Droxidopa and Reduced Falls in a Trial of Parkinson Disease Patients With Neurogenic Orthostatic Hypotension

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Objectives: Droxidopa is a prodrug of norepinephrine indicated 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 caused by primary autonomic failure including Parkinson disease (PD). The objective of this study was to compare fall rates in PD patients with symptomatic neurogenic orthostatic hypotension randomized to droxidopa or placebo.

Methods: Study NOH306 was a 10-week, phase 3, randomized, placebo-controlled, double-blind trial of droxidopa in PD patients with symptomatic neurogenic orthostatic hypotension that included assessments of falls as a key secondary end point. In this report, the principal analysis consisted of a comparison of the rate of patient-reported falls from randomization to end of study in droxidopa versus placebo groups.

Results: A total of 225 patients were randomized; 222 patients were included in the safety analyses, and 197 patients provided efficacy data and were included in the falls analyses. The 92 droxidopa patients reported 308 falls, and the 105 placebo patients reported 908 falls. In the droxidopa group, the fall rate was 0.4 falls per patient-week; in the placebo group, the rate was 1.05 falls per patient-week (prespecified Wilcoxon rank sum \( P = 0.704; \) post hoc Poisson-inverse Gaussian test \( P = 0.014 \)), yielding a relative risk reduction of 77% using the Poisson-inverse Gaussian model.

Conclusions: Treatment with droxidopa appears to reduce falls in PD patients with symptomatic neurogenic orthostatic hypotension, but this finding must be confirmed.

Key Words: droxidopa, falls, Parkinson disease, neurogenic orthostatic hypotension, treatment

Falls in patients with Parkinson disease (PD) are common and potentially catastrophic. They can lead to serious injuries including hip fractures or head trauma; furthermore, fear of falling can limit mobility and physical activity. A meta-analysis of 6 prospective studies of falling in PD identified a 3-month fall rate of 46% overall and 21% in patients without prior falls. The proportion of patients with injurious falls was approximately 25%. Moreover, quality of life is reduced in PD patients with falls even after adjusting for age, disease severity, and gait disturbances.

The underlying cause of falls in PD may be varied, complex, and multifactorial. During the development of practice recommendations for the examination and management of falls in PD, van der Mark and colleagues identified generic and PD-specific risk factors. Generic risk factors included older age, female sex, polypharmacy (≥4 drugs other than PD medications), fear of falling, depression, daily alcohol use, visual impairment, weakness due to inactivity, use of an assistive device, orthostatic hypotension (OH), and cardiac arrhythmia, among others. Parkinson disease–specific risk factors included prior falls, worse disease severity, PD medications (higher daily levodopa dosage, dopamine agonist, or anticholinergic use), slow or shuffling gait, freezing of gait (FOG), postural instability (balance impairment), flexed posture, axial rigidity, dyskinesia, cognitive impairment, urinary incontinence, and deep brain stimulation. In 1 study that analyzed direct causes of falls, sudden falls were most common (31%), followed by freezing and festination (20%), neurologic and sensory disturbances (mostly vertigo; 12%), postural instability (11%), OH (4%), and severe dyskinesia (4%); 6.2% of falls were unclassified.

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an oral produrg that is metabolized to norepinephrine by dopa decarboxylase both centrally and peripherally. It is approved in the United States for the treatment of orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out” in adult patients with symptomatic neurogenic OH (nOH) caused by primary autonomic failure (PD, multiple system atrophy, and pure autonomic failure), dopamine β-hydroxylase deficiency, and nonidiopathic autonomic neuropathy.

Analysis of falls reported as an adverse event (AE) during the early clinical development of droxidopa suggested that droxidopa might reduce falls in patients with nOH. Studies NOH3012 and NOH3023 enrolled patients with symptomatic nOH caused by primary autonomic failure. After open-label droxidopa dose titration, responders were washed out for 1 week and then randomized to either droxidopa or placebo for 1 week (NOH301) or continued on droxidopa for 1 week and then randomized to either droxidopa or placebo for 2 weeks (NOH302). When the combined data from the blinded phases of the 2 studies were examined, there was 1 (0.8%) AE of fall in the droxidopa group compared with 9 (6.8%) AEs of falls in the placebo group.

