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# The Efficacy Profile of Rotigotine During the Waking Hours in Patients With Advanced Parkinson's Disease: A Post Hoc Analysis

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**Objectives:** Transdermal delivery of rotigotine maintains stable plasma concentrations for 24 hours. Three phase 3 studies of rotigotine as add-on to levodopa in advanced Parkinson's disease showed a significant reduction in "off" time from baseline to end of maintenance (EoM). However, detailed analyses over the range of a day have not yet been performed. The objective was to examine the time course of the efficacy profile of rotigotine throughout the day.

**Methods:** Post hoc analysis of diary data from 3 double-blind, placebo-controlled studies of rotigotine in patients with advanced Parkinson's disease inadequately controlled with levodopa, with average "off" time of  $\geq 2.5$  h/d (CLEOPATRA-PD [NCT00244387], 16-week maintenance; PREFER, 24-week maintenance; SP921 [NCT00522379], 12-week maintenance). Patients marked 30-minute intervals as "off," "on without troublesome dyskinesia," "on with troublesome dyskinesia," or "sleep." Diaries completed on the 3 days before EoM were analyzed. A 2-sample *t* test was performed for comparison of rotigotine + levodopa versus placebo + levodopa for mean percentage of time per status during four 6-hour

periods: 12:00AM (midnight) to 6:00AM, 6:00AM to 12:00PM (noon), noon to 6:00PM, and 6:00PM to midnight.

**Results:** Data were available for 967 patients (placebo + levodopa, 260; rotigotine + levodopa, 707). During the 24-hour period at EoM, an advantage in mean percentage time spent "off" and "on without troublesome dyskinesia" was observed with rotigotine + levodopa versus placebo + levodopa during the three 6-hour periods from 6:00AM to midnight ( $P < 0.05$ ; exploratory analysis).

**Conclusions:** These exploratory analyses of patients with motor fluctuations suggest that the efficacy of rotigotine transdermal patch, as captured by diary data, in reducing "off" time and increasing "on time without troublesome dyskinesia" may cover the full waking day.

**Key Words:** dopamine receptor agonist, efficacy profile, motor fluctuations

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In many patients with Parkinson's disease (PD), the long-term use of levodopa becomes complicated by the development of motor complications including "wearing-off" fluctuations and drug-induced dyskinesias.<sup>1-4</sup> Fluctuations in medication response, characterized by the intermittent reappearance of PD motor symptoms (eg, motor tremor, slowness, stiffness), may be predictable, such as "wearing-off" symptoms that occur toward the end of levodopa dosing, or may be more unpredictable, such as those related to levodopa failing to provide the anticipated therapeutic benefit (dose failure) and those unrelated to levodopa dosing.<sup>5</sup> Motor complications associated with levodopa use also often include dyskinesias; indeed, nearly 40% of patients will develop dyskinesias after approximately 5 years of levodopa therapy.<sup>1,4</sup> Motor fluctuations are often the most troublesome complaints by patients with longstanding PD,<sup>6</sup> and patients with "wearing-off"-related symptoms report worse quality of life than patients without such symptoms.<sup>7</sup>

Adjunctive therapy with dopamine receptor agonists, catechol-O-methyltransferase inhibitors, or monoamine oxidase B inhibitors reduce "off" time and improve Unified Parkinson's Disease Rating Scale scores in patients with PD who develop motor complications while receiving levodopa therapy.<sup>8,9</sup> Although indirect comparisons of studies suggest that adjunctive treatment with dopamine receptor agonists may be more effective than adjunctive treatment with catechol-O-methyltransferase or monoamine oxidase B inhibitors in reducing motor fluctuations, the available comparisons have not observed relevant differences between different dopamine receptor agonists.<sup>9</sup> Rotigotine is a nonergolinic dopamine receptor agonist with activity across D1 through D5 receptors, as well as select adrenergic and serotonergic receptors.<sup>10</sup> A pharmacokinetic analysis has demonstrated that transdermal delivery maintains stable plasma levels of rotigotine for 24 hours with a daily application.<sup>11</sup> Efficacy of rotigotine transdermal patch in patients with advanced PD has been observed in 3 major phase 3 studies when used as add-on therapy to levodopa

