Droxidopa for the Short-Term Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Parkinson’s Disease (nOH306B)

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ABSTRACT: Neurogenic orthostatic hypotension (nOH) results from failure of norepinephrine responses to postural change to maintain standing systolic blood pressure (s-SBP). Droxidopa is an oral prodrug of norepinephrine. Study nOH306 enrolled patients with Parkinson’s disease (PD) and symptomatic nOH. Subjects underwent up to 2 weeks of double-blind titration of droxidopa or placebo, followed by 8 weeks of double-blind maintenance treatment (100-600 mg thrice-daily). For the initial 51 subjects (study nOH306A, previously reported), the primary efficacy measure, Orthostatic Hypotension Questionnaire (OHQ) composite score, did not demonstrate significant change versus placebo at maintenance week 8. For the subsequent 171 subjects (study nOH306B, reported here), the primary efficacy measure was change versus placebo on item 1 (“dizziness, lightheadedness, feeling faint, or feeling like you might black out”) of the Orthostatic Hypotension Symptom Assessment (OHSA) subsection of the OHQ at maintenance week 1. At week 1, mean (standard deviation) improvement on OHSA item 1 was 2.3 (2.95) for droxidopa versus 1.3 (3.16) for placebo ($P=0.018$). In addition, mean increase in s-SBP at week 1 was 6.4 (18.85) for droxidopa versus 0.7 (20.18) mmHg for placebo (nominal $P$ value: 0.032). Differences in change in OHSA item 1 scores from baseline to maintenance weeks 2, 4, and 8 were not statistically significant. Adverse-event (AE) incidence was similar across groups, but 12.4% of droxidopa and 6.1% of placebo subjects withdrew because of AEs. The most common AEs on droxidopa (vs. placebo) were headache (13.5% vs. 7.3%) and dizziness (10.1% vs. 4.9%). Study nOH306B demonstrated subjective (OHSA item 1) and objective (s-SBP) evidence of short-term droxidopa efficacy (vs. placebo) for symptomatic nOH in PD. © 2014 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: hypotension; orthostatic; Parkinson’s disease; droxidopa; falls; treatment; lightheadedness

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Neurogenic orthostatic hypotension (nOH) results from failure of the autonomic nervous system to generate adequate norepinephrine responses to changes in posture.1-3 This failure leads to decreases in standing systolic blood pressure (s-SBP) and often to supine hypertension. If the s-SBP decreases cannot adequately maintain cerebral perfusion, nOH can become symptomatic and can vary through the day. Symptoms can include dizziness, lightheadedness, syncope, visual disturbances, neck/shoulder pain, difficulty in concentrating, and nonspecific complaints, such as weakness or fatigue. nOH is common in Parkinson’s disease (PD): In a single-center review of 1,125 PD patients, the prevalence of symptomatic nOH was 18%,4 and in studies defining nOH solely by s-SBP change, the reported prevalence was as high as 47% in community-based5 and 58% in hospital-based6 PD populations. In PD, nOH may contribute to falls,7,8 which have been reported to occur in 81% of PD patients within 15 years after PD diagnosis.9 Such falls may necessitate hospitalization10 and can lead to significant morbidity.8,9

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an oral prodrug converted to norepinephrine by dopa decarboxylase both centrally and peripherally.11 In early, small clinical studies of patients with symptomatic nOH in MSA and pure autonomic failure, the agent provided hemodynamic12-14 and symptomatic13 benefit. More recently, droxidopa has been evaluated in several large, multicenter clinical trials (studies nOH301, nOH302, and nOH306). Studies nOH30115 (n = 162) and nOH30216 (n = 101) included patients with symptomatic nOH in PD, MSA, pure autonomic failure, and nondiabetic autonomic neuropathy. In study nOH301, responders to open-label droxidopa titration underwent a 7-day washout and then were randomized in a 7-day double-blind trial of droxidopa versus placebo. Significant improvement versus placebo was demonstrated by measures including composite score (primary endpoint) on the Orthostatic Hypotension Questionnaire (OHQ), a validated nOH-specific severity scale,17 scores on individual OHQ items, such as dizziness/lightheadedness, and mean s-SBP. In study nOH302, responders to open-label droxidopa titration received additional open-label treatment for 7 days and then were randomized to droxidopa or placebo for 14 days. In this trial, changes in dizziness/lightheadedness score (primary outcome) and mean s-SBP were not significantly different between droxidopa- and placebo-treated subjects. However, change in OHQ composite score significantly favored droxidopa. In addition, an integrated analysis of studies nOH301 and nOH302 demonstrated a significant increase in mean s-SBP (without a marked increase in supine hypertension), accompanied by significant improvement on OHQ items for dizziness/lightheadedness, weakness, fatigue, and nOH impact on activities requiring standing a short or long time and walking a short or long time.18

