Droxidopa for neurogenic orthostatic hypotension
A randomized, placebo-controlled, phase 3 trial

ABSTRACT

Objective: To determine whether droxidopa, an oral norepinephrine precursor, improves symptomatic neurogenic orthostatic hypotension (nOH).

Methods: Patients with symptomatic nOH due to Parkinson disease, multiple system atrophy, pure autonomic failure, or nondiabetic autonomic neuropathy underwent open-label droxidopa dose optimization (100–600 mg 3 times daily), followed, in responders, by 7-day washout and then a 7-day double-blind trial of droxidopa vs placebo. Outcome measures included patient self-ratings on the Orthostatic Hypotension Questionnaire (OHQ), a validated, nOH-specific tool that assesses symptom severity and symptom impact on daily activities.

Results: From randomization to endpoint (n = 162), improvement in mean OHQ composite score favored droxidopa over placebo by 0.90 units (p = 0.003). Improvement in OHQ symptom subscore favored droxidopa by 0.73 units (p = 0.010), with maximum change in “dizziness/lightheadedness.” Improvement in symptom-impact subscore favored droxidopa by 1.06 units (p = 0.003), with maximum change for “standing a long time.” Mean standing systolic blood pressure (BP) increased by 11.2 vs 3.9 mm Hg (p < 0.001), and mean supine systolic BP by 7.6 vs 0.8 mm Hg (p < 0.001). At endpoint, supine systolic BP >180 mm Hg was observed in 4.9% of droxidopa and 2.5% of placebo recipients. Adverse events reported in ≥3% of double-blind droxidopa recipients were headache (7.4%) and dizziness (3.7%). No patients discontinued double-blind treatment because of adverse events.

Conclusions: In patients with symptomatic nOH, droxidopa improved symptoms and symptom impact on daily activities, with an associated increase in standing systolic BP, and was generally well tolerated.

Classification of evidence: This study provides Class I evidence that in patients with symptomatic nOH who respond to open-label droxidopa, droxidopa improves subjective and objective manifestation of nOH at 7 days. Neurology® 2014;83:328–335

GLOSSARY

AE = adverse event; BP = blood pressure; CI = confidence interval; DDI = dopa decarboxylase inhibitor; FDA = Food and Drug Administration; MSA = multiple system atrophy; NDAN = nondiabetic autonomic neuropathy; nOH = neurogenic orthostatic hypotension; OHQ = Orthostatic Hypotension Questionnaire; PAF = pure autonomic failure; PD = Parkinson disease; SAE = serious adverse event.

Neurogenic orthostatic hypotension (nOH) is a disabling disorder defined as a sustained blood pressure (BP) reduction when the patient stands, caused by impairment of compensatory autonomic reflexes.1–3 Additional hemodynamic abnormalities4–6 frequently include supine hypertension.7 The disorder results from deficient noradrenergic activation of vascular adrenoceptors due to degenerative loss of postganglionic sympathetic neurons, as in Parkinson disease (PD) and pure autonomic failure (PAF), or loss of central pathways that regulate sympathetic drive, as in multiple system disorders.
Methods

Patients. All patients were aged 18 years or older and were required to have a clinical diagnosis of symptomatic nOH due to PD, PAF, MSA, nondiabetic autonomic neuropathy (NDAN), or dopamine-β-hydroxylase deficiency, with a documented decrease ≥20 mm Hg in systolic or ≥10 mm Hg in diastolic BP upon standing ≥3 minutes. Key exclusion criteria were use of vasoconstrictor agents within 2 days before baseline; use of long-acting antihypertensives or norepinephrine reuptake inhibitors; sustained, severe supine hypertension; and significant systemic, hepatic, cardiac, or renal disease.