(CLEOPATRA-PD,<sup>12</sup> PREFER,<sup>13</sup> and SP921<sup>14</sup>). All 3 studies reported significant reduction from baseline to end of maintenance (EoM) in absolute daily “off” time versus placebo as assessed by patient home diary data (the primary efficacy variable). Improvements in absolute daily time spent “on” and “on without troublesome dyskinesia” (secondary variables) from baseline to EoM were also reported.<sup>12–14</sup>

Although the improvement in motor fluctuations in patients with advanced PD has been demonstrated in terms of overall change from baseline to EoM, the time course of effectiveness over the entire rotigotine 24-hour drug delivery range has not been analyzed. Therefore, the objective of this post hoc analysis was to examine the time course of the efficacy profile over the entire 24-hour range of a day in patients with advanced PD, based on further analysis of the patient home diary data. These analyses were performed to better understand, from the patients' perspective, how the benefit provided by rotigotine is distributed during the course of the morning, afternoon, and evening.

## METHODS

### Study Designs

The CLEOPATRA-PD (Clinicaltrials.gov NCT00244387), PREFER, and SP921 (Clinicaltrials.gov NCT00522379) studies were phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical studies of rotigotine in patients with advanced PD. The eligibility criteria for each of the 3 phase 3 studies have been published in detail.<sup>12–14</sup> Briefly, eligible patients were 30 years or older, had been diagnosed with idiopathic PD for at least 3 years, were Hoehn & Yahr stages 2 to 4, and were judged by the treating physician to be inadequately controlled on levodopa (and at a stable dose for  $\geq 4$  weeks before baseline); and to further validate their suboptimal parkinsonian control, patients

needed to demonstrate an average “off” time of  $\geq 2.5$  h/d as recorded in self-reported home diaries.

In all studies, patients were receiving a stable dose of levodopa; patients were randomized to placebo (ie, received placebo + levodopa) or rotigotine (ie, received rotigotine + levodopa). In CLEOPATRA-PD, patients were titrated to an optimal rotigotine dose of 4 to 16 mg/24 h and maintained on that dose for 16 weeks.<sup>12</sup> In PREFER, patients were titrated to either  $\leq 8$  or  $\leq 12$  mg/24 h of rotigotine and maintained at that dose for 24 weeks.<sup>13</sup> In SP921, patients were titrated to 2, 4, 6, or 8 mg/24 h of rotigotine and maintained at that dose for 12 weeks.<sup>14</sup> Patients in all studies provided written informed consent. All studies were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study protocols and amendments were approved by a national, regional, or independent ethics committee or institutional review board.

### Patient Diary Assessments

Data for this post hoc analysis were obtained from the self-reported 24-hour home diaries used during each of the 3 studies. Patients were asked to provide at least 4 (of 6) days of valid patient diary data before baseline and 2 (of 3) days of valid data before each visit during treatment. Patients recorded the presence of only one of the following outcomes every 30 minutes for 24 hours: “off;” “on with troublesome dyskinesias;” “on without troublesome dyskinesias;” or “sleep.”

### Post Hoc Analysis of Efficacy Profile Over 24-Hour Drug Delivery

Data from the diaries completed on the 3 days before EoM are presented: for each 30-minute interval, the mean percentage of time spent (ie, mean of the valid diary cards) in the respective outcome (“off;” “on with troublesome dyskinesia;” “on without

