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Research Report

Droxidopa in Patients with Neurogenic Orthostatic Hypotension Associated with Parkinson's Disease (NOH306A)

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Abstract.
Background: Neurogenic orthostatic hypotension (nOH) is common in Parkinson's disease (PD), and represents a failure to generate norepinephrine responses appropriate for postural change. Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an oral norepinephrine prodrug.
Objective: Interim analyses of the initial patients enrolled in a multicenter, randomized, double-blind, placebo-controlled phase 3 trial of droxidopa for nOH in PD (ClinicalTrials.gov Identifier: NCT01176240).
Methods: PD patients with documented nOH underwent $\leq$2 weeks of double-blind droxidopa or placebo dosage optimization followed by 8 weeks of maintenance treatment (100–600 mg t.i.d.). The primary efficacy measure was change in Orthostatic Hypotension Questionnaire (OHQ) composite score from baseline to Week 8. Key secondary variables included dizziness/lightheadedness score (OHQ item 1) and patient-reported falls.
Results: Among 24 droxidopa and 27 placebo recipients, mean OHQ composite-score change at Week 8 was -2.2 versus -2.1 ($p = 0.98$); in response to this pre-planned futility analysis, the study was temporarily stopped and all data from these patients were considered exploratory. At Week 1, mean dizziness/lightheadedness score change favored droxidopa by 1.5 units ($p = 0.24$), with subsequent numerical differences favoring droxidopa throughout the observation period, and at Week 1, mean standing systolic blood-pressure change favored droxidopa by 12.5 mmHg ($p = 0.04$). Compared with placebo, the droxidopa group exhibited an approximately 50% lower rate of reported falls ($p = 0.16$) and fall-related injuries (*post-hoc* analysis).
Conclusions: This exploratory analysis of a small dataset failed to show benefit of droxidopa, as compared with placebo by the primary endpoint. Nonetheless, there were signals of potential benefit for nOH, including improvement in dizziness/lightheadedness and reduction in falls, meriting evaluation in further trials.

Keywords: Hypotension, orthostatic, Parkinson's disease, droxidopa, falls, treatment

INTRODUCTION

Orthostatic hypotension (OH) is defined as a blood-pressure decrease $\geq$20 mmHg systolic or $\geq$10 mmHg diastolic, recorded within 3 minutes after the patient stands [1]. In neurogenic OH (nOH), the decrease represents a failure to generate norepinephrine responses appropriate for postural changes, either peripherally, at postganglionic sympathetic neurons innervating vascular adrenoceptors, or centrally, in central nervous system pathways governing sympathetic function [2]. In symptomatic cases, patients may experience not only dizziness and lightheadedness (or actual syncope) but also visual disturbances and nonspecific complaints of weakness or fatigue [2].

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The disorder appears to be a common feature of Parkinson's disease (PD). In a retrospective study of 1,125 PD patients seen at a single center, the prevalence of symptomatic nOH was found to be 18% [3]. In studies defining the disorder purely by blood-pressure change, the prevalence has been as high as 47% in community-based [4] and 58% in hospital-based [5] PD samples (with at most a statistically insignificant relation [4] to usage of antihypertensive drugs). In PD, nOH may contribute, along with other PD features (e.g., gait dysfunction, freezing, and postural instability), to falls [6, 7], which constitute an important source of morbidity [7, 8]. In the United States, the only pharmacotherapy currently approved for the treatment of symptomatic OH is midodrine, an oral prodrug converted peripherally into desglymidodrine, a selective α-1-adrenoceptor agonist [9]. However, in patients with nOH, midodrine therapy has been associated with heightened risk of side effects including supine hypertension [10].