Study nOH306 differed from these other trials in that it enrolled only patients with symptomatic nOH resulting from PD and was designed as an intention-to-treat study, rather than only including initial responders. In addition, it was originally designed to evaluate the clinical efficacy of droxidopa over an 8-week double-blind period. In a preplanned interim efficacy analysis, the initial 51 subjects (study nOH306A) did not demonstrate a significant difference across groups in the trial’s primary efficacy measure, change in OHQ composite score.19 However, exploratory analyses19 suggested potential efficacy for dizziness/lightheadedness score and for falls and led to further hypotheses and a corresponding change in the trial’s primary efficacy measure while data for subsequent subjects remained blinded. The resulting analyses of the subsequent 171 enrolled patients (Study nOH306B) are presented here.

Patients and Methods

Study Subjects

For all study nOH306 subjects, key inclusion criteria included a clinical diagnosis of PD and age ≥18 years. In addition, subjects were required to have signs and symptoms of nOH, including a blood pressure (BP) decrease ≥20 mmHg systolic or ≥10 mmHg diastolic upon standing for up to 3 minutes,2 an OHQ composite score ≥3, and a study-investigator nOH rating of ≥3 (at least “mild”) on the clinician-reported Clinical Global Impression-Severity (cCGI-S) scale. Key exclusion criteria included use of vasoconstricting agents or long-acting antihypertensive medications; sustained, severe hypertension (≥180/110 mmHg while seated or supine); and a Mini–Mental State Examination score ≤23. Patients with significant uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or a history of myocardial infarction were also excluded.

Study Design

Study nOH306 was a phase III, multicenter, randomized, placebo-controlled, double-blind, parallel-group trial (ClinicalTrials.gov identifier: NCT01176240). Subjects were randomized (1:1 ratio) to double-blind droxidopa or placebo titration (up to 2 weeks), followed by 8 weeks of double-blind maintenance at each subject’s optimized dosage (100-600 mg thrice-daily [TID]). During titration, study drug was increased from 100 mg TID in 100-mg TID increments until the subject either (1) became asymptomatic for nOH (cCGI-S score of 1), or nearly asymptomatic (cCGI-S score of 2), (2) had a systolic BP (SBP) ≥180 mmHg or diastolic BP (DBP) ≥110 mmHg after 10 minutes supine, on three consecutive measurements during 1 hour, (3)
experienced intolerable adverse events (AEs), or (4) reached the maximum dosage of 600 mg TID. Subjects meeting criteria 2 or 3 at a dosage >100 mg TID were eligible to continue at their previous lower dosage.

During the maintenance period, a single 100-mg TID study-drug reduction was permitted for subjects with AEs considered to be related to study drug. Throughout the study, all PD medications were to be held stable. Midodrine was disallowed, but fludrocortisone could be continued at a dosage that had been stable for ≥2 weeks before start of study drug. Bedtime use of a short-acting antihypertensive was also permitted.