**TABLE 1.** Demographic and Baseline Characteristics (Pooled Safety Set\*)

	Placebo (n = 329)	Rotigotine (n = 839)
Age, mean $\pm$ SD (range), y	65.3 $\pm$ 9.9 (31–87)	64.7 $\pm$ 10.0 (33–86)
Male, n (%)	219 (66.6)	567 (67.6)
Time since diagnosis, mean $\pm$ SD (range), y	7.77 $\pm$ 4.27 (1.9–29.3)	7.89 $\pm$ 4.30 (1.4–31.3)
Hoehn & Yahr stage during “on,” n (%)		
1	0	5 (0.6)
2	199 (60.5)	521 (62.1)
3	114 (34.7)	287 (34.2)
4	16 (4.9)	26 (3.1)
5	0	0
Hoehn & Yahr stage during “off,” n (%)		
1	0	1 (0.1)
2	79 (24.0)	215 (25.6)
3	177 (53.8)	471 (56.1)
4	70 (21.3)	146 (17.4)
5	0	2 (0.2)
Daily absolute “off” time, mean $\pm$ SD, h <sup>†</sup>		
CLEOPATRA-PD <sup>12</sup>	6.6 $\pm$ 2.8 (n = 100)	6.2 $\pm$ 2.5 (n = 201)
PREFER <sup>13</sup>	6.4 $\pm$ 2.6 (n = 120)	$\leq 8$ mg/24 h, 6.7 $\pm$ 2.5 (n = 117)
SP921 <sup>14</sup>	6.4 $\pm$ 2.5 (n = 105)	$\leq 12$ mg/24 h, 6.3 $\pm$ 2.6 (n = 111)
		6.4 $\pm$ 2.6 (n = 397)

\*Safety set: all patients who were randomized and received at least 1 dose of study medication.

<sup>†</sup>Daily absolute “off” time presented for the individual studies; full analysis set.

troublesome dyskinesia”) was calculated for each patient; the mean was then calculated for all patients.

**Statistical Analyses**

Data from the 3 studies and for all rotigotine doses (2–16 mg/24 h) were pooled. Demographics and baseline characteristics are reported for the safety set (ie, all randomized patients who received at least 1 dose of study medication). The efficacy data are reported for the full analysis set (ie, all randomized patients who received at least 1 dose of study medication and had a valid baseline and at least 1 valid postbaseline diary data).<sup>12–14</sup> The data at EoM are reported as observed cases; no imputation method was used for missing values. A 2-sample *t* test assuming equal variances was performed for comparison of patients treated with placebo + levodopa versus those treated with rotigotine + levodopa for mean percentage of time per outcome during four 6-hour periods: 12:00 AM (midnight) to 6:00 AM, 6:00 AM to 12:00 PM (noon), noon to 6:00 PM, and 6:00 PM to midnight. As post hoc analyses, all *P* values are exploratory and do not infer statistical significance.