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an oral prodrug that is converted to norepinephrine both peripherally and centrally [11]. Because the endogenous converting enzyme, aromatic amino acid decarboxylase, is widely expressed, droxidopa replenishes norepinephrine both as a neurotransmitter (in surviving postganglionic sympathetic motor neurons) and as a circulating hormone. Droxidopa is currently being evaluated for efficacy and safety in treating symptomatic nOH in a variety of underlying disorders [12–14]. In an integrated analysis of 2 phase 3 studies with placebo control [15], droxidopa recipients showed statistically significant improvement in self-ratings of dizziness/lightheadedness, weakness, fatigue, and nOH impact on activities requiring standing a short or long time and walking a short or long time. Recipients also exhibited a significant increase in standing systolic blood pressure without a marked increase in incidence of supine hypertension. Here we present an interim, exploratory analysis of the initial 51 PD patients with nOH enrolled in a phase 3 study of droxidopa versus placebo, including descriptive *post-hoc* analyses of patients who reported 2 or more falls ("repeat fallers") during the 10 weeks of study-drug treatment, versus those who reported not more than 1 fall.

METHODS

Study patients

All patients were required to be ≥18 years old and have a clinical diagnosis of PD plus signs and symptoms of nOH. The objective nOH criterion was a decrease ≥20 mmHg in systolic or ≥10 mmHg in diastolic blood pressure within 3 minutes after going from supine to standing. The subjective criteria were a patient-reported composite score ≥3 on the Orthostatic Hypotension Questionnaire (OHQ [16]) and a study investigator rating of ≥3 (at least "mild") on the Clinical Global Impression–Severity scale (CGI-S), in reference to the patient's nOH. Key exclusion criteria included current use of vasoconstrictive agents or long-acting antihypertensive medications; sustained severe hypertension (≥180/110 mmHg while seated or supine [with head and torso elevated ∼30° from horizontal] on 3 consecutive measurements during 1 hour); or a Mini-Mental State Examination score ≤23. Because the hemodynamic abnormalities seen in nOH and in PD commonly include nocturnal supine hypertension [17], bedtime use of a short-acting antihypertensive was allowed.

Study design

This is an exploratory analysis of 51 patients enrolled in a multicenter, randomized, double-blind, parallel-group trial (ClinicalTrials.gov Identifier: NCT01176240), in which enrolled patients underwent up to 2 weeks of double-blind study-drug dosage optimization followed by 8 weeks of double-blind maintenance treatment at the optimized dosage (100–600 mg t.i.d.). During optimization, droxidopa or placebo, initiated at 100 mg t.i.d., was titrated upward in 100-mg t.i.d. increments until the patient: (i) became asymptomatic for nOH (a CGI-S score of 1); (ii) reached the maximum permitted dosage of 600 mg t.i.d.; (iii) had a systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg after 10 minutes supine, on 3 consecutive measurements during 1 hour; or (iv) experienced intolerable adverse events (AEs). Patients meeting either of the latter 2 criteria at a dosage level exceeding 100 mg t.i.d. were eligible to continue at their previous lower dosage. Throughout the study, all PD medications were held stable. Midodrine was disallowed, but fludrocortisone could be continued at a dosage that had been stable throughout the 2 weeks prior to start of study drug.

Efficacy measures

The study's pre-specified primary efficacy measure was mean change in OHQ composite score from baseline (i.e., at randomization for study-drug optimization) to end of study. The OHQ [16] is a

patient-reported outcome measure consisting of 10 items, 6 of which assess potential nOH symptoms (dizziness/lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort). The remaining 4 items rate nOH symptom impact on daily activities requiring standing or walking for a short or long time. Each item is scored on a Likert scale from 0 (none/no interference) to 10 (worst possible/complete interference) for the preceding week. The responses yield composite scores for symptoms and symptom impact (each being the average of the relevant item scores, excluding items scored 0 at baseline), which in turn yield the overall composite score (the average of the symptom and symptom-impact composite scores).

Key secondary efficacy variables included dizziness/lightheadedness score (item 1 of the OHQ), and patient-reported falls from baseline to end of study. Patients were instructed to record, by daily entries in an electronic diary, all of their falls, defined as "unexpectedly coming to rest on the ground, floor, or a lower level from where the patient started." Additional secondary efficacy variables included the OHQ symptom and symptom-impact composite scores and individual item scores. Hemodynamic efficacy variables including standing systolic blood pressure were measured in all patients in both the supine and standing positions.