**Study Assessments**

The OHQ, cCGI-I ratings, and patient-reported Clinical Global Impression-Severity (pCGI-S) ratings were completed at baseline (i.e., at randomization for study-drug titration) and at maintenance weeks 1, 2, 4, and 8 (hereafter simply called weeks). Clinician- and patient-reported Clinical Global Impression-Improvement (cCGI-I and pCGI-I) ratings were obtained at weeks 1, 2, 4, and 8. The International Parkinson and Movement Disorder Society (MDS) UPDRS (MDS-UPDRS) and the 39-item Parkinson’s Disease Questionnaire (PDQ-39) were completed at baseline and week 8. An orthostatic standing test was conducted at time points including baseline and weeks 1, 2, 4, and 8. In each test, supine BP and heart-rate measurements (head and torso elevated ~30 degrees from horizontal) were obtained at −10 minutes, −5 minutes, and immediately before standing, followed by values upon standing (minute 0) and after 3 minutes of standing.

Study assessments were conducted ~3 hours after the subject’s first daily study-drug dose (during an ON state, if the subject was having motor fluctuations). Additionally, subjects were instructed to record, in a daily 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”—a phrasing consistent with standard characterizations. Fall-related injuries were defined as prespecified AEs (e.g., contusions) on the day of or the day after a reported fall.

**Efficacy Measures**

The OHQ consists of the six-item Orthonastic Hypotension Symptom Assessment (OHSAs), assessing dizziness/lightheadedness (OHSA item 1), vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort, and the four-item Orthonastic Hypotension Daily Activity Scale (OHDAS), assessing nOH interference with daily activities requiring standing a short time, standing a long time, walking a short time, and walking a long time. Each item is scored from 0 (not bothered/no interference) to 10 (worst possible/complete interference), describing the preceding week. The responses yield a composite OHSAs score and a composite OHDAS score (each is the average of the item scores not rated 0 at baseline) and also an overall composite score (the average of the OHSA and OHDAS composite scores).

The original primary outcome measure in study nOH306 had been OHQ composite score at 8 weeks. A subsequent change in primary outcome measure emerged from an interplay between regulatory requirements and the outcomes of other droxidopa trials. Study nOH306 was undertaken shortly after study nOH302, a 2-week double-blind trial with a randomized-withdrawal design, had failed to demonstrate significant efficacy by its primary outcome measure, OHSA item 1 score, perhaps owing to an unanticipated carryover of droxidopa effect among subjects switched to placebo. However, OHQ composite score, assessed post hoc, did identify efficacy. Accordingly, study nOH306 was designed as an 8-week double-blind trial with OHQ composite score change as its primary endpoint. Because PD patients had been only a subgroup in study nOH302, but would compose all the subjects in study nOH306, study nOH306 included a preplanned interim analysis of the primary outcome, which ultimately predicted futility, as described above. Meanwhile, the U.S. Food and Drug Administration (FDA) had consented to use study nOH301, a 1-week double-blind trial of droxidopa inception, in a new drug application (NDA). Hence, the remainder of study nOH306 could be repurposed, as study nOH306B, to examine fall rates. In March 2012, the NDA was rejected, and the FDA advised that resubmission would require a study corroborating the efficacy noted in study nOH301. By protocol amendment, and without data unblinding, the study nOH306B primary outcome was changed to OHSA item 1 score change at 1 week, thereby aligning it with the duration of study nOH301 while focusing the evaluation of subjective efficacy on a patient self-rating of the primary symptoms of nOH. OHSA item 1 asks respondents to rate their “dizziness, lightheadedness, feeling faint, or feeling like you might black out.”

In study nOH306B, secondary efficacy variables (in hierarchical order) included mean change on OHSA item 1 from baseline to week 2; mean change on OHSA item 1 from baseline to week 4; mean change in lowest s-SBP between 0 and +3 minutes of standing, from baseline to week 1; mean change on OHSA item 1 from baseline to week 8; aggregated patient-reported falls from baseline to week 8, expressed as falls per patient-week; and mean change in OHQ composite score from baseline to week 8.

**Safety Data**

Treatment-emergent AEs (TEAEs), vital signs, clinical laboratory values, and electrocardiographic
findings were collected as safety parameters. Safety assessments also included change in PD, as measured by MDS-UPDRS and PDQ-39 scores.

