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Research Report

A Randomized Study of Rotigotine Dose Response on 'Off' Time in Advanced Parkinson's Disease

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Abstract.
Background: Previous phase III studies in patients with advanced Parkinson's disease (PD) not adequately controlled on levodopa demonstrated significant reduction of 'off' time with rotigotine transdermal system up to 16 mg/24 h. However, the minimal effective dose has not been established.
Objective: This international, randomized, double-blind, placebo-controlled study (SP921; NCT00522379) investigated rotigotine dose response up to 8 mg/24 h.
Methods: Patients with advanced idiopathic PD (≥2.5 h of daily 'off' time on stable doses of levodopa) were randomized 1:1:1:1:1 to receive rotigotine 2, 4, 6, or 8 mg/24 h or placebo, titrated over 4 weeks and maintained for 12 weeks. The primary efficacy variable was change from baseline to end of maintenance in absolute time spent 'off'.
Results: 409/514 (80%) randomized patients completed maintenance. Mean (±SD) baseline daily 'off' times (h/day) were placebo: 6.4 (±2.5), rotigotine 2–8 mg/24 h: 6.4 (±2.6). Rotigotine 8 mg/24 h was the minimal dose to significantly reduce 'off' time versus placebo. LS mean (±SE) absolute change in daily 'off' time (h/day) from baseline was −2.4 (±0.28) with rotigotine 8 mg/24 h, and −1.5 (±0.26) with placebo; absolute change in 'off' time in the 8 mg/24 h group compared with placebo was −0.85 h/day (95% CI −1.59, −0.11; $p = 0.024$). There was an apparent dose-dependent trend. Adverse events (AEs) reported at a higher incidence in the rotigotine 8 mg/24 h group versus placebo included application site reactions, nausea, dry mouth, and dyskinesia; there was no worsening of insomnia, somnolence, orthostatic hypotension, confusional state or hallucinations, even in patients ≥75 years of age.
Conclusions: The minimal statistically significant effective dose of rotigotine to reduce absolute 'off' time was 8 mg/24 h. The AE profile was similar to previous studies.

Keywords: Parkinson's disease, randomized controlled trial, dopamine receptor agonist, dose-response relationship, rotigotine

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INTRODUCTION

Most patients with Parkinson's disease (PD) on levodopa eventually develop motor fluctuations – 'wearing off' and 'on-off' effect – or dyskinesias [1, 2]. The duration of therapeutic benefit ('on') typically shortens following months to years of levodopa exposure, and the period lacking therapeutic benefit ('off') increases [3]. Adjunctive treatment with dopamine receptor agonists has been used to reduce levodopa-related motor complications [4].

Rotigotine is a non-ergolinic dopamine receptor agonist with activity across D1 through D5 receptors, as well as at select serotonergic and adrenergic sites [5]. Transdermal delivery of rotigotine maintains stable plasma levels over 24 hours with a single daily application [6]. Efficacy of rotigotine transdermal system has been shown in five major double-blind, placebo-controlled studies: as monotherapy in patients with early PD [7–9], as add-on therapy to levodopa in advanced PD [10, 11], and in patients with PD and unsatisfactory control of early morning motor function [12].

In two phase III studies in patients with advanced PD not adequately controlled with levodopa, adjunctive therapy with rotigotine at dosages of 8 mg/24 h, 12 mg/24 h [11], and up to 16 mg/24 h [10] significantly decreased absolute time spent 'off' versus placebo. However, the minimal effective dose of rotigotine for reduction of 'off' time has not yet been established. The objective of this study was to investigate rotigotine dose response of 2, 4, 6 or 8 mg/24 h in patients with advanced PD.