Study NOH306 was a phase 3, randomized, placebo-controlled, double-blind trial of droxidopa in PD patients with symptomatic nOH that included assessments of falls as a key secondary end point. Study NOH306 was divided into 2 separate trials (NOH306A and NOH306B) after an interim analysis based on evaluation of...
end points related to nOH. The primary manuscripts describing these trials included brief summaries of falls data. Here, we report composite analyses of falls data from study NOH306 and provide additional details not previously reported.

**METHODS**

Study NOH306 was a phase 3, multicenter, randomized, placebo-controlled, double-blind, parallel-group trial (ClinicalTrials.gov identifier: NCT01176240). Patients were randomized 1:1 in a double-blind fashion to droxidopa or placebo titration (up to 2 weeks), followed by 8 weeks of maintenance treatment at each patient's optimized dosage (100–600 mg TID; Fig. 1). During titration, study drug was increased from 100 mg TID in 100-mg TID increments until the patient either (1) became asymptomatic for nOH (Clinical Global Impression–Severity [CGI-S] score of 1) or nearly asymptomatic (CGI-S score of 2), (2) had a systolic blood pressure (BP) of 180 mm Hg or higher or diastolic BP of 110 mm Hg or higher after 10 minutes in supine position on 3 consecutive measurements during 1 hour, (3) experienced an intolerable AE, or (4) reached the maximum dosage of 600 mg TID. Patients meeting criterion 2 or 3 at a dosage greater than 100 mg TID continued at their previous lower dosage.

Throughout the study, all PD medications were held stable. Midodrine was prohibited, but fludrocortisone could be continued at a stable dosage beginning at least 2 weeks before start of study drug. Bedtime use of a short-acting antihypertensive was permitted.

Key inclusion criteria included a clinical diagnosis of PD and age 18 years or older. In addition, patients were required to have signs and symptoms of nOH, including a BP decrease to 20 mm Hg or higher systolic or 10 mm Hg or higher diastolic upon standing for up to 3 minutes, an OH Questionnaire composite score of 3 or higher, and a study investigator nOH rating of 3 or higher (at least “mild”) on the CGI-S. Key exclusion criteria included the use of vasoconstricting agents or long-acting antihypertensive medications; sustained, severe hypertension (≥180/110 mm Hg while seated or supine); and a Mini-Mental State Examination score of 23 or lower. Patients with significant uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or a history of myocardial infarction were excluded.

In-office study assessments were conducted at baseline and maintenance weeks 1, 2, 4, and 8. In addition, from baseline to end of study (EoS), patients 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 commonly used, standard definition of a fall. If patients reported a fall on a particular day, the electronic diary would ask how many times they fell that day. The device would then ask the patient a series of questions based on the worst fall of the day, including whether they experienced freezing, were lightheaded, or lost consciousness just before the fall. Patients could choose none, 1, or more than 1 of these options. Adverse events were collected in the usual manner, and fall-related injuries were defined as prespecified AEs (eg, fractures) that occurred on the day of or the day after a reported fall (Table 1). The Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) was completed at baseline and week 8.

**Statistical Analysis**

The safety set consisted of all patients who received at least 1 dose of study medication. The full analysis set (FAS) consisted

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**TABLE 1. MedDRA Preferred Terms Prospectively Defined as a Fall-Related Injury**

| 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 |
| Noncardiac chest pain | Pain |
| Pain | Skin laceration |
| Skin lesion | Tooth fracture |
| Traumatic brain injury | Traumatic hematoma |

*The reported AE was required to have occurred on the day of or the day after a reported fall.

MedDRA, Medical Dictionary for Regulatory Activities, version 13.0.