Statistical Analyses
The primary efficacy analysis was based on the full analysis set (FAS), comprising all randomized subjects who received at least one dose of study drug and provided week 1 OHSA item 1 data. Treatment-group differences were tested using an analysis of covariance (ANCOVA) model with effects for baseline and treatment. Where the assumptions of an ANCOVA were not met, a rank ANCOVA was used, based on Cochran-Mantel-Haenszel’s test. Statistical significance was set at the two-sided, 5% level. Secondary efficacy endpoints were analyzed using a similar ANCOVA, except for falls, which were assessed by Wilcoxon’s rank-sum tests. A hierarchical testing strategy was used to control the family-wise error rate at the 5% level. For responder analyses of the primary efficacy endpoint, Fisher’s exact test was used.

Sample-Size Calculation
The sample size for study nOH306B was based on the study nOH306A finding of a 1.5-unit difference between droxidopa and placebo in improvement of dizziness/lightheadedness (OHSA item 1) at 1 week, with a 3.3-unit standard deviation (SD). Consequently, a two-sided test with \( P \leq 0.05 \) would require 154 patients for an 80% power to detect a difference between groups.

Study Oversight
The study was conducted in full conformance with International Conference on Harmonization guidelines for good clinical practice. The study protocol was approved by an institutional review board for each study site. Before study procedures, all subjects provided written informed consent. Data were collected by investigators and study-site staff and were analyzed by the study sponsor, Lundbeck NA Ltd.

Results
Eighty sites, all in the United States, participated in the trial. Data collection began in June 2010 and ended in October 2012.

Study Subjects
Of the 225 patients who entered study nOH306, 174 were randomized in study nOH306B (Fig. 1). Three of them did not receive study drug; hence, the safety set comprised 171 subjects, of whom 147 (86.0%) provided an OHSA item 1 self-rating at week 1, thereby composing the FAS. Two subjects were randomized to placebo, but erroneously received droxidopa (for 3 days and for an estimated 12 days) resulting from study-site error in dispensing study drug. They are included in the safety set’s droxidopa group and the FAS’s placebo group. There were no meaningful differences in baseline characteristics between FAS subjects randomized to droxidopa and those randomized to placebo (Table 1). Carbidopa/levodopa was the most common concomitant PD medication, taken by 70 subjects (78.7%) in the safety set’s droxidopa group and 65 (79.3%) in the safety set’s placebo group. A larger proportion of subjects took fludrocortisone in the droxidopa group (30 safety-set subjects; 33.7%) than in the placebo group (16 safety-set subjects; 19.5%).

Study-Drug Optimization
In the FAS, the most common reason for stopping dosage titration was that the subject reached the maximum dose allowed, which occurred in 28 subjects (40.6%) in the droxidopa group and 42 (53.8%) in the placebo group. Additional reasons for stopping dosage titration were that the subject became asymptomatic (29 [42.0%] vs. 26 [33.3%]), experienced sustained SBP >180 mmHg or DBP >110 mmHg (4 [5.8%] vs. 12 [15.4%]), or experienced intolerable AEs (8 [11.6%] vs. 2 [2.6%]). The mean (SD) daily study-drug dosage after dose optimization was 436 (163) mg in the droxidopa group and 468 (163) mg in the placebo group.

Primary Efficacy Analysis
From baseline to week 1, mean (SD) improvement in OHSA item 1 score was 2.3 (2.95) units in the droxidopa group versus 1.3 (3.16) in the placebo group. Additionally, reasons for stopping dosage titration were that the subject became asymptomatic (29 [42.0%] vs. 26 [33.3%]), experienced sustained SBP >180 mmHg or DBP >110 mmHg (4 [5.8%] vs. 12 [15.4%]), or experienced intolerable AEs (8 [11.6%] vs. 2 [2.6%]). The mean (SD) daily study-drug dosage after dose optimization was 436 (163) mg in the droxidopa group and 468 (163) mg in the placebo group.

