Compliance With Ethics Guidelines. This study was approved by WIRB (Study 2015204), an institutional review board and is being conducted in compliance with the institutional review board, independent ethics committee, International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and all local regulatory requirements and laws. Written informed consent from participating patients was obtained before any study-related procedure was performed.

Data Availability. The data sets analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69–72.

2. Gibbons CH, Schmidt P, Biaggioni I, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol. 2017;264(8):1567–82.

3. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018;18(1):125.

4. Lundbeck NA Ltd. Northera® (droxidopa). Full prescribing information. 2019. https://www.lundbeck.com/content/dam/lundbeck-com/americas/united-states/products/neurology/northera_pi_us_en.pdf. Accessed 7 Jan 2022.

5. Biaggioni I, Hewitt LA, Rowse GJ, Kaufmann H. Integrated analysis of droxidopa trials for neurogenic orthostatic hypotension. BMC Neurol. 2017;17(1):90.

6. Hauser RA, Isaacson S, Lisk JP, Hewitt LA, Rowse G. Droxidopa for the short-term treatment of symptomatic neurogenic orthostatic hypotension in Parkinson's disease (nOH306B). Mov Disord. 2015;30(5):646–54.

7. Kaufmann H, Freeman R, Biaggioni I, et al. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. Neurology. 2014;83(4):328–35.

8. U.S. Department of Health and Human Services. Northera FDA approval letter. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/203202Orig1s000ltr.pdf. Accessed 10 May 2021.

9. François C, Shibao CA, Biaggioni I, et al. Six-month use of droxidopa for neurogenic orthostatic hypotension. Mov Disord Clin Pract. 2019;6(3):235–42.

10. Isaacson S, Shill HA, Vernino S, Ziemann A, Rowse GJ. Safety and durability of effect with long-term, open-label droxidopa treatment in patients with symptomatic neurogenic orthostatic hypotension (NOH303). J Parkinsons Dis. 2016;6(4):751–9.

11. ClinicalTrials.gov. Sustained effect of droxidopa in symptomatic neurogenic orthostatic hypotension (RESTORE; NCT02586623). https://clinicaltrials.gov/ct2/show/NCT02586623?term=NCT02586623. Accessed 10 May 2021.

12. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res. 2012;22(2):79–90.

13. Guy W. ECDEU assessment manual for psychopharmacology. Rockville: US Department of Health, Education, and Welfare; 1976.

14. Biaggioni I, Freeman R, Mathias CJ, et al. Randomized withdrawal study of patients with symptomatic neurogenic orthostatic hypotension responsive to droxidopa. Hypertension. 2015;65(1):101–7.

15. Isaacson S, Vernino S, Ziemann A, Rowse GJ, Kalu U, White WB. Long-term safety of droxidopa in patients with symptomatic neurogenic orthostatic hypotension. J Am Soc Hypertens. 2016;10(10):755–62.

16. Fanciulli A, Jordan J, Biaggioni I, et al. Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS): endorsed by the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH). Clin Auton Res. 2018;28(4):355–62.