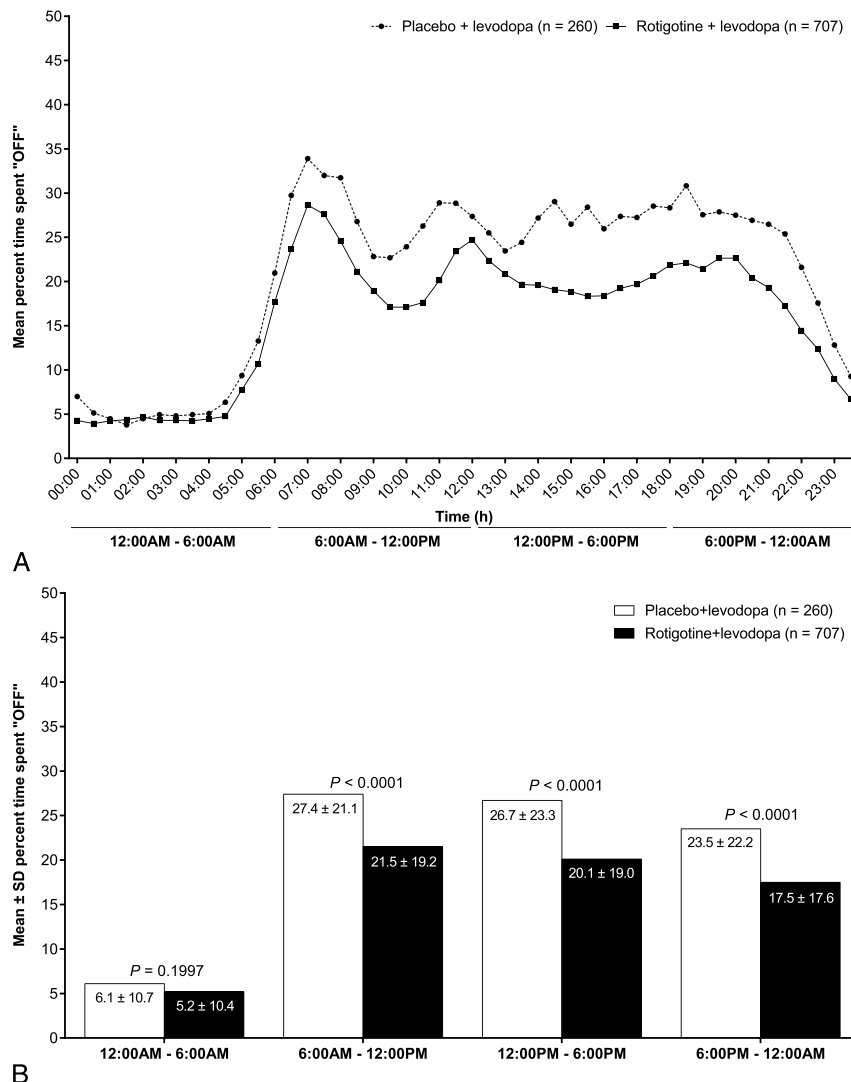
**RESULTS**

**Demographics and Baseline Clinical Characteristics**

The demographics and baseline clinical characteristics of the pooled study population were similar between treatment groups (Table 1). Patients had a mean (SD) age of 64.9 (10.0) years, and 67.3% were men. The mean (SD) time since the first diagnosis for all patients was 7.86 (4.29) years.

**Efficacy Profile Over 24-Hour Drug Delivery**

Data for the full analysis set were available for 967 patients (placebo + levodopa, *n* = 260; rotigotine + levodopa, *n* = 707) at EoM. The mean times spent “off” during the entire 24-hour period at EoM for patients who received rotigotine + levodopa and those who received placebo + levodopa are shown in Figure 1A. Overall, the mean (SD) percentage of “off” time during the entire 24-hour dosing period at EoM was 16.1% (13.1) for the patients treated with rotigotine + levodopa compared with 20.9% (15.4) for patients treated with placebo + levodopa (*P* < 0.0001).



**FIGURE 1.** Mean percent time spent “off” (A) during the 30-minute intervals for the 24-hour period at EoM and (B) during the four 6-hour periods at EoM (full analysis set [FAS]). *P* values: *t* test, rotigotine + levodopa versus placebo + levodopa (exploratory analyses; FAS).

An advantage was observed with rotigotine + levodopa versus placebo + levodopa in the mean percentage time spent “off” ( $P < 0.0001$ ) during each of the three 6-hour periods when the patients were awake (6:00 AM-noon, noon-6:00 PM, and 6:00 PM-midnight) (Fig. 1B).