Safety data

AEs, clinical laboratory values, vital signs, and electrocardiographic findings were all collected as safety parameters. Supine hypertension was predefined as a systolic blood-pressure value >180 mmHg. Safety assessments also included change in PD, as measured by Hoehn & Yahr (H&Y) PD stage [18] and by individual part scores and total score (Parts I, II, III, and IV) on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS [19]). As a *post-hoc* analysis, fall-related injuries were defined as reported AEs matching any of a select set of Medical Dictionary for Regulatory Activities preferred terms (Table 1) that occurred on the day of or the day after a reported fall.

Statistical analyses

The original study included a planned futility analysis [20] by an independent data-monitoring committee, to be conducted after approximately 60% of patients had completed the study or were lost to follow-up ($n = 51$). The original study was initially stopped for futility based on data from the primary endpoint alone (change in OHQ composite score from baseline to maintenance Week 8). Subsequent to stopping the study, all data from the 51 patients were unblinded for exploratory analyses, as described here, based on the original statistical analysis plan.

For OHQ data, mean change from randomization to end of study in the droxidopa and placebo groups was compared using analysis of covariance (ANCOVA), with value at randomization as the covariate and treatment group as the main effect. Missing data were imputed using last observation carried forward (LOCF). For falls, relative risk between treatment groups was tested by negative binomial regression. For all analyses, statistical significance was set at the 2-sided, 5% level. As descriptive *post-hoc* analyses, repeat fallers (with ≥ 2 patient-reported falls during study-drug treatment) were compared with nonrepeat fallers (≤ 1 fall). The comparisons assessed mean change from randomization to end of study in dizziness/lightheadedness score, H&Y stage, and MDS-UPDRS part scores and total score.

Table 1
Adverse-event preferred terms potentially qualifying as fall-related injuries*

- Arthralgia
- Back pain
- Conjunctival hemorrhage
- Contusion
- Excoriation
- Face edema
- Facial bones fracture
- Fall
- Fibula fracture
- Foot fracture
- Headache
- Injury
- Joint sprain
- Laceration
- Musculoskeletal chest pain
- Musculoskeletal pain
- Musculoskeletal stiffness
- Neck pain
- Non-cardiac chest pain
- Pain
- Pain in extremity
- Skin laceration
- Skin lesion
- Tooth fracture
- Traumatic brain injury
- Traumatic hematoma

*Provided the AE occurred on the day of or the day after a reported fall. Medical Dictionary for Regulatory Activities, Version 13.0.

Table 2
Patients' characteristics

Variable	Placebo recipients ($N = 27$)	Droxidopa recipients ($N = 24$)
Age at screening, years		
Mean (SD)	72.9 (7.8)	72.2 (7.3)
Median (range)	74.0 (56–85)	72.5 (62–89)
Age group, n (%)		
<65 years old	4 (14.8)	4 (16.7)
≥65 years old	23 (85.2)	20 (83.3)
Sex, n (%)		
Male	17 (63.0)	14 (58.3)
Female	10 (37.0)	10 (41.7)
Race, n (%)		
White	24 (88.9)	24 (100.0)
Other	3 (11.1)	0
OHQ scores		
Composite		
Mean (SD)	5.6 (1.4)	6.0 (1.5)
Median (range)	5.3 (4–9)	6.4 (3–8)
Item 1 (dizziness/lightheadedness)		
Mean (SD)	5.4 (2.1)	6.1 (2.2)
Median (range)	5 (1–9)	7 (2–10)
*Standing systolic BP, mmHg**		
Mean (SD)	103.7 (14.8)	99.2 (15.9)
Median (range)	100 (82–134)	97.5 (76–145)
H&Y stage		
Mean (SD)	2.2 (1.3)	1.8 (1.0)
MDS-UPDRS scores		
Part I (nonmotor experiences of daily living)		
Mean (SD)	21.3 (7.4)	18.8 (7.4)
Median (range)	20 (8–37)	18 (8–35)
Part II (motor experiences of daily living)		
Mean (SD)	23.0 (8.2)	20.1 (9.7)
Median (range)	24 (3–37)	21 (5–37)
Part III (motor examination)		
Mean (SD)	34.8 (18.0)	35.0 (22.0)
Median (range)	32.5 (10–93)	33 (4–88)
Part IV (motor complications)		
Mean (SD)	6.8 (5.0)	5.2 (5.0)
Median (range)	7 (0–17)	5 (0–17)
Total		
Mean (range)	86.0 (23–176)	80.1 (20–169)

*Assessed after 3 minutes of standing in patients who completed the study per protocol; $N = 18$ for droxidopa and 22 for placebo. BP, blood pressure; H&Y, Hoehn & Yahr; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; OHQ, Orthostatic Hypotension Questionnaire; SD, standard deviation.