Responder Analyses of the Primary Endpoint
Compared with placebo subjects, significantly greater proportions of droxidopa subjects met a variety of primary endpoint responder criteria, including improvement ≥2 units, ≥3 units, ≥4 units, ≥25%, and ≥50% (Supporting Fig. A).
Exploratory BP Analyses

Mean changes from baseline in lowest s-SBP (Supporting Table A) favored the droxidopa group at week 2 by 6.1 mmHg (nominal P value: 0.087) and at week 8 by 4.1 mmHg (nominal P value, 0.160). The mean changes from baseline to week 4 slightly favored the placebo group, by 0.2 mmHg (nominal P value: 0.799).

Exploratory Falls Analyses

The droxidopa group had 229 reported falls, whereas the placebo group had 716 (nominal P value: 0.677). The difference in number of falls was evident as early as the end of titration, by which time there had been 46 reported falls in the droxidopa group and 232 in the placebo group.

Exploratory OHQ Analyses

In general, changes from baseline in OHQ composite score, OHSA composite score, and OHDAS composite score favored the droxidopa group (see Supporting Table A).

Exploratory CGI Analyses

Changes in cCGI-S scores favored droxidopa over placebo (see Supporting Table A), with nominal P values < 0.05 at weeks 1 and 2. pCGI-S scores showed no notable differences between treatment groups. Similarly, cCGI-I scores favored droxidopa at weeks 1, 2, and 8, but pCGI-I scores showed no notable differences.

Safety

Overall, 82.0% of the droxidopa group and 79.3% of the placebo group reported TEAEs (Table 3). In the droxidopa group, the incidence of headache, dizziness, nausea, and hypertension was higher than in the placebo group. For hypertension, it was 7.9%, compared with 1.2% for placebo. However, for the combined terms “hypertension,” “blood pressure increased,” and “blood pressure systolic increased,” it was 12.4%, compared with 8.5%. In both groups, most TEAEs were mild or moderate in severity.

TEAEs leading to discontinuation occurred in 11 subjects (12.4%) in the droxidopa group and 5...
(6.1%) in the placebo group. In the droxidopa group, 2 such AEs were severe (BP increased and hypertension), 6 were moderate (atrial fibrillation, BP increased, hallucination, hypotension, mental status changes, and PD), and 3 were mild (2 cases of hypertension and 1 of abnormal dreams). In the placebo group, 1 such AE was severe (hypertension). The remaining 4 were moderate (BP increased, gastroenteritis, malaise, and syncope). No subjects died during the study.

The proportion of subjects with a reported fall-related injury was higher in the placebo group than in the droxidopa group, at 25.6% compared with 16.9% (no statistical analysis). The incidence of contusion, excoriation, and skin laceration was also higher (see Table 3). Injuries in the placebo group included 2 subjects with fractures and 1 with traumatic brain injury. There were no similar injuries in the droxidopa group.

Overall, vital signs, clinical laboratory values, and electrocardiographic findings showed no clinically significant trends or differences between treatment groups. At orthostatic standing tests, a total of 7 droxidopa recipients (7.9% of 89) and 4 placebo recipients (4.9% of 82) exhibited supine hypertension, defined as an SBP >180 mmHg at all 3 assessments during a 10-minute supine period (see Table 3). No subject in either group had a recorded supine SBP >180 mmHg after week 2.

Among PD parameters (Supporting Table B), MDS-UPDRS scores showed similar mean decreases (improvements) across treatment groups, and PDQ-39 scores showed mean decreases (improvements) on almost all scales and in the index score.