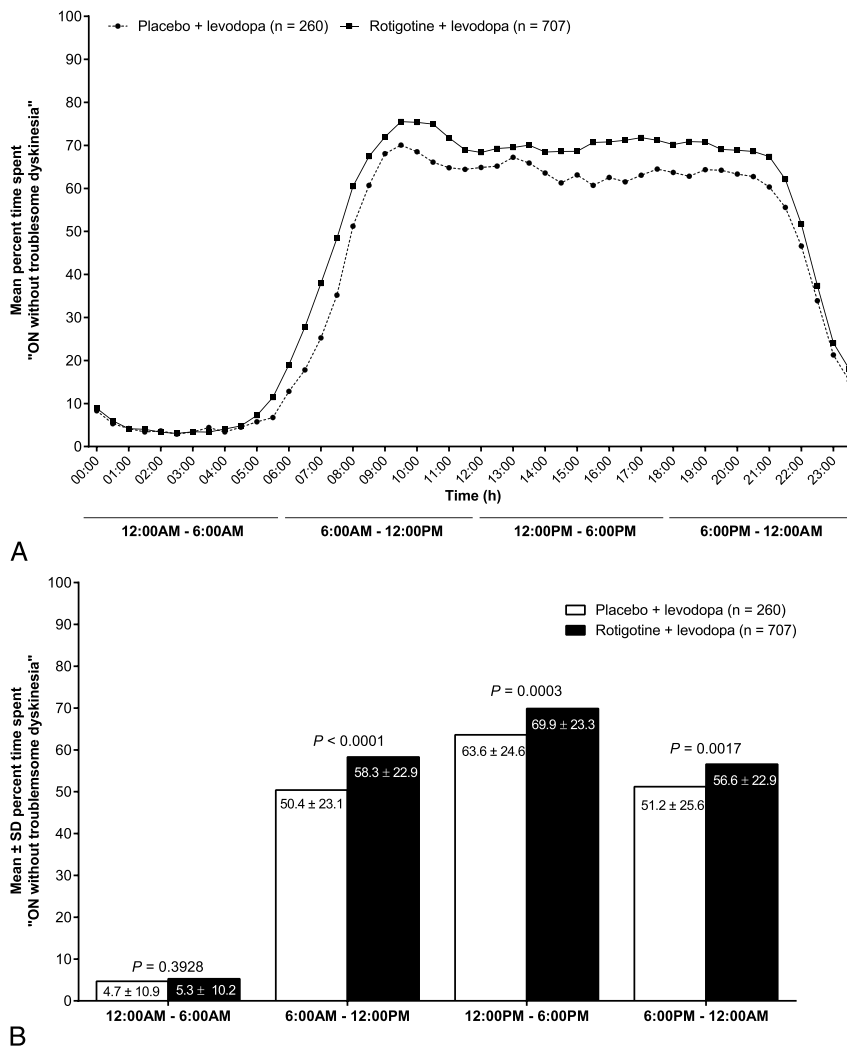
The overall mean (SD) percentage of time spent “on without troublesome dyskinesia” during the entire 24-hour dosing period at EoM for patients who received rotigotine + levodopa was 47.5% (14.7) compared with 42.5% (15.8) in those who received placebo + levodopa ( $P < 0.0001$ ). Figure 2 shows the mean percentage of time spent “on without troublesome dyskinesia” during the entire 24-hour period at EoM. During each of the three 6-hour periods when the patients were awake, an advantage was observed with rotigotine + levodopa versus placebo + levodopa in the mean percentage time spent “on without troublesome dyskinesia” ( $P < 0.05$ ; Fig. 2B). Of note, the overall mean (SD) percentage of time spent “on with troublesome dyskinesia” during the 24-hour dosing period at EoM were similar between the rotigotine + levodopa and placebo + levodopa treatment groups (3.8% [8.4] vs 2.8% [6.7], respectively;  $P = 0.1015$ ), as well as for each of the three 6-hour time intervals when patients were awake (Figs. 3A, B).

The overall mean (SD) percentage of time spent asleep over the entire 24-hour dosing period at EoM was similar between the treatment groups: 32.6% (6.7) for rotigotine + levodopa versus 33.8% (7.0) for placebo + levodopa ( $P = 0.0244$ ).