Study oversight

The study was conducted in full conformance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, and in accord with the Helsinki Declaration of 1975. The study protocol was approved by the institutional review board at each study site. Before study procedures, all patients provided written informed consent. Data were collected by the academic investigators and were analyzed by the study sponsor, Chelsea Therapeutics, Inc. The sponsor, in collaboration with the investigators, interpreted the data, to which the investigators had full access.

RESULTS

Study patients

Of the 51 patients included in these analyses, the first was enrolled in June 2010 and the last completed treatment in December 2010. The demographic and baseline PD and nOH characteristics of the 24 droxidopa recipients were similar to those of the 27 placebo recipients (Table 2). The majority of patients (61%) were men, and the mean (SD) age was 72.5 (7.5) years. Of the 51 patients, 6 discontinued from the study, 3 in each treatment group (Fig. 1). During the study,

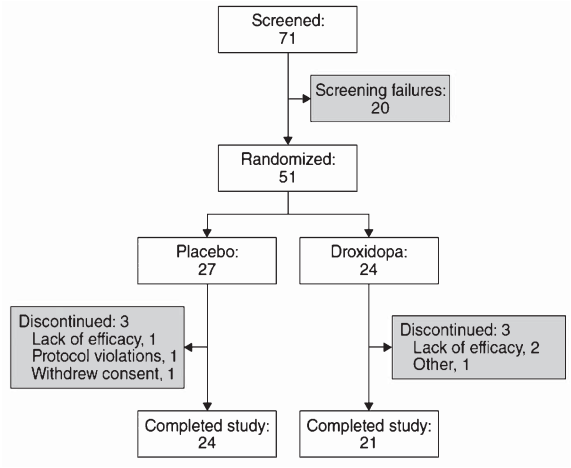

Fig. 1. Patient disposition.

3 patients used short-acting antihypertensive drugs (a beta-blocker or calcium-channel blocker), taken as single bedtime doses by 2 patients in the droxidopa group and 1 patient in the placebo group, and 11 patients used fludrocortisone, 3 in the droxidopa group and 8 in the placebo group.

Study-drug dosage

At the beginning of double-blind treatment, the mean (SD) study-drug dosage was 433.3 (155.1) mg for droxidopa and 488.9 (134.0) mg for placebo. The proportions of patients beginning their double-blind treatment at the highest study-drug doses were greater for placebo (500 mg t.i.d.: 6 patients, or 22%; 600 mg t.i.d.: 13 patients, or 48%) than for droxidopa (2 patients, or 8%, and 9 patients, or 38%). Among randomized patients, 10 droxidopa recipients (42%) and 10 placebo recipients (38%) ended their up-titration because they became asymptomatic for nOH, 9 (38%) and 13 (50%) because they reached maximum dosage, 1 (4%) and 1 (4%) because they became hypertensive, and 4 (17%) and 2 (8%) because they experienced intolerable AEs.

nOH severity

From randomization to end of study (maintenance Week 8), the mean (SD) decrease (improvement) in OHQ composite score (the primary outcome measure) was −2.2 (2.4) in the droxidopa group versus −2.1 (2.5) in the placebo group ($p = 0.98$). For OHQ composite score and dizziness/lightheadedness score, mean changes after Weeks 1, 2, 4, and 8 are displayed in Fig. 2. Both outcome measures show a larger treatment effect at earlier time points. For OHQ composite score, the mean change was −2.7 (2.6) for droxidopa versus −2.1 (2.5) for placebo after Week 1 ($p = 0.53$) and −2.3 (2.4) versus −1.7 (2.2) after Week 2 ($p = 0.37$). For dizziness/lightheadedness score, the mean change was −3.1 (3.4) for droxidopa versus −1.6 (3.1) for placebo after Week 1 ($p = 0.24$) and −2.3 (3.0) versus −1.0 (3.0) after Week 2 ($p = 0.24$). Dizziness/lightheadedness scores showed numerically greater improvements for droxidopa than for placebo at all time points.