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of all patients who received at least 1 dose of study medication and provided postrandomization nOH efficacy data. Fall analyses were completed using data from patients included in the FAS. The principal falls analysis consisted of a comparison of the rate of patient-reported falls from baseline to EoS, comparing droxidopa and placebo groups. The statistical analysis plan specified an analysis of the rate of falls (average number of falls per patient per week) using a zero-inflated negative binomial (ZINB) distribution. If the data did not fit the prespecified model using defined criteria as outlined in the statistical analysis plan, the rate of falls was to be analyzed by the nonparametric Wilcoxon rank sum test. Upon analysis of the data, it was found that the distribution of falls was extremely skewed, with a different dispersion in the placebo and droxidopa groups. The ZINB distribution did not adequately fit the data, and the Wilcoxon rank sum test was used by default. However, it should be noted that because of the substantial difference in dispersion across the treatment arms, the Wilcoxon rank sum test has extremely low power to detect differences between groups. Further exploration of the data revealed that a Poisson-inverse Gaussian model, which had been previously used to fit highly dispersed falls data in the PD-Fit study of patients with PD, provided an excellent fit. The main difference with the PD-Fit modeling is that both the effects of treatment on the mean and on the dispersion parameter are included in the model using the R function generalized additive models for location, scale, and shape to capture the data features.

Data regarding fall-related injuries and associated symptoms (freezing, lightheadedness, loss of consciousness) were tabulated and are presented descriptively. Treatment-group differences in MDS-UPDRS scores were tested using an analysis of covariance model with effects for baseline and treatment.

RESULTS

A total of 225 patients were randomized; 222 patients were included in the safety analyses, and 197 patients provided nOH efficacy data and were included in the falls analyses (Fig. 2). The

![Diagram of patient disposition]

FIGURE 2. Patient disposition. *Three patients randomized to placebo were exposed to droxidopa and are included in the droxidopa group for safety analyses.

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mean (SD) age was 72.4 (7.8) years (Table 2). Electronic falls data were provided for 1441 of 1661 patient-days (86.8%) in the placebo group and for 1296 of 1475 patient-days (87.9%) in the droxidopa group.

Falls

During the 10 weeks of the study, the 92 droxidopa patients reported 308 falls and the 105 placebo patients reported 908 falls (Fig. 3). This translates to fall rates of 0.4 falls per patient-week in the droxidopa group and 1.05 falls per patient-week in the placebo group, a crude relative risk reduction (RR) of 62% (Fig. 4). However, the data were skewed and displayed extreme dispersion, with approximately 40% of patients experiencing no falls and some patients experiencing many falls, particularly in the placebo group (Fig. 5). The prespecified ZINB model was found inappropriate and the preplanned Wilcoxon rank sum test was conducted to assess the mean difference across groups (P = 0.704). However, this test lacks efficiency in situations where the distributions are different in shape and dispersion. A post hoc analysis using Poisson-inverse Gaussian regression showed that droxidopa reduced the number of falls (RR = 77%; P = 0.014) and the dispersion (P = 0.02). Goodness of fit was examined using residuals plots that confirmed the model was appropriate. These model-dependent findings were also supported by a nonparametric analysis based on the basic bootstrap that returned a comparable falls rate ratio of 0.38 (95% confidence interval, 0.13–0.92).

Fall-Associated Symptomatology

In the droxidopa group, 54 patients reported 245 days with at least 1 fall. On those days, the worst fall of the day (which could have been the only fall of the day) was associated with lightheadedness 46.5% of the time, loss of consciousness 9.4% of the time, and FOG 26.9% of the time. In the placebo group, 63 patients reported 372 days with at least 1 fall. On those days, the worst fall of the day (which could have been the only fall of the day) was associated with lightheadedness 43.5% of the time, loss of consciousness 9.8% of the time, and FOG 26.9% of the time.
time, losing consciousness 5.4% of the time, and with FOG 23.9% of the time.

**Fall-Related Injuries**

Fall-related injuries are displayed in Table 3. A smaller proportion of patients receiving droxidopa reported fall-related injuries compared with placebo (19/114 [16.7%] vs 29/108 [26.9%]). In both groups, the most frequent fall-related AEs reported were contusions, skin lacerations, and excoriations; reports of these types of injuries were less common in patients receiving droxidopa than placebo (contusion 4.4% vs 11.1%; skin lacerations 4.4% vs 9.3%; and excoriations 5.3% vs 7.4%). In addition, in the placebo group, fractures (facial bones, fibula, and tooth; each n = 1 [0.9%]) and a traumatic brain injury (n = 1, 0.9%) were reported, whereas no patients in the droxidopa group reported these more severe types of injuries.