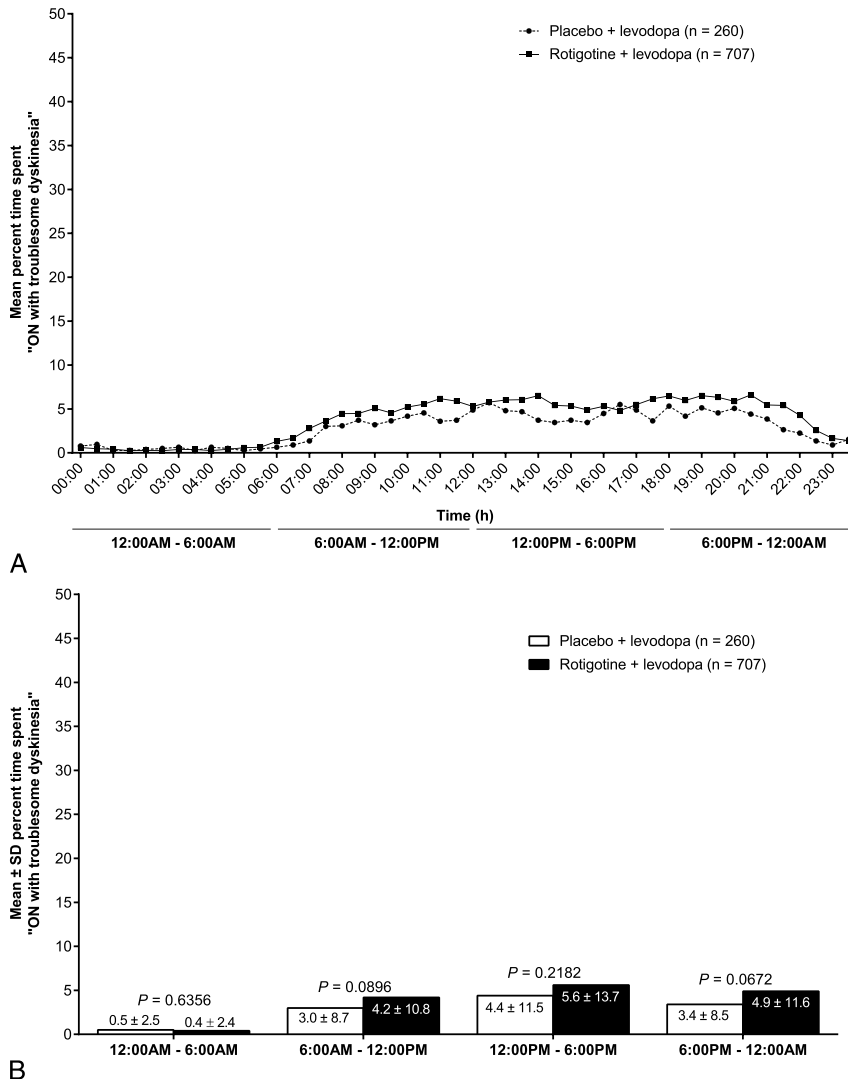
### DISCUSSION

The results of this post hoc analysis of patients with advanced PD suggest that, during the periods of the day when patients were awake at the 24-hour dosing period at EoM, an advantage was observed in the mean percentage of “off” time and mean percentage of time spent “on without troublesome dyskinesia” in patients treated with rotigotine + levodopa versus patients treated with placebo + levodopa.

These randomized placebo-controlled studies with rotigotine transdermal patch in patients with advanced PD demonstrated that rotigotine treatment significantly improved mean absolute daily “off” time from baseline to EoM compared with placebo.<sup>12-14</sup> In the CLEOPATRA-PD, PREFER, and SP921 studies, the mean reduction in “off” time was 2.5 h/d ( $\leq 16$  mg/24 h, optimal dose), 2.7 h/d ( $\leq 8$  mg/24 h group [2.1 h/d for  $\leq 12$  mg/24 h group]),



**FIGURE 2.** Mean percent time spent “on without troublesome dyskinesia” (A) during the 30-minute intervals for the 24-hour period at EoM and (B) during the four 6-hour periods at EoM (full analysis set [FAS]). *P* values: *t* test, rotigotine + levodopa versus placebo + levodopa (exploratory analyses; FAS).



**FIGURE 3.** Mean percent time spent “on with troublesome dyskinesia” (A) during the 30-minute intervals for the 24-hour period at EoM and (B) during the four 6-hour periods at EoM (full analysis set [FAS]). *P* values: *t* test, rotigotine + levodopa versus placebo + levodopa (exploratory analyses; FAS).

and 2.4 h/d (8 mg/24 h group) at EoM, respectively.<sup>12–14</sup> Although rotigotine doses and study length varied somewhat between each of these studies, the reductions in absolute “off” time in the patients treated with rotigotine were consistent. The PREFER study also demonstrated that the rotigotine-treated patients were more than twice as likely to be “on” when awakening as the placebo group.<sup>13</sup> Furthermore, rotigotine has been demonstrated to significantly improve early morning motor impairment and nocturnal sleep disturbances from baseline to EoM compared with placebo in the RECOVER study, a phase 3b study in patients with PD and early morning motor impairment.<sup>15</sup> This post hoc analysis extends these previous observations by demonstrating that rotigotine may be effective (ie, advantages in “off” time and time spent “on without troublesome dyskinesia”) during all periods of the day when patients are awake (ie, morning, afternoon, and evening).