Figure 2 also displays mean changes in standing systolic blood pressure. Blood pressure was highly variable at all time points, as demonstrated by large standard deviations. The difference between treatment groups was significant at Week 1, at +8.4 (17.4) versus −4.1 (20.5) mmHg ($p = 0.04$), and among droxidopa recipients the mean change from baseline was positive at all time points. From randomization to end of study, the mean change (without LOCF) was +7.0 (18.7) mmHg for droxidopa versus +7.7 (22.2) for placebo ($p = 0.72$).

Falls and fall-related injuries

Overall, similar numbers of patients reported falls in each group: 54% of the droxidopa group (13 of 24) and 59% of the placebo group (16 of 27). However, droxidopa recipients reported fewer total falls (79) than placebo recipients (192). Normalized for days of reporting, the average number of falls per patient per week was 0.4 for droxidopa versus 0.8 for placebo (relative risk, 0.5; $p = 0.16$). This finding is consistent with the safety finding of a 50% difference in the number of patients reporting fall-related injuries (e.g., contusion, skin laceration), at 4 patients in the droxidopa group versus 8 in the placebo group (see below, under "safety").

PD severity

From randomization to end of study, the mean (SD) decrease (improvement) in MDS-UPDRS total score was −19.0 (18.4) for droxidopa versus −11.3 (24.9) for placebo ($p = 0.13$). MDS-UPDRS Part I (nonmotor experiences of daily living) score change was −7.3 (7.1) versus −5.2 (6.9) ($p = 0.08$); Part II (motor experiences of daily living) score change was −5.3 (7.7) versus −3.1 (6.7) ($p = 0.15$); Part III (motor examination) score change was −4.7 (8.4) versus