### Table 2. Demographic and Clinical Characteristics at Baseline (FAS)

| Variable | Droxidopa, n = 92 | Placebo, n = 105 | Total, N = 197 |
|----------|------------------|-----------------|----------------|
| **Age, y** | | | |
| Mean (SD) | 72.5 (7.8) | 72.3 (7.7) | 72.4 (7.8) |
| Range | 41–92 | 54–86 | 41–92 |
| **Sex, n (%)** | | | |
| Male | 59 (64.1) | 69 (65.7) | 128 (65.0) |
| Female | 33 (35.9) | 36 (34.3) | 69 (35.0) |
| **Race, n (%)** | | | |
| White | 88 (95.7) | 99 (94.3) | 187 (94.9) |
| Other | 4 (4.3) | 6 (5.7) | 10 (5.1) |
| **Weight, kg** | | | |
| Mean (SD) | 77.0 (16.9) | 77.1 (15.2) | 77.1 (16.0) |
| Range | 48.6–122.0 | 38.6–122.3 | 38.6–122.3 |
| **Hoehn-Yahr rating,** n (%) | | | |
| 0 | 8 (8.8) | 20 (19.4) | 28 (14.4) |
| 1 | 6 (6.6) | 5 (4.9) | 11 (5.7) |
| 2 | 46 (50.6) | 28 (27.2) | 74 (38.1) |
| 3 | 26 (28.6) | 38 (36.9) | 64 (33.0) |
| 4 | 3 (3.3) | 12 (11.7) | 15 (7.7) |
| 5 | 2 (2.2) | 0 | 2 (1.0) |
| **OHSA dizziness/lightheadedness score** | | | |
| Mean (SD) | 5.4 (2.1) | 5.1 (2.3) | 5.2 (2.2) |
| Range | 0–10 | 0–10 | 0–10 |
| **OHQ composite score** | | | |
| Mean (SD) | 5.6 (1.5) | 5.7 (1.6) | 5.7 (1.6) |
| Range | 3–9 | 3–9 | 3–9 |
| **Standing SBP, mm Hg** | | | |
| Mean (SD) | 94.1 (19.8) | 95.6 (18.6) | 94.9 (19.2) |
| Range | 52–145 | 44–144 | 44–145 |
| **MDS-UPDRS score** | | | |
| Mean (SD) | 33.9 (17.3) | 34.1 (16.7)‡ | — |
| Range | 0–88 | 2–93‡ | — |

*Hoehn-Yahr scale: 0, asymptomatic; 1, unilateral involvement, with minimal or no functional disability; 2, bilateral or midline involvement without impairment of balance; 3, mild to moderate disability with impaired postural reflexes (physically independent); 4, severely disabling disease (still able to walk or stand unassisted); 5, confinement to bed or wheelchair unless aided.

‡n = 91 (droxidopa group); n = 103 (placebo group).

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FIGURE 3. Cumulative incidence of falls over time.
Movement Disorder Society-Unified Parkinson’s Disease Rating Scale

There were no significant differences across groups in change from baseline to EoS in MDS-UPDRS motor, postural stability, or freezing scores (Table 4).

DISCUSSION

Our analysis suggests that droxidopa may reduce falls in PD patients with nOH. We hypothesize that the observed reduction in falls in the droxidopa group is due to improvement in OH, but other mechanisms such as improvement in freezing or attention are conceivable.

Although an association between OH and falling would seem logical, some studies in older adults identified such an association while others did not.14 In assessing the literature, Shaw and Claydon14 point out that differences in results could potentially be related to differences in BP assessment techniques (auscultatory, finger cuff plethysmography, arterial tonometry, intra-arterial cannula), timing of assessments (beat-to-beat, 1 minute, 3 minutes, >3 minutes), orthostatic test (sit-to-stand, lying-to-standing, head-up tilt), and OH criteria employed (1996 consensus definition,15 Fedorowski criteria,16 initial OH, delayed OH, steady-state recovery from OH). Of the 8 studies examined that used lying-to-standing BP assessments, only 3 identified a direct association between OH and falls. In contrast, both studies that used head-up tilt tests with beat-to-beat BP measurements found this association. Overall, their review and the available literature indicate that there is an association between OH and falls but that standard auscultatory BP testing supine and through 3 minutes standing may miss this association.