### TABLE 1. Subjects’ Baseline Characteristics

| Variable                        | Droxidopa Group | Placebo Group |
|--------------------------------|-----------------|---------------|
| **Demographic characteristics (FAS)** |                 |               |
| N                              | 69              | 78            |
| Age at screening, years         |                 |               |
| Mean (SD)                      | 72.5 (8.0)      | 71.9 (7.7)    |
| Range                          | 41.4-91.7       | 53.5-86.3     |
| Sex, n (% of group)            |                 |               |
| Male                           | 45 (65.2)       | 52 (66.7)     |
| Female                         | 24 (34.8)       | 26 (33.3)     |
| Race, n (% of group)           |                 |               |
| White                          | 65 (94.2)       | 75 (96.2)     |
| Other                          | 4 (5.8)         | 3 (3.8)       |
| Weight, kg                     |                 |               |
| Mean (SD)                      | 78.1 (17.4)     | 78.2 (15.5)   |
| Range                          | 48.6-122.0      | 52.7-122.3    |
| OHSA characteristics (FAS)      |                 |               |
| N                              | 69              | 78            |
| OHSA item 1 score              |                 |               |
| Mean (SD)                      | 5.1 (2.04)      | 5.1 (2.33)    |
| Range                          | 0-9             | 0-10          |
| OHQ composite score            |                 |               |
| Mean (SD)                      | 5.5 (1.54)      | 5.7 (1.64)    |
| Range                          | 3-9             | 3-9           |
| OHSA composite score           |                 |               |
| Mean (SD)                      | 5.1 (1.66)      | 5.3 (1.58)    |
| Range                          | 2-9             | 2-9           |
| OHQAS composite score          |                 |               |
| Mean (SD)                      | 5.8 (1.97)      | 6.2 (2.14)    |
| Range                          | 2-10            | 1-10          |
| cCIG-S rating                  |                 |               |
| Mean (SD)                      | 4.4 (0.95)      | 4.6 (0.94)    |
| Range                          | 3-6             | 3-7           |
| pCIG-S rating                  |                 |               |
| Mean (SD)                      | 4.3 (1.27)      | 4.1 (1.26)    |
| Range                          | 1-7             | 2-7           |
| Lowest s-SBPa                   |                 |               |
| Mean (SD)                      | 94.7 (21.53)    | 95.7 (20.09)  |
| Range                          | 52-145          | 44-144        |
| PD characteristics (safety set) |                 |               |
| N                              | 89b             | 82            |
| H & Y stage, n (% of group)    |                 |               |
| 0                              | 8 (9.0)         | 15 (18.3)     |
| 1                              | 2 (2.2)         | 4 (4.9)       |
| 2                              | 42 (47.2)       | 24 (29.3)     |
| 3                              | 29 (32.6)       | 26 (31.7)     |
| 4                              | 5 (5.6)         | 11 (13.4)     |
| 5                              | 2 (2.2)         | 0             |
| Not recorded                   | 1 (1.1)         | 2 (2.4)       |

*aDuring an orthostatic standing test, between 0 and +3 minutes standing.

*bIncludes 2 subjects randomized to placebo who erroneously received droxidopa.

[FIG. 2. OHSA item 1 changes from baseline in study nOH306B and study nOH306 overall (observed cases). *P<0.05 versus placebo, ANCOVA; **P<0.01 versus placebo, ANCOVA. BL, baseline; SE, standard error.]
Discussion

OH is a potentially incapacitating disorder associated with significant morbidity, including falls and hospitalization.\(^{23}\) In the present study of symptomatic nOH in PD, droxidopa improved cardinal nOH symptoms of dizziness/lightheadedness, as demonstrated by the primary outcome measure, change in OHSA item 1 score (compared with placebo) from baseline to week 1. This subjective outcome was supported by objective improvement in s-SBP from baseline to week 1. Thus, study 306B provides evidence for the short-term efficacy of droxidopa to treat nOH in PD.

In study nOH306B, changes from baseline in OHSA item 1 score and s-SBP favored droxidopa at weeks 2 through 8, but the differences from placebo were not statistically significant. Exactly why sustained benefit was not observed is a matter of speculation. It is possible that a pretreatment adrenoreceptor hypersensitivity diminished after the introduction of norepinephrine replacement therapy.\(^{14,24}\) If so, further dose titration may be required to maintain clinical benefit. Subjects may also have exhibited response shift in their patient-reported outcomes, in which a continuing experience of improvement recalibrates patients’ recollections of their baseline symptoms.\(^{25,26}\) In addition, the study did not control for subjects’ usage of nonpharmacological strategies addressing nOH, such as increased hydration. However, we also note that the lack of a significant difference across groups at week 8 may have been a result of

| Endpoint | Droxidopa Group | Placebo Group | P Value or Nominal P Value\(^b\) (ANCova) |
|----------|-----------------|---------------|------------------------------------------|
| Primary  |                 |               |                                          |
| OHSA item 1 score, baseline to week 1 | N 69 78 | N 68 75 | 0.018 |
| Mean (SD) change | -2.3 (2.95) | -1.3 (3.16) |                          |
| Secondary, assessed hierarchically | | |  |
| OHSA item 1 score, baseline to week 2 | N 68 75 | N 67 73 | 0.600 |
| Mean (SD) change | -1.9 (2.86) | -1.6 (2.97) |                          |
| OHSA item 1 score, baseline to week 4 | N 67 73 | N 66 70 | 0.308 |
| Mean (SD) change | -2.0 (3.08) | -1.5 (2.74) |                          |
| Lowest standing systolic BP,\(^c\) mmHg, baseline to week 1 | N 68 78 | N 67 75 | 0.032\(^b\) |
| Mean (SD) change | +6.4 (18.85) | +0.7 (20.18) |                          |
| OHSA item 1 score, baseline to week 8 | N 63 68 | N 62 67 | 0.187\(^b\) |
| Mean (SD) change | -2.1 (3.03) | -1.5 (2.91) |                          |
| Falls\(^d\) | | |  |
| N 69 78 | N 63 70 | 0.853\(^b\)\(^e\) |
| Mean falls per patient-week | 0.39 1.09 |                          |
| OHQ composite score, baseline to week 8 | N 63 68 | N 62 67 | 0.286\(^b\) |
| Mean (SD) change | -2.2 (2.29) | -2.0 (2.18) |                          |

\(^a\)FAS, missing data excluded.

\(^b\)P values after OHSA item 1 score change from baseline to week 2 are nominal values unadjusted for nonsignificant outcomes in the preceding hierarchical analyses.

\(^c\)During an orthostatic standing test, between 0 and +3 minutes standing.

\(^d\)Subject-reported (by electronic diary) throughout the study and aggregated across all subjects in each treatment group.

\(^e\)Wilcoxon’s rank-sum test.

| Variable | Droxidopa Group | Placebo Group |
|----------|-----------------|---------------|
| TEAEs, n (% of group) | | |
| Any TEAEs | 73 (82.0) | 65 (79.3) |
| Any severe TEAEs | 12 (13.5) | 9 (11.0) |
| Any serious TEAEs | 7 (8.5) | 5 (6.1) |
| Any TEAEs leading to discontinuation | 4 (4.5) | 4 (4.7) |
| Deaths | 0 | 0 |
| TEAE types,\(^b\) n (% of group) | | |
| Headache | 17 (19.2) | 7 (8.5) |
| Dizziness | 9 (10.1) | 4 (4.9) |
| Fatigue | 7 (8.1) | 6 (7.3) |
| Nausea | 7 (8.1) | 2 (2.4) |
| Hypertension | 7 (8.1) | 6 (7.3) |
| Excititation | 5 (5.6) | 7 (8.5) |
| Edema peripheral | 5 (5.6) | 4 (4.9) |
| Contusion | 4 (4.5) | 2 (2.4) |
| Diarrhea | 4 (4.5) | 2 (2.4) |
| PD | 4 (4.5) | 5 (6.1) |
| Gait disturbance | 4 (4.5) | 5 (6.1) |
| Skin laceration | 3 (3.4) | 7 (8.5) |
| BP increased | 3 (3.4) | 5 (6.1) |
| Urinary tract infection | 3 (3.4) | 3 (3.7) |
| Insomnia | 3 (3.4) | 2 (2.4) |
| Dehydration | 3 (3.4) | 1 (1.2) |
| Dyspepsia | 3 (3.4) | 1 (1.2) |
| Hematuria | 3 (3.4) | 0 |
| Back pain | 2 (2.2) | 5 (6.1) |
| Paresthesia | 2 (2.2) | 3 (3.7) |
| Nasopharyngitis | 1 (1.1) | 4 (4.9) |

Supine hypertension,\(^c\)\(^d\) n/N (% of group) | | |
| At baseline | 0/89 2/82 (2.4) |
| During study drug optimization | 2/87 (2.3) | 1/82 (1.2) |
| Week 1 | 4/82 (4.9) | 2/80 (2.5) |
| Week 2 | 1/70 (1.4) | 0/75 |
| Week 4 | 0/67 | 0/72 |
| Week 8 | 0/65 | 0/69 |
| Overall | 7/89 (7.9) | 4/82 (4.9) |

\(^c\)Includes 2 subjects randomized to placebo who erroneously received droxidopa.

\(^d\)The types listed (by Medical Dictionary for Regulatory Activities preferred term) are all those reported in \(>3.0\%\) of subjects in either treatment group.

\(^e\)SBP = 180 mmHg at all three supine assessments over a 10-minute period (before standing) during an orthostatic standing test.

\(^f\)Observed cases.
of inadequate power. When results from studies nOH306A and nOH306B are combined (Fig. 2, bottom), the difference across groups in change on OHSA item 1 from baseline to week 8 approached statistical significance ($P = 0.077$ vs. placebo).

Among potential efficacy signals during study nOH306, droxidopa appears to have had an impact on patient-reported falls. In the present study (nOH306B), the droxidopa group had 68% fewer patient-reported falls than the placebo group (229 vs. 716). Among the first 51 PD patients to enter this study’s protocol (nOH306A), the difference was 59% (79 vs. 192). In both comparisons, falls were normally distributed among subjects and hence were difficult to model. In a post-hoc analysis of the nOH306B falls data, use of the Poisson inverse Gaussian distribution\(^{27}\) showed a statistically significant difference between droxidopa and placebo ($P = 0.018$). Signals of potential droxidopa benefit in this study also included an impact on fall-related injuries.

Overall, droxidopa was safe and reasonably well tolerated. The incidence of AEs was similar in both groups, but 11 subjects (12.4%) in the droxidopa group and 5 in the placebo group (6.1%) withdrew because of AEs. The most common AEs associated with droxidopa were headache, dizziness, fatigue, nausea, and hypertension. In patients with nOH, supine hypertension is a particular safety concern.\(^{28}\) In this study, the rates of supine hypertension were relatively low. However, the study excluded patients with an observed BP $\geq 180/110$ mmHg while seated or supine at screening.

As described above, previous droxidopa studies have shown short-term benefit for signs and symptoms of nOH across a variety of underlying neurological disorders involving autonomic dysfunction.\(^{15,16,18}\) The present study provides evidence for short-term benefit in patients with PD. It is important to recognize that trials to date have only demonstrated efficacy over 1 or 2 weeks. Whether droxidopa is effective beyond this time frame is unclear. In February 2014, droxidopa received U.S. approval with an indication for the treatment of symptomatic nOH caused by primary autonomic failure (PD, MSA, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. The prescribing information states that “effectiveness beyond 2 weeks of treatment has not been demonstrated” and that “continued effectiveness… should be assessed periodically.”\(^{29}\) We anticipate that in clinical practice, treating physicians will want to assess both initial and continuing symptomatic benefit. If no benefit is obtained with initial titration to the highest recommended or well-tolerated dose, the medication should be discontinued. If initial benefit is achieved, but symptoms of nOH re-emerge or worsen, one might consider increasing the dose (while not exceeding the recommended range) to see if symptoms can be ameliorated. If benefit for nOH appears to have been lost, one can withdraw the medication to assess continued efficacy. A planned phase IV trial of the durability of droxidopa efficacy will have a design in which the dose can be adjusted over time as clinically appropriate.

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Supporting Data

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