MATERIALS AND METHODS

Patients

Patients enrolled in the SP921 study included men and women aged ≥30 years with idiopathic PD of longer than 3 years' duration, presenting with bradykinesia plus at least one of the following: rest tremor, rigidity, or impairment of postural reflexes. Other inclusion criteria required that the patients were within Hoehn and Yahr Stage II–IV in both the 'on' and 'off' states, had a Mini Mental State Examination (MMSE) score of at least 25, and were judged by the treating physician to be inadequately controlled on levodopa (≥200 mg/day short-acting or sustained-release, administered in at least two daily intakes, and at a stable dose ≥28 days prior to baseline) in combination with benserazide or carbidopa, with an average 'off' time of ≥2.5 h/day as demonstrated on several self-reported 24-hour home diaries. To meet this latter requirement, patients viewed a training video and worked with the investigators in order to differentiate between 'off' and 'on' states. Patients who were unable to differentiate these states were excluded from the study. After completing six pre-treatment days of diary recordings, patients were also excluded if two or more of the screening diaries were invalid (i.e. more than 2 of 24 hours of data were missing [missing values or double entries]).

Permitted PD medications included anticholinergics, monoamine oxidase B (MAO-B) inhibitors, N-Methyl-D-aspartate antagonists, and entacapone that were at stable doses for ≥28 days prior to baseline. Prohibited medications included dopamine receptor agonists (during the study or within 28 days prior to baseline), dopamine-releasing (e.g. methylphenidate, amphetamine) or modulating substances (e.g. reserpine), MAO-A inhibitors, tolcapone, budipine, and dopamine receptor antagonists such as antiemetics and neuroleptics (except for stable doses of specific atypical neuroleptics with negligible dopamine blocking capabilities, such as clozapine and quetiapine). All patients provided written, informed consent before study participation, and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol and amendments were approved by a national, regional, or Independent Ethics Committee or Institutional Review Board.

Study design and procedures

SP921 (ClinicalTrials.gov: NCT00522379) was a phase III, randomized, double-blind, placebo-controlled, five-arm dose-response study of rotigotine transdermal system in patients with advanced PD undertaken in 77 centers in the US, India, Mexico, Peru, and Chile. The study was run in two cohorts due to changes in the patch manufacturing process: Cohort 1 (recruitment July 2007 to December 2008) received room temperature patches produced by the original manufacturing process, and Cohort 2 (recruitment February 2010 to February 2011) received cold chain patches produced by a modified manufacturing process. Bioequivalence of the rotigotine patches from the different manufacturing processes has been demonstrated [13], and thus the different patches were not considered to have an influence on efficacy measurements.

During a screening period of up to 6 weeks before baseline, eligible patients were randomized by computer 1:1:1:1:1 to one of four doses of rotigotine (2, 4, 6

or 8 mg/24 h) or matching placebo. Study investigators telephoned an IVRS to allocate patients, based on a randomization schedule produced by UCB Pharma. Rotigotine and placebo were administered as once-daily patches of two different sizes (10 cm^2 and 20 cm^2) that were identical in appearance. Active patches contained rotigotine 2 mg/24 h (10 cm^2) or 4 mg/24 h (20 cm^2). Blinding of investigators and patients was maintained by applying upwards from one to three patches daily to achieve the assigned daily dose.

Treatment was titrated to the randomized dose over 1 to 4 weeks in weekly increments of 2 mg/24 h rotigotine or placebo and maintained for 12 weeks. During titration, rotigotine doses could be back-titrated once to the previous dose, at which point the patient began the maintenance period immediately at the back-titrated dose. Back-titration was not permitted during the maintenance period, which was followed by a de-escalation period of up to 4 days, prior to a 28-day safety follow-up. Clinic visits occurred at screening and baseline, every week during the titration period, start of maintenance, and weeks 2, 4, 8 and 12 of the maintenance period. Patients who withdrew prematurely were asked to return for a final withdrawal visit.

If a patient experienced an adverse event (AE) thought to be the result of excessive dopaminergic stimulation during the first 2 weeks of maintenance, levodopa intake could be reduced once at this 2-week visit. These patients were subsequently allowed to increase their levodopa intake to their original dose before the end of maintenance period (EoM), but were not permitted to further adjust this dose at any other time.