In our study, in the droxidopa group, the percentages of worst falls of the day reported to be associated with lightheadedness (46.5%) or syncope (9.4%) were similar to that reported in the placebo group (43.5% and 5.4%), thus failing to provide supportive evidence that droxidopa specifically reduced falls by ameliorating lightheadedness and syncope. However, this analysis is limited by the fact that a substantial percentage of individuals with falls due to syncope may not experience presyncope symptoms and are amnestic for loss of consciousness.17,18

There is also evidence to suggest that FOG is associated with a central norepinephrine deficiency and that treatment with droxidopa might ameliorate this condition, but this has yet to be proven. In an analysis of the relationship between clinical symptoms of PD and cerebrospinal fluid monoamines, FOG was found to be associated with a reduction in cerebrospinal fluid norepinephrine.19 More recently, in an autopsy study of 46 patients who had PD, FOG was significantly associated with the degree of neuronal loss or gliosis in the locus coeruleus.20 In the 1980s, a series of small open-label studies conducted in Japan suggested that droxidopa could increase norepinephrine brain concentrations and reduce FOG, culminating in its 1989 approval in Japan for an indication that included “freezing phenomenon in PD.”21 Tohgi et al22 initially reported improvement in FOG in 3 of 6 patients and later reported23 improvement in FOG in 6 of 8 Hoehn-Yahr stage III patients and 1 of 5 stage IV patients. More recently, Fukada et al24 reported improvement in FOG in a small group of patients (n = 6) treated with droxidopa plus entacapone. Thus, it is possible that droxidopa could reduce falls by ameliorating FOG. However, in our study, the percentage of worst falls reported to be associated with freezing in the droxidopa group (26.9%) was similar to that reported in the placebo group (23.9%). In addition, change in MDS-UPDRS freezing scores was not significantly different across groups.

In addition to a lower fall rate, we observed a lower incidence of fall-associated injuries in the droxidopa group compared with...
the placebo group. There were cases of a facial fracture, a fibula fracture, and a traumatic brain injury in the placebo group with no similar injuries in the droxidopa group. These observations suggest that the lower rate of falls in the droxidopa group was clinically relevant and may have important health implications.

Our study has important limitations. Although falls were a key secondary outcome in the NOH306 trial, they were not the primary outcome. In addition, falls data were not collected before randomization and patients were not stratified based on fall status or possible fall-related risk factors. Inspection of baseline characteristics indicates that 34.1% of droxidopa patients were Hoehn-Yahr stage 3 or higher, compared with 48.6% of placebo patients. Furthermore, in this study, falls were patient reported and could potentially be affected by recall bias, different interpretations of what constitutes a fall (despite receiving instructions regarding a standard definition of a fall), and syncope-related amnesia. In future studies, electronic monitoring for falls may help standardize the assessment of falls. Fall-associated symptoms were also patient reported and only given for the worst fall of the day. Furthermore, we made the assumption that traumatic injuries reported the day of or the day after a fall were related to the fall. Although the small group of placebo patients who reported a larger number of falls was influential on the results, these findings were not identified as model departures.

In study NOH306, improvements in OH symptomatology (eg, lightheadedness) and BP were significant for droxidopa versus placebo only through the first week of double-blind treatment. Nonetheless, numeric changes favored droxidopa for the full 10 weeks of treatment (dizziness/lightheadedness improvement, \( P = 0.077 \) at week 10), and group scores can mask robust individual responses. Thus, it remains possible that fall rates in the droxidopa group could have been reduced throughout the study owing to improvements in OH.

Overall, falls were very common in this group of PD patients with nOH. Notably, we observed a substantially lower fall rate in patients treated with droxidopa compared with placebo. This observation needs to be confirmed in future studies. Such studies might ideally include a period of falls assessment before initiation of the intervention, randomization stratification based on frequency of falls, and electronic monitoring to identify falls. Clinicians should be aware of the potential for OH to cause falls and understand that patients may not report lightheadedness (presyncope) or may be amnestic for syncope. Careful evaluation of orthostatic BP is indicated in patients with unexplained falls.