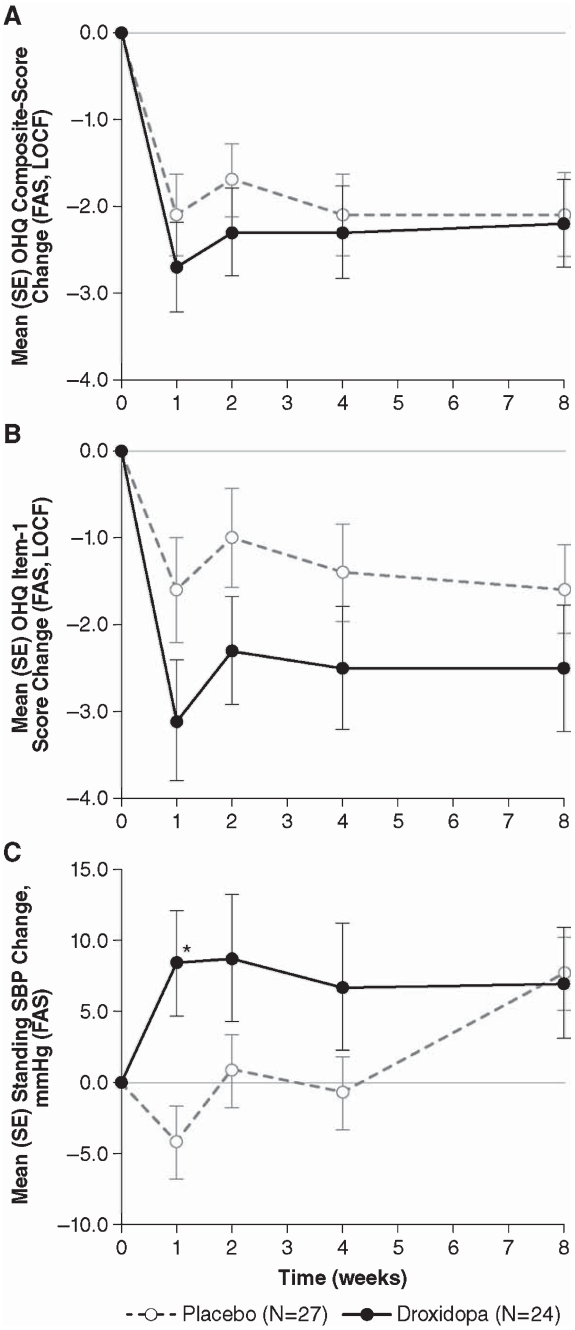

Fig. 2. Mean (SE) change after randomization in OHQ composite score (A), OHQ Item-1 (dizziness/lightheadedness) score (B), and standing systolic blood pressure (C), as assessed after maintenance-treatment Weeks 1, 2, 4, and 8 (end of study). $^{*}p < 0.05$. FAS, full analysis set; LOCF, last observation carried forward; OHQ, Orthostatic Hypotension Questionnaire; SBP, systolic blood pressure; SE, standard error.

−0.6 (12.9) ($p = 0.18$); and Part IV (motor complications) score change was −1.7 (5.3) versus −0.7 (4.0) ($p = 0.22$).

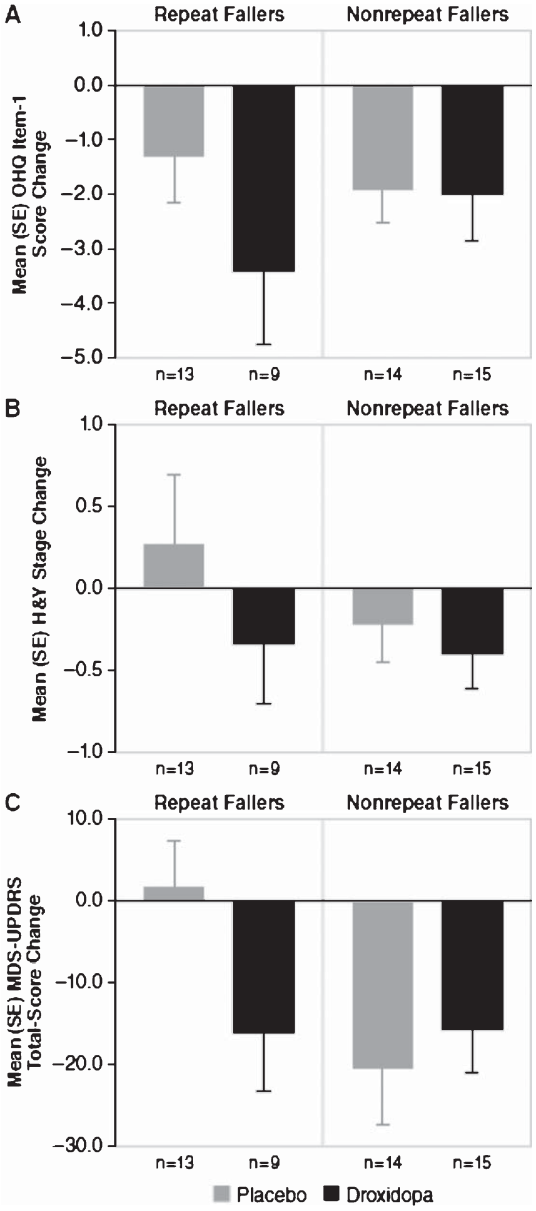

Fig. 3. Mean (SE) change from randomization to end of study in OHQ Item-1 (dizziness/lightheadedness) score (A), H&Y stage (B), and MDS-UPDRS total score (C) among repeat fallers* and non-repeat fallers in each treatment group. *≥2 falls during study-drug treatment. H&Y, Hoehn & Yahr; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; OHQ, Orthostatic Hypotension Questionnaire; SE, standard error.

On 6 individual MDS-UPDRS items, the difference in mean score change between treatment groups was ≥0.5. Four of these items favored droxidopa, with greatest difference for "time spent with dyskinesias" (0.96, under motor complications). Two items favored placebo, with greatest difference for "postural

Table 3
Incidence of adverse events among repeat fallers* and nonrepeat fallers in each treatment group