Wearing-off symptoms in patients treated with levodopa are thought to be due to, at least in part, the short half-life of levodopa and consequent fluctuating plasma levels.<sup>16</sup> Early morning motor symptoms also may be considered “off” time and are mostly related to the end of the previous dose’s effectiveness.<sup>5,15</sup> However,

a reduced or lack of responsiveness to levodopa therapy, and greater “off” time, may occur at other times during the day, most notably in the afternoon.<sup>17,18</sup> The effectiveness of rotigotine over the 24-hour dosing window as demonstrated in this analysis is supported by the compound’s pharmacokinetic profile. Plasma concentration-time profiles in healthy volunteers and in patients with early-stage idiopathic PD demonstrated stable rotigotine steady-state plasma concentrations during a 24-hour dosing period.<sup>11</sup> Pharmacokinetic studies with the dopamine receptor agonists pramipexole and ropinirole also have shown more stable plasma concentration over 24 hours with the extended-release (ER) formulations over the immediate-release formulations.<sup>19–22</sup> The ER formulations of pramipexole and ropinirole are orally administered and undergo first-pass metabolism after absorption in the gut. Although ER formulations of pramipexole and ropinirole have demonstrated efficacy in alleviating motor symptoms and time spent “off” in patients with advanced PD, those studies have not evaluated the effects of the agents during a 24-hour dosing window.<sup>23,24</sup>

Safety and tolerability assessments from the 3 studies included in the current analyses of rotigotine in patients with

advanced PD have previously been reported in full.<sup>12–14</sup> In brief, the most commonly reported adverse events in rotigotine-treated patients were application site reactions and those consistent with dopaminergic stimulation or complications related to PD, for example, nausea, dizziness, somnolence, and dyskinesia.<sup>12–14</sup> In long term, open-label extensions of two of these studies (CLEOPATRA-PD and PREFER), in which patients were followed for 6 years, the spectrum of adverse events reported was similar to those in the preceding double-blind studies.<sup>25</sup> Moreover, in a post hoc analysis of pooled data from studies of advanced-PD (CLEOPATRA-PD and PREFER), which compared adverse event profiles of younger and older patients, rotigotine was generally well tolerated with a safety profile that seems to be relatively unaffected by increasing age.<sup>26</sup>

This analysis has several limitations. First, rotigotine dosing was slightly different among each of these studies. In the CLEOPATRA-PD study, optimal dosing was permitted up to 16 mg/24 h, whereas the PREFER study used 2 rotigotine dose groups:  $\leq 8$  mg/24 h and  $\leq 12$  mg/24 h. SP921 was a dose-response study in the lower dose range (2–8 mg/24 h), and the minimal statistically significant effective dose of rotigotine to reduce “off” time was found to be 8 mg/24 h in this study.<sup>12–14</sup> The current analyses pooled all rotigotine doses, and thus, the efficacy profile by dose over the 24-hour dosing period cannot be determined. However, the pooling of patient data from each of the 3 studies resulted in a relatively large sample population. In addition, as post hoc analyses, all *P* values are exploratory in nature. However, given these limitations, the results from this study provide important insights into the efficacy of rotigotine in alleviating motor fluctuations in patients with advanced disease.

In summary, these post hoc analyses of 3 randomized clinical studies in patients with advanced-stage PD suggest that rotigotine transdermal patch may be effective during all periods of the day when patients are awake. The results provide additional evidence in support of the clinical benefits of a long-acting dopamine receptor agonist in the reduction of motor fluctuations and help to better understand, from the patients' perspective, how the benefit provided by rotigotine is spread over the course of a day.

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