### TABLE 3. Fall-Related Injuries (Safety Set)*

| AE, n (%) | Droxidopa, n = 114 | Placebo, n = 108 |
|-----------|-------------------|-----------------|
| Any AE    | 19 (16.7)         | 29 (26.9)       |
| Injury, poisoning, and procedural complications | 15 (13.2) | 28 (25.9) |
| Excioration | 6 (5.3)          | 8 (7.4)         |
| Contusion   | 5 (4.4)          | 12 (11.1)       |
| Skin laceration | 5 (4.4) | 10 (9.3) |
| Laceration  | 2 (1.8)          | 1 (0.9)         |
| Injury     | 1 (0.9)          | 2 (1.9)         |
| Soft tissue injury | 1 (0.9) | 0 |
| Facial bones fracture | 0 | 1 (0.9) |
| Fall       | 0                | 1 (0.9)         |
| fibula fracture | 0 | 1 (0.9) |
| Head injury | 0                | 1 (0.9)         |
| Joint sprain | 0                | 1 (0.9)         |
| Mouth injury | 0                | 2 (1.9)         |
| Tooth fracture | 0 | 1 (0.9) |
| Traumatic brain injury | 0 | 1 (0.9) |
| Musculoskeletal and connective tissue disorders | 3 (2.6) | 3 (2.8) |
| Back pain  | 2 (1.8)          | 2 (1.9)         |
| Arthralgia  | 1 (0.9)          | 1 (0.9)         |
| Eye disorders | 1 (0.9) | 1 (0.9) |
| Conjunctival hemorrhage | 1 (0.9) | 1 (0.9) |
| Skin and subcutaneous tissue disorders | 0 | 1 (0.9) |
| Scab       | 0                | 1 (0.9)         |
| General disorders and administration site conditions | 3 (2.6) | 0 |
| Pain       | 2 (1.8)          | 0               |
| Face edema | 1 (0.9)          | 0               |
| Psychiatric disorders | 1 (0.9) | 0 |
| Posttraumatic amnestic disorder | 1 (0.9) | 0 |
| Vascular disorders | 1 (0.9) | 0 |
| Hematoma   | 1 (0.9)          | 0               |

*By Medical Dictionary for Regulatory Activities, version 13.0 preferred term.

### TABLE 4. Mean MDS-UPDRS Scores for Freezing and Postural Stability

|                | Droxidopa  | Placebo  | P     |
|----------------|------------|----------|-------|
| Part III       |            |          |       |
| Baseline, n    | 104        | 92       |       |
| Mean (SD)      | 34.1 (16.7)| 33.9 (17.3)| NS    |
| EoS, n         | 84         | 91       |       |
| Mean (SD)      | 30.2 (14.8)| 30.6 (15.6)| NS    |
| Change from baseline to EoS, n | 84 | 90 |
| Mean (SD)      | −3.8 (11.0)| −3.3 (10.9)| NS    |
| Freezing*      |            |          |       |
| Baseline, n    | 92         | 105      |       |
| Mean (SD)      | 0.9 (1.1)  | 1.3 (1.3) | NS    |
| EoS, n         | 89         | 98       |       |
| Mean (SD)      | 0.9 (1.2)  | 1.2 (1.2) | NS    |
| Change from baseline to EoS, n | 89 | 98 |
| Mean (SD)      | 0.0 (0.9)  | −0.1 (1.0)| NS    |
| Postural stability† |      |          |       |
| Baseline, n    | 91         | 104      |       |
| Mean (SD)      | 1.0 (1.3)  | 1.5 (1.3) | NS    |
| EoS, n         | 84         | 90       |       |
| Mean (SD)      | 1.0 (1.2)  | 1.3 (1.3) | NS    |
| Change from baseline to EoS, n | 83 | 89 |
| Mean (SD)      | 0.0 (1.1)  | −0.3 (1.2)| NS    |

*Assessed by item 2.13 of the MDS-UPDRS.
†Assessed by item 3.12 of the MDS-UPDRS.
NS, not significant.

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