Adverse event, by MedDRA preferred term**	Repeat fallers		Nonrepeat fallers	
	Placebo recipients ($n=13$)	Droxidopa recipients ($n=9$)	Placebo recipients ($n=14$)	Droxidopa recipients ($n=15$)
Any	13 (100%)	4 (44%)	10 (71%)	13 (87%)
Nausea	3	0	0	3
Headache	0	0	2	3
Skin laceration	3	2	0	0
Contusion	2	2	0	0
Diarrhea	2	0	2	0
Urinary tract infection	3	0	0	1
Blood pressure increased	1	0	1	1
Dizziness	1	0	0	2
Disorientation	0	0	2	0
T wave amplitude decrease	0	0	2	0
Insomnia	0	1	0	1
Mouth injury	2	0	0	0
Edema peripheral	2	0	0	0

*≥2 falls during study-drug treatment. **Medical Dictionary for Regulatory Activities Version 13.0. Types listed each were reported in >1 patient.

stability" (0.65, under motor examination). On items of special interest that might explain a reduction in falls, small differences were recorded for "freezing" (0.13, under motor experiences of daily living), "freezing of gait" (0.08, under motor examination), and "walking and balance" (0.08, under motor experiences of daily living), each favoring droxidopa, and for "lightheadedness on standing" (0.07, under nonmotor experiences of daily living), favoring placebo.

Mean (SD) H&Y stage decreased (improved) by −0.4 (0.9) units in droxidopa- versus 0.0 (1.2) in placebo-treated patients ($p=0.13$).

Post-hoc analyses: Repeat fallers versus nonrepeat fallers

Over this 10-week study, nearly all falls—269 of 276, or 98%—were reported by the 22 patients (43% of 51) who experienced repeat falls (≥2 falls). Droxidopa-group repeat fallers ($n=9$) experienced 1.0 (1.2) mean (SD) falls per patient per week while placebo-group repeat fallers ($n=13$) experienced 1.9 (2.1). This represents a 47% lower fall rate among droxidopa-group versus placebo-group repeat fallers.

In terms of mean change from randomization to end of study, repeat fallers treated with droxidopa experienced less dizziness/lightheadedness and less PD symptomatology than repeat fallers receiving placebo. For dizziness/lightheadedness score (Fig. 3A), the difference favoring droxidopa over placebo was 2.1 units. For H&Y score (Fig. 3B), the difference favoring droxidopa was 0.6 units. For MDS-UPDRS total score (Fig. 3C), the difference favoring droxidopa was 17.7 units.

Safety

During the study, 17 droxidopa recipients (71% of 24) and 23 placebo recipients (85% of 27) reported AEs. No AEs were serious. More placebo-treated patients ($n=8$) than droxidopa-treated patients ($n=4$) reported fall-related AEs (e.g., contusion, skin laceration). AE incidence in repeat fallers versus nonrepeat fallers is summarized in Table 3.

There was no evidence associating droxidopa with increased laboratory or electrocardiographic abnormalities. One patient treated with droxidopa and 1 patient treated with placebo exhibited supine hypertension >180 mmHg, in both cases during dosage optimization.

DISCUSSION

The original objective of Study 306 was to evaluate the clinical efficacy of droxidopa over an 8-week maintenance period in patients with nOH in PD. Previous, shorter-term studies had identified symptomatic benefits in patients with nOH in several settings, including PD [15]. At the present study's pre-planned interim efficacy analysis, there was no evidence of reduced nOH symptoms and nOH impact on daily activities, as measured by the study's primary endpoint (change in OHQ composite score from baseline to Week 8).

As a result, the study was temporarily discontinued for futility while exploratory analyses were performed.

Because the ability of the OHQ composite score to assess clinically relevant changes in nOH in PD is not known, additional analyses were performed. Among them, change in dizziness/lightheadedness score, assessing the cardinal symptom of nOH, showed a numerical (but statistically nonsignificant) clinical benefit for droxidopa compared with placebo, although the analysis was not powered for statistical significance. The magnitude of benefit at maintenance Week 8 was less than at Week 1, raising the possibility that during the study's relatively brief titration period ($\leq$2 weeks), adequate droxidopa dosage may not have been achieved. Indeed, only 46% of the droxidopa group reached a dosage level of 500 or 600 mg t.i.d., compared with 70% of the placebo group. Further titration may be required during treatment to attain maximal benefit. This issue can be addressed in future trials.