Outcome measures

The study was designed to determine the minimal effective dose of rotigotine transdermal system (2, 4, 6 and 8 mg/24 h) required to significantly reduce 'off' time in patients with advanced PD not adequately controlled on levodopa. The primary efficacy measure was the change in the absolute time spent 'off' from baseline to the EoM. 'Off' time was assessed by self-reported 24-hour home diaries, during which patients marked 30-minute intervals as being 'off', 'on without troublesome dyskinesia', 'on with troublesome dyskinesia', or asleep. Diary evaluations were completed for the 6 pre-treatment assessment days prior to baseline, and for 3 days prior to each subsequent visit.

Secondary efficacy measures included relative time spent 'off', number of 'off' periods, absolute time spent 'on' (and absolute time spent 'on' with or without troublesome dyskinesias), motor status of the patient upon awakening ('on' with or without troublesome dyskinesias or 'off'), and Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (activities of daily living), III (motor), and IV (complications of therapy). Other measures examined included Clinical Global Impression (CGI), change in levodopa dosage, duration of sleep, Parkinson's Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), and Nocturnal Akinesia, Dystonia and Cramps Score (NADCS).

Safety and tolerability assessments included incidence, seriousness and intensity of AEs, and discontinuations because of AEs. The incidence of AEs was also evaluated categorically to allow the comparison of patients aged < 75 with those ≥75 years. Due to a low number of patients aged ≥75 years, data from the rotigotine groups were pooled. AEs that occurred in ≥5% in one treatment group and had a difference in incidence of ≥10% between younger and older rotigotine-treated patients were identified. In addition, AEs considered to be of particular importance to the elderly – hallucinations, somnolence, and orthostatic hypotension – were evaluated.

Changes in the vital signs, body weight, electrocardiograms (ECGs), clinical laboratory values, and physical and neurological examinations were assessed.

Statistical analyses

To detect a difference of 1.5 hours (with an approximate SD of 3.1 hours [10, 11, 14]) in absolute time spent 'off' between any rotigotine group and the placebo group, a closed testing procedure for the comparison of multiple rotigotine dose levels versus placebo was employed, with 90% conditional power at each step, requiring a minimum of 91 patients per treatment group. The overall power of the study to demonstrate superiority of all four rotigotine doses was at least 65.6%. The closed testing procedure started between the highest rotigotine dose (8 mg/24 h) and placebo (two-sided, $\alpha = 0.05$ level); if the result at any rotigotine dose level was not statistically significant, then the testing procedure stopped and all lower doses were also considered to be not superior versus placebo. Approximately 700 patients were planned for enrollment (screening) in order to obtain 500 patients (100 per treatment arm) for the primary analysis. Efficacy analyses were performed on the full analysis set (FAS), including all randomized patients who received at least one dose of study medication, and had at least one post-baseline assessment for the primary efficacy measure. Patients were analyzed 'as randomized', irrespective of back-titration during the titration

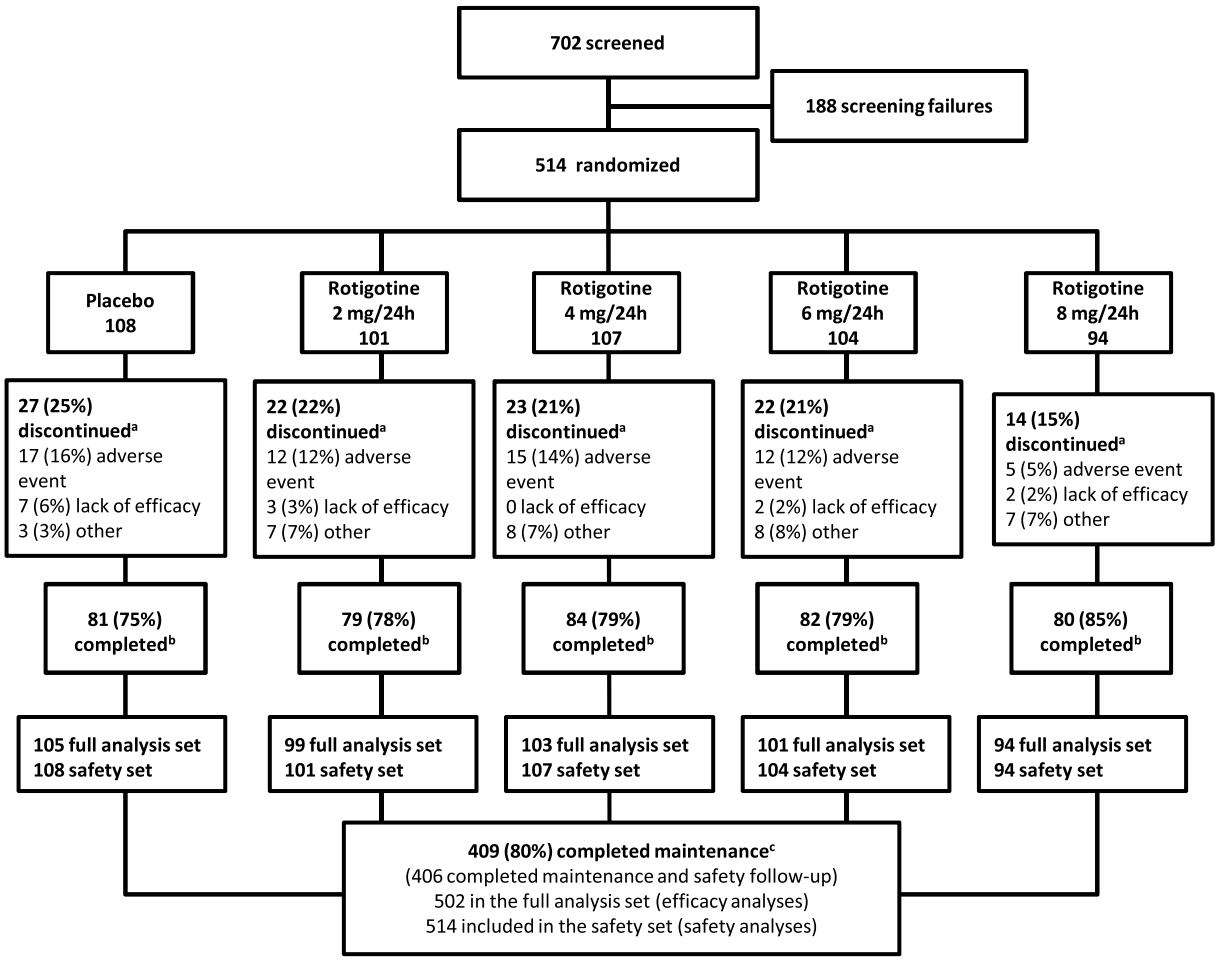

Fig. 1. Study flow chart. [a]Discontinuations include those during titration, maintenance, de-escalation, and safety follow-up. [b]Defined as completed the maintenance phase and safety follow-up. [c]82 (76%) placebo, 80 (79%) rotigotine 2 mg/24 h, 84 (79%) 4 mg/24 h, 82 (79%) 6 mg/24 h, and 81 (86%) 8 mg/24 h. 'other': withdrawal by patient, protocol violation, unsatisfactory compliance, lost to follow-up, and other reasons.

period. A last observation carried forward (LOCF) imputation approach was used for missing values at EoM, unless otherwise stated. To estimate treatment differences for change from baseline to EoM, analyses of covariance (ANCOVA) were performed with treatment and pooled site as factors and baseline value as the covariate. Analyses of safety were performed on all patients who were randomized and received at least one dose of study medication.

RESULTS

Patient disposition and baseline characteristics

Of 702 patients screened, 514 were randomized, 409 (80%) completed the maintenance period, and 406 (79%) completed the maintenance period and safety follow-up (Fig. 1). Baseline demographic and clinical characteristics were similar between groups (Table 1).

Rotigotine dosing and levodopa adjustments

The majority of patients who entered the maintenance period received their assigned rotigotine dose at the start of maintenance: 89/89 (100%) patients assigned to 2 mg/24 h rotigotine, 83/96 (86%) assigned to 4 mg/24 h, 77/91 (85%) assigned to 6 mg/24 h, and 70/89 (79%) assigned to 8 mg/24 h. At the EoM, levodopa dose was reduced from baseline in 2 (2%) placebo patients, 8 (10%) patients in the rotigotine 2 mg/24 h group, 2 (2%) in the 4 mg/24 h group, 6 (7%) in the 6 mg/24 h group, and 6 (8%) in the 8 mg/24 h group. There were only negligible adjustments in the mean ± SD daily doses of concomitant levodopa from

Table 1
Demographic and baseline characteristics, safety set

	Placebo ($n = 108$)	Rotigotine 2 mg/24 h ($n = 101$)	Rotigotine 4 mg/24 h ($n = 107$)	Rotigotine 6 mg/24 h ($n = 104$)	Rotigotine 8 mg/24 h ($n = 94$)
Age, mean ± SD, years	64.8 ± 10.2	65.4 ± 10.5	64.6 ± 9.0	64.6 ± 10.4	63.2 ± 11.6
Male, *n* (%)	74 (69)	77 (76)	79 (74)	73 (70)	56 (60)
Race, *n* (%)					
Caucasian	65 (60)	63 (62)	66 (62)	59 (57)	57 (61)
Asian	34 (31)	29 (29)	30 (28)	32 (31)	29 (31)
Black	2 (2)	2 (2)	3 (3)	3 (3)	3 (3)
Other	7 (6)	7 (7)	8 (7)	10 (10)	5 (5)
Time since diagnosis, mean ± SD, years	7.23 ± 3.76	7.51 ± 3.87	7.27 ± 3.94	7.79 ± 3.92	7.49 ± 4.75
Levodopa, mean ± SD, mg/day	642.8 ± 420.3	643.3 ± 344.5	627.7 ± 359.4	619.0 ± 376.4	643.0 ± 365.8
UPDRS II total score, mean ± SD[a]	12.8 ± 6.4	12.1 ± 6.4[b]	11.8 ± 6.0[c]	12. 6 ± 6.4[c]	11.7 ± 6.2
UPDRS III total score, mean ± SD[a]	26.1 ± 12.5	25.3 ± 12.4[b]	23.1 ± 11.3[d]	24.7 ± 13.1[c]	23.9 ± 9.8
Hoehn and Yahr Stage during 'on', *n* (%)					
2	70 (65)	61 (60)	73 (68)	63 (61)	65 (69)
3	29 (27)	37 (37)	32 (30)	38 (37)	28 (30)
4	9 (8)	3 (3)	2 (2)	3 (3)	1 (1)
Hoehn and Yahr Stage during 'off', *n* (%)					
2	27 (25)	25 (25)	29 (27)	25 (24)	24 (26)
3	60 (56)	58 (57)	67 (63)	57 (55)	54 (57)
4	21 (19)	18 (18)	11 (10)	22 (21)	16 (17)
Daily absolute 'off' time, mean ± SD, h[a]	6.35 ± 2.55	6.37 ± 2.96	6.27 ± 2.32	6.39 ± 2.66	6.41 ± 2.34
Prior dopamine receptor agonist	6 (6)	6 (6)	9 (8)	9 (9)	11 (12)

[a]Data are presented for the FAS: placebo $n = 105$, rotigotine 2 mg/24 h $n = 99$, 4 mg/24 h $n = 103$, 6 mg/24 h $n = 101$, 8 mg/24 h $n = 94$; data missing from [b]1 patient, [c]2 patients, [d]3 patients.

baseline to EoM, e.g. a reduction of 4.3 ± 45.9 mg/day (mean dose at EoM: 630.8 ± 453.5 mg/day) in the placebo group, and an increase of 4.4 ± 187.1 mg/day (mean dose at EoM: 596.9 ± 395.9 mg/day) in the 8 mg/24 h group. There were no obvious differences between treatment groups in the use of prior and concomitant MAO-B inhibitors or entacapone; MAO-B inhibitors: placebo 10 (9%) patients, 2 mg/24 h 4 (4%) patients, 4 mg/24 h 5 (5%) patients, 6 mg/24 h 10 (10%) patients, 8 mg/24 h 3 (3%) patients; entacapone: placebo 13 (12%) patients, rotigotine 2 mg/24 h 17 (17%) patients, 4 mg/24 h 10 (9%) patients, 6 mg/24 h 15 (14%) patients, and 8 mg/24 h 13 (14%) patients.

Efficacy

Primary efficacy outcome: Absolute time spent 'off'

After 12 weeks maintenance the LS mean ± SE absolute change in daily 'off' time from baseline was −2.4 ± 0.28 h/day with 8 mg/24 h rotigotine and −1.5 ± 0.26 h/day with placebo. The absolute change in daily 'off' time in the 8 mg/24 h rotigotine group compared with placebo was −0.85 h/day (95% CI −1.59, −0.11; $p = 0.02$). There was an apparent dose-dependent trend (Fig. 2).

Secondary efficacy outcomes

Significant rotigotine–placebo treatment differences were observed in relative 'off' time (4 and 8 mg/24 h rotigotine groups), absolute 'on' time (4, 6 and 8 mg/24 h groups), and absolute 'on' time without troublesome dyskinesia (8 mg/24 h group) (Supplemental Figure 1). There were no rotigotine–placebo treatment differences in the patients' motor status upon awakening, incidence at EoM of early morning dystonia, total dyskinesia, or disabling dyskinesia (Supplemental Table 1). In patients with disabling dyskinesia, they were reported as mildly or moderately disabling in almost all cases.

Safety and tolerability

Adverse events

The most frequently reported AEs are presented in Table 2, and the majority of AEs were mild to moderate in intensity (ranging from 93% [placebo] to 98% [8 mg/24 h rotigotine]).

Application site reactions (ASRs), nausea, dyskinesia, and dry mouth were reported more frequently by patients receiving rotigotine than those receiving placebo. However, incidences of somnolence and orthostatic hypotension across all doses of rotigotine

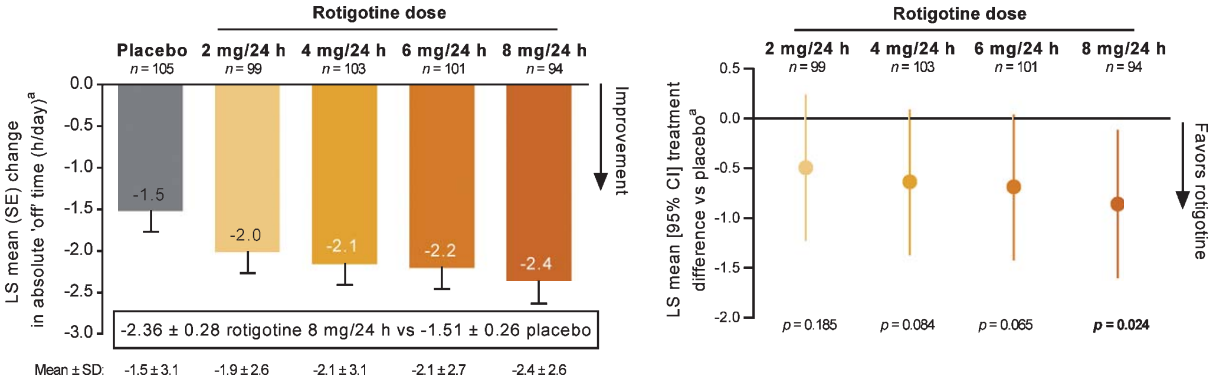

Fig. 2. Primary outcome: Absolute time spent 'off' (FAS, LOCF). [a]ANCOVA model with treatment and pooled site as factors and baseline value as covariate.

Table 2
Adverse events occurring with a frequency of at least 5% in one treatment group; safety set, n (%)

Preferred term	Placebo ($n = 108$)	Rotigotine 2 mg/24 h ($n = 101$)	Rotigotine 4 mg/24 h ($n = 107$)	Rotigotine 6 mg/24 h ($n = 104$)	Rotigotine 8 mg/24 h ($n = 94$)	Rotigotine overall ($n = 406$)
Any AE	78 (72)	71 (70)	78 (73)	77 (74)	69 (73)	295 (73)
Application site reactions[a]	8 (7)	9 (9)	17 (16)	19 (18)	15 (16)	60 (15)
Nausea	8 (7)	13 (13)	11 (10)	15 (14)	11 (12)	50 (12)
Dyskinesia	3 (3)	5 (5)	4 (4)	11 (11)	14 (15)	34 (8)
Dizziness	9 (8)	8 (8)	11 (10)	7 (7)	6 (6)	32 (8)
Headache	12 (11)	10 (10)	8 (7)	6 (6)	8 (9)	32 (8)
Insomnia	7 (6)	6 (6)	8 (7)	6 (6)	6 (6)	26 (6)
Fall	7 (6)	7 (7)	7 (7)	5 (5)	6 (6)	25 (6)
Somnolence	9 (8)	7 (7)	6 (6)	8 (8)	4 (4)	25 (6)
Fatigue	6 (6)	7 (7)	5 (5)	2 (2)	4 (4)	18 (4)
Dry mouth	0	3 (3)	7 (7)	7 (7)	5 (5)	22 (5)
Constipation	8 (7)	1 (1)	4 (4)	8 (8)	4 (4)	17 (4)
Tremor	3 (3)	3 (3)	3 (3)	3 (3)	5 (5)	14 (3)
Confusional state	2 (2)	5 (5)	2 (2)	6 (6)	1 (1)	14 (3)
Arthralgia	3 (3)	1 (1)	3 (3)	3 (3)	5 (5)	12 (3)
Back pain	5 (5)	2 (2)	1 (1)	5 (5)	5 (5)	13 (3)
Urinary tract infection	4 (4)	7 (7)	2 (2)	2 (2)	1 (1)	12 (3)
Upper respiratory tract infection	4 (4)	4 (4)	6 (6)	0	2 (2)	12 (3)
Orthostatic hypotension	7 (6)	3 (3)	1 (1)	0	2 (2)	6 (1)

[a]MedDRA (Version 9.1) high-level term "application and instillation site reactions"; data are number of patients reporting at least 1 AE (%).

were either equivalent to or lower than those with placebo (Table 2). In addition, the incidence of other AEs commonly associated with dopaminergic therapy was similar between rotigotine- and placebo-treated patients: hallucination (placebo 1 [1%] vs. rotigotine overall 10 [2%]), impulse control disorders (high level term; 0 vs. 5 [1%]; 'pathological gambling' ($n = 2$), 'impulse-control disorder' ($n = 1$), and 'impulsive behaviour' ($n = 1$)), and peripheral edema (3 [3%] vs. 11 [3%]). A total of 61 patients (12%) withdrew from the study because of AEs (Fig. 1).

Dizziness and falls were the only AEs that occurred with a ≥ 10% increased incidence in older (≥75 years) compared with younger (<75 years) rotigotine-treated patients (dizziness: <75 years 21/337 [6%] vs. ≥75 years 11/69 [16%]; fall: <75 years 14/337 [4%] vs. ≥75 years 11/69 [16%]). These trends were also seen among placebo-treated patients (dizziness: 6/88 [7%] vs. 3/20 [15%]; fall 2/88 [2%] vs. 5/20 [25%]) (Supplemental Table 2).

A total of 25 serious AEs (SAEs) were reported