Study design. This was a randomized, placebo-controlled, parallel-group trial conducted between August 2008 and July 2010 at 94 US, Canadian, and European centers. Open-label dose optimization lasting up to 14 days (but preferably ≤6) was followed by 7-day washout and then 7-day double-blind treatment. During dose-optimization, open-label droxidopa initiated at 100 mg 3 times daily was titrated in 100-mg increments until each patient: (1) had a self-rating of 0 on a 0-to-10 Likert scale for “dizziness, lightheadedness, feeling faint, or feeling like you might black out” (item 1 of the Orthostatic Hypotension Questionnaire [OHQ]; described below), plus an increase in standing systolic BP ≥10 mm Hg compared with the baseline value, as measured 5 minutes poststanding (and 3 hours after a droidopa dose); (2) reached the maximum permitted dosage, 600 mg 3 times daily; (3) had a sustained BP >180 mm Hg systolic or >110 mm Hg diastolic while standing, sitting, or supine; or (4) experienced intolerable side effects considered to be related to study drug.

Responders were defined as having any improvement from baseline (i.e., ≥1 unit) on OHQ item 1, plus a ≥10 mm Hg increase from baseline in standing systolic BP. After 7-day washout, responders were assigned by a centralized, computerized randomization schedule to double-blind droxidopa or matching placebo (1:1) for 1 week at each patient’s optimized dosage (100–600 mg 3 times daily). Patients in categories 3 or 4 received study drug at the highest tolerated dosage to which they were responders. All patients were counseled to take their last daily dose ≥4 hours before bedtime.

Efficacy measures. The OHQ,25 was administered at baseline, randomization, and end of study. Of its 10 items, 6 address nOH symptoms, namely, dizziness/lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort. The other 4 ask the respondents to judge the nOH impact on daily activities requiring “standing a short time,” “standing a long time,” “walking a short time,” and “walking a long time.” Each item is scored on a Likert scale from 0 (not bothered/no interference) to 10 (worst possible/complete interference), describing the preceding week. The responses yield a composite symptom score and a composite symptom-impact score (each is the average of the item scores not rated 0 at baseline), and also an overall composite score (the average of the symptom and symptom-impact composite scores). The study’s prespecified primary efficacy endpoint was the change in overall composite score from randomization to end of study. Secondary endpoints included changes in the symptom and symptom-impact composite scores, and in the individual OHQ items.

BP and heart rate were measured at screening, at baseline, on each day of dose optimization, at randomization, and at end of study (3 hours postdose during treatment periods). Brachial-arterial BP values were obtained by mercury, aneroid, or automated sphygmomanometry 3 times during 10 minutes while the patient was supine (with head and torso elevated approximately 30° from horizontal) and once 3 minutes poststanding. Change in standing systolic BP from randomization to end of study was an efficacy endpoint.

Safety was assessed by adverse events (AEs), clinical laboratory values, vital signs, and ECG.

Statistical analysis. For OHQ data, mean change from randomization to end of study in the droidopa and placebo groups was compared using analysis of covariance, with value at randomization as covariate and treatment group as main effect. Missing data were imputed by last observation carried forward, and statistical significance was set at the 2-sided, 5% level (at which n = 75 per group was predicted to have >80% power to detect a 1.2-unit group difference). BP changes from randomization to end of study were assessed by analysis of covariance, with missing data excluded. Post hoc analyses of change in OHQ composite score and standing systolic BP were performed in patient subsets defined by primary diagnosis and by concurrent dopa decarboxylase inhibitor (DDI) usage (carbidopa or benserazide). Relationships between changes in OHQ composite score and standing systolic BP were tested by Spearman correlation coefficients.

Classification of evidence. This trial provides Class I evidence that droidopa (100–600 mg 3 times daily) was significantly superior to placebo for treating nOH, both subjectively, including a mean OHQ composite-score improvement of 1.83 vs 0.39 units, a difference of 0.90 units (95% confidence interval [CI] 0.30–1.48;
and objectively, including a mean standing systolic BP increase of 11.2 vs 3.9 mm Hg, a difference of 7.3 mm Hg (95% CI 1.1–13.5; *p* < 0.001).

**Standard protocol approvals, registrations, and patient consents.** The study protocol was approved by the institutional review board at each study site, and all patients provided written informed consent. The study was registered with ClinicalTrials.gov (NCT00782340).

**RESULTS Patients and study-drug dosage.** Of 263 patients participating in open-label droxidopa dose optimization, 162 responders (61.6%) were treated in the double-blind study phase, 80 with placebo and 82 with droxidopa (figure 1). The 101 nonrandomized patients had nOH characteristics and primary diagnoses resembling those of the 162 responders (table 1), but they differed in being older (mean age, 64.6 vs 56.6 years) and had slightly higher likelihoods of being male and being US participants. Among responders, 40.7% had PD, 33.3% PAF, 16.0% MSA, and 4.9% NDAN. None had dopamine-β-hydroxylase deficiency. One patient assigned to droxidopa but erroneously administered placebo is included in the droxidopa group for efficacy analysis and in the placebo group for safety reporting.

Among randomized patients, the mean (SD) final study-drug dose was 430 (163) mg for droxidopa and 381 (144) for placebo, with 37.0% of droxidopa and 18.5% of placebo recipients taking the maximum 600 mg 3 times daily. By returned-capule counts, mean dosage compliance was 99.2% for droxidopa and 100.7% for placebo. Among 65 patients using DDIs, the mean final study-drug dose was 438 (166) mg for droxidopa and 394 (154) for placebo.

**OHQ outcomes.** From randomization to end of study, droxidopa recipients had a mean (SD) change of −1.83 (2.07) units in OHQ composite score, vs −0.93 (1.69) among placebo recipients, favoring droxidopa by 0.90 units (95% CI 0.30–1.48; *p* = 0.003). The improvement was ≥3 units in 27.2% of droxidopa recipients vs 11.4% of placebo recipients (*p* = 0.016), and ≥4 units in 17.3% vs 2.5% (*p* = 0.003). For symptom composite score, mean change was −1.68 (2.13) vs −0.95 (1.90) units, favoring droxidopa by 0.73 units (95% CI 0.10–1.36; *p* = 0.010), with statistically significant differences from placebo on 4 of 6 symptom items (dizziness/lightheadedness, vision disturbance, weakness, and fatigue). For symptom-impact composite score, mean change was −1.98 (2.31) vs −0.92 (1.82) units, favoring droxidopa by 1.06 units (95% CI 0.41–1.71; *p* = 0.003), with statistically significant differences from placebo on all symptom-impact items (figure 2). Mean values at randomization and end of study for all OHQ and hemodynamic variables are shown in table e-1 on the Neurology® Web site at Neurology.org.

**Hemodynamic outcomes.** From randomization to end of study, standing systolic BP increased by a mean

![Figure 1 Patient disposition](image-url)
### Table 1 Demographic and baseline nOH characteristics (full-analysis set and unrandomized subjects)

<table>
<thead>
<tr>
<th>Variable</th>
<th>DB placebo group</th>
<th>DB droxidopa group</th>
<th>Unrandomized subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>80</td>
<td>82</td>
<td>101*</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>42 (52.5)</td>
<td>42 (51.2)</td>
<td>64 (63.4)</td>
</tr>
<tr>
<td>Women</td>
<td>38 (47.5)</td>
<td>40 (48.8)</td>
<td>37 (36.6)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75 (93.8)</td>
<td>82 (100.0)</td>
<td>99 (98.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6.3)</td>
<td>0</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Primary clinical diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>31 (38.8)</td>
<td>35 (42.7)</td>
<td>45 (44.6)</td>
</tr>
<tr>
<td>Pure autonomic failure</td>
<td>28 (35.0)</td>
<td>26 (31.7)</td>
<td>33 (32.7)</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>11 (13.8)</td>
<td>15 (18.3)</td>
<td>18 (17.8)</td>
</tr>
<tr>
<td>Nondiabetic autonomic neuropathy</td>
<td>6 (7.5)</td>
<td>2 (2.4)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3.8)</td>
<td>4 (4.9)</td>
<td>3 (3.0)</td>
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<tr>
<td>Age at screening, y</td>
<td>55.7 (20.0)</td>
<td>57.4 (16.9)</td>
<td>64.6 (15.4)</td>
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<tr>
<td>Weight, kg</td>
<td>18-87</td>
<td>20-84</td>
<td>19-91</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>74.6 (14.1)</td>
<td>74.5 (14.8)</td>
<td>74.9 (15.1)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td>47.0-110.0</td>
<td>46.0-103.2</td>
<td>44.0-113.4</td>
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<tr>
<td>OHQ composite score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-10^a</td>
<td>3-10^f</td>
<td>2-10^k</td>
</tr>
<tr>
<td>Standing systolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>90.7 (16.8)</td>
<td>90.8 (15.6)</td>
<td>94.4 (21.4)</td>
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<tr>
<td>Range</td>
<td>50-130</td>
<td>45-142</td>
<td>38-154</td>
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<tr>
<td>Supine systolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>61.1 (13.2)</td>
<td>58.6 (12.7)</td>
<td>62.1 (12.5)</td>
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<tr>
<td>Range</td>
<td>30-95</td>
<td>0-86</td>
<td>35-100</td>
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<td>Standing diastolic BP, mm Hg</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
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<td>127.6 (17.4)</td>
<td>130.7 (21.4)</td>
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<tr>
<td>Range</td>
<td>60-173</td>
<td>90-172</td>
<td>83-192</td>
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<tr>
<td>Supine diastolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>76.0 (11.9)</td>
<td>77.6 (10.6)</td>
<td>77.8 (11.54)</td>
</tr>
<tr>
<td>Range</td>
<td>45-110</td>
<td>50-105</td>
<td>51-112</td>
</tr>
<tr>
<td>Standing heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>69.8 (10.1)</td>
<td>70.0 (9.3)</td>
<td>79.3 (13.8)</td>
</tr>
<tr>
<td>Range</td>
<td>48-109</td>
<td>44-96</td>
<td>38-124</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; bpm = beats per minute; DB = double-blind; nOH = neurogenic orthostatic hypotension; OHQ = Orthostatic Hypotension Questionnaire; US = United States.

*Includes 6 patients randomized in error, who did not receive double-blind study drug.

†All 4 patients were diagnosed as having "likely pure autonomic failure." Three patients were diagnosed as having "likely pure autonomic failure" and the fourth as having "likely multiple system atrophy."

‡One patient was diagnosed as having "likely pure autonomic failure," one as having a cervical spinal cord lesion, and one as having nOH of idiopathic cause.

§n = 79.

¶n = 81.

‖n = 99.

¶¶n = 100.

1After 3 minutes.

‡‡Impalpable in one patient.

§§After 10 minutes.
Safety. During open-label dose escalation, 100 patients (38.0% of 263) reported AEs (table e-3), most frequently headache (9.9%), dizziness (6.5%), or nausea (4.6%). Cardiac AEs were reported in 3.0% of patients, most frequently palpitations (1.9%). Two patients reported serious AEs (SAEs): one experienced nausea and vomiting; the other experienced urinary tract infection and urinary obstruction. Thirteen patients (4.9%) had AEs leading to discontinuation, most frequently nausea (1.5%) or hypertension (0.8%).

During double-blind treatment, 15 droxidopa (18.5% of 81) and 12 placebo (14.8% of 81) recipients reported AEs (see table e-3), most frequently headache (in 7.4% of droxidopa and no placebo recipients), dizziness (in 3.7% vs 1.2%), fatigue (2.5% vs 2.5%), syncope (2.5% vs 1.2%), and falls (0.0% vs 3.7%). No cardiac AEs occurred, no SAEs were reported, and there were no discontinuations because of AEs.

At randomization, no patients assigned to droxidopa and 2 assigned to placebo (2.5%) had supine hypertension, defined as a systolic BP >180 mm Hg. At end of study, 4 droxidopa recipients (4.9%) and 2 placebo recipients (2.5%) had supine hypertension. Overall, a supine systolic value exceeded 200 mm Hg in 2 patients assigned to placebo and none assigned to droxidopa. Neither treatment group showed clinically significant trends in laboratory and ECG parameters.

DISCUSSION In patients with symptomatic nOH, double-blind, placebo-controlled droxidopa yielded statistically significant improvement, as assessed by patient-reported outcome scores and by an increase in standing systolic BP. Among patient-reported outcomes, significant benefit was documented for 4 of 6 nOH symptoms on a validated nOH-specific severity scale, with greatest improvement for "dizziness, lightheadedness, feeling faint, or feeling like you might black out," the cardinal nOH symptoms, and for the impact of symptoms on daily activities requiring walking or standing, with greatest improvement in tolerance for "standing a long time."

In nOH studies, patient-reported outcomes deserve emphasis but pose interpretive challenges. The severity of nOH symptoms often varies day to day and throughout the day. Symptoms can also be affected by ambient temperature, physical exertion, and food and fluid intake. Most importantly, symptoms depend on posture. Study subjects feeling unwell from their primary neurologic illness may become reluctant to stand, easing or preventing nOH symptoms. Conversely, subjects feeling well may increase their standing and walking periods, provoking nOH symptoms.

Objective nOH outcome measures are also imperfect. BP values obtained when the OHQ is administered may not represent BP values during the time span to which the questionnaire refers (the previous week). Furthermore, hypotension is not the proximate cause of nOH symptoms; the direct relationship is with tissue hypoperfusion. Hence, between BP and nOH symptoms, the crucial intermediate factor is that the brain autoregulates its blood supply. Symptoms of nOH occur when BP levels decrease below the individual patient’s critical cerebral perfusion pressure. Accordingly, a large treatment-related increase in standing BP is not necessarily more beneficial than a small increase, provided the small increase places BP within the patient’s autoregulatory range.

Despite these potential confounders, the observed treatment effects of droxidopa were statistically robust and appear to be clinically meaningful. In psychometric analyses of data from a phase 4 midodrine study, including analyses anchored to Clinical Global Impression ratings of subjects’ nOH, an improvement of 0.8 to 1.0 units was judged to constitute
a minimal important change in OHQ composite score, symptom composite score, or symptom-impact composite score.\textsuperscript{25} In the present study, the mean changes from randomization to end of study on all these scores were 1.7 to 2.0 units for droxidopa (and 0.9–1.0 for placebo), and from baseline (i.e., predroxidopa inception) to end of study, the mean changes were 2.5 to 2.8.

Change in OHQ composite score correlated with change in standing systolic BP both in droxidopa and in placebo recipients. This reassuringly implies that the subjective and objective findings are related—i.e., that nOH symptoms change in parallel (but opposite) direction to standing BP—strongly supporting the validity of OHQ composite score as an nOH severity measure. Nevertheless, there was an impressive placebo effect, both in symptoms, as measured by OHQ, and in BP. In patients with nOH, classic placebo response presumably would have a limited capacity to affect BP consistently. More plausibly, the placebo recipients may have improved just by their study participation, e.g., via increased physical activity, adherence to sleeping in a head-up tilt position, or increased water and salt intake (for which the study did not control). It is apparent that whenever an intervention alleviates or worsens nOH, it acts through BP changes.

Although post hoc subgroup analyses were hampered by small sample sizes and lack of appropriate matching, the results are suggestive. Across all primary diagnoses, symptomatic improvement was numerically greater for droxidopa than for placebo, but statistically significant only in PAF (see table e-2). For its part, improvement in standing systolic BP was numerically greater both in PAF and in PD than in MSA (see table e-2). These patterns are not surprising: patients with PAF and PD have significant postganglionic noradrenergic denervation, whereas patients with MSA have mostly preganglionic neuronal loss.\textsuperscript{11} Accordingly, a more pronounced droxidopa pressor effect might be expected in PAF or PD than in MSA, attributable to adrenoceptor supersensitivity to circulating noradrenaline.\textsuperscript{22,24} This hypothesis should be explored in clinical studies with adequate power.

Because DDIs block peripheral decarboxylation of droxidopa to norepinephrine, there has been concern that DDI usage might blunt the pressor effect of droxidopa.\textsuperscript{22} The literature is inconclusive: in one study, high carbidopa doses (200 mg) abolished the pressor effect,\textsuperscript{22} but for the lower DDI doses routinely used for parkinsonism, another study implies no reduction of pressor effect.\textsuperscript{21} Although the present study suggests the possibility of lessened droxidopa benefit among DDI users, the subgroups of patients taking and not taking DDIs were not matched for diagnosis. In particular, most of the DDI nonusers had PAF, while none of the DDI users had it, a difference that may have contributed to the droxidopa benefit observed in the nonusers. The issue of DDI comedication should be addressed in studies designed for that purpose.
Potential limitations of the present study include the absence of continuous BP monitoring (e.g., overnight, or beyond 3 minutes of standing), the absence of diary-based AE reporting, and the possibility of treatment unmasking (because of open-label pretreatment). Another limitation was the 1-week duration of double-blind treatment. The efficacy, safety, and tolerability of long-term droxidopa therapy will require separate investigation. In consonance with current standards for clinical research, in which pharmacotherapies are increasingly tested for benefit in patient subsets, the study utilized an enrichment design.31 The criteria for prerandomization discontinuation included subjective response to droxidopa without an objective BP improvement (to exclude "placebo" response, plus patients with nOH-like symptoms not due to hemodynamic causes). Patients were also excluded for safety reasons. Nonrandomized subjects resembled the randomized subjects at least in their primary diagnoses and baseline nOH characteristics. During optimization, however, their mean OHQ item 1 score improved less, by 2.8 (n = 100) vs 5.0 (n = 162) units, and their mean standing systolic BP increased less, by 6.0 (n = 93) vs 23.2 (n = 161) mm Hg. The results emphasize the need to individualize nOH therapy.

Droxidopa was generally well tolerated, including a low incidence or no occurrence of SAEs and of discontinuations because of AEs. The incidence of supine hypertension was also low, with no values >200 mm Hg. In a dose-response study of midodrine in nOH, 17% of patients exhibited such values after a 10-mg dose (and 41% did so after 20 mg).18 Overall, this short-term, multicenter trial showed that droxidopa treatment led to significant amelioration of multiple symptoms of nOH (dizziness, vision disturbance, weakness, and fatigue) and of nOH impact on activities requiring standing or walking, with an associated increase in standing systolic BP. These phase 3 findings expand the evidence supporting droxidopa for treatment of nOH.

AUTHOR CONTRIBUTIONS

Dr. Kaufmann was involved in the study concept and design, the acquisition, analysis, and interpretation of data, and writing the first draft of the manuscript, as well as critical revision of the manuscript for important intellectual content, and was the study principal investigator. Dr. Freeman was involved in the study concept and design and in the acquisition, analysis, and interpretation of data, as well as critical revision of the manuscript for important intellectual content. Dr. Biagioni was involved in the study concept and design and in the acquisition, analysis, and interpretation of data, as well as critical revision of the manuscript for important intellectual content. Dr. Low was involved in the study concept and design and in the acquisition, analysis, and interpretation of data, as well as critical revision of the manuscript for important intellectual content, and was a study investigator. Dr. Pedder was involved in the research project as part of his duties as an employee of Chelsea Therapeutics, Inc. He had substantial involvement in the study concept, design, oversight, and management, and in critical revision of the manuscript for important intellectual content. Dr. Hewitt was involved in the research project as part of his duties as an employee of Chelsea Therapeutics, Inc. He had substantial involvement in the study concept, design, oversight, and management, and in critical revision of the manuscript for important intellectual content. Dr. Mathias was involved in the study concept and design and in the acquisition, analysis, and interpretation of data, as well as critical revision of the manuscript for important intellectual content.

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