Compared with placebo, droxidopa recipients also showed a significant increase in standing systolic blood pressure at Week 1 and numerical improvements at Weeks 2 and 4, suggesting a hemodynamic benefit. The difference between treatment groups was lost at Week 8, when the placebo group exhibited a previously unseen increase in standing systolic blood pressure. The explanation for this is unclear. In general, the variability inherent in blood-pressure point estimates may impede the interpretation of hemodynamic data. More studies would be needed to assess the observed increase.

Droxidopa recipients showed a trend for fewer falls, with a relative risk reduction of 50%. *Post-hoc* analyses revealed that almost all of the study's reported falls (98%) occurred in the 22 patients (43%) who had repeat falls. This suggests that droxidopa might be useful to reduce falls in PD patients who are repeat fallers, a possibility that should be examined in a clinical trial designed for this purpose. The mechanisms by which droxidopa could potentially reduce falls include improvement in nOH, but also might include reduction in freezing, improvement in bradykinesia and gait, or even improved postural stability. Due to the small number of repeat fallers, we were unable to conduct meaningful evaluations of droxidopa's impact on these PD symptoms.

A descriptive review of results suggested that while nonrepeat fallers showed little or no difference across treatment groups, repeat fallers showed signals of droxidopa-related benefit in dizziness/lightheadedness score, H&Y score, and MDS-UPDRS total score. Why repeat fallers would have the largest response to droxidopa is unclear. Repeat falls might be a marker for a substantial norepinephrine deficit responsive to droxidopa. Whether such a deficit reflects PD severity or indicates a distinct PD subtype is not known. Nor is it known whether such a deficit is expressed exclusively as nOH and resultant falls, or more widely, to include other autonomic or specific PD features such as freezing, gait dysfunction, and postural instability. Future trials might attempt to capture this information.

In summary, this small exploratory study of droxidopa for treatment of nOH in PD did not meet its pre-specified primary efficacy outcome. Because the interim analysis was not powered to examine other outcomes with statistical rigor, a firm conclusion cannot be drawn. However, data from several potentially clinically relevant endpoints suggested signals of benefit, e.g., dizziness/lightheadedness and frequency of falls, meriting further investigation in larger trials.

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CONFLICTS OF INTEREST

RAH has received honoraria or payments for consulting, advisory services, speaking services in the past 12 months from Abbott Laboratories, Allergan, AstraZeneca, Ceregene, Chelsea Therapeutics, Inc., GE Healthcare, Impax Laboratories, Ipsen Biopharmaceuticals, Lundbeck, Med-IQ, Merck/MSD, Noven Pharmaceuticals, Straken Pharmaceuticals, Targacept, Teva Pharmaceuticals Industries, Teva Neuroscience, Upsher-Smith Laboratories, UCB, UCB Pharma SA, XenoPort. RAH's institution has received research support in the past 12 months from Abbott Laboratories, Addex Therapeutics, Allergan, AstraZeneca, Chelsea Therapeutics, Inc., GE Healthcare, Impax Laboratories, Ipsen Biopharmaceuticals, Merck/MSD, Merz, the Michael J Fox Foundation for Parkinson's Research, Schering-Plough, Teva Neuroscience, UCB, Vita-Pharm.RAH has received royalties in the past 12 months from the University of South Florida (FL,

USA). In addition, RAH has consulted in litigation with lawyers representing various current and former manufacturers of welding consumables.

AH is an employee and stockholder of Chelsea Therapeutics, Inc.

SI has received honoraria or payments for consulting, advisory services, speaking services in the past 12 months from Acadia, Allergan, Brittania, Chelsea Therapeutics, Inc., GE, GSK, Impax, Ipsen, Lundbeck, Medtronics, Merz, Novartis, Teva, UCB, and US World Meds. SI has received research support in the past 12 months from Abbvie, Acadia, Adamas, Addex, Allergan, Allon, Astra Zeneca, Biotie, Chelsea Therapeutics, Inc., Civitas, Eisia, GSK, Ipsen, Kyowa, Lilly, Merck Schering-Plough, Merz, Michael J Fox Foundation, Novartis, Neurocrine, NIH, Novartis, Orion, Parkinson Study Group, Phytopharm, Purdue, Roche, Santhera, Serono, Shire, Teva, UCB, and US World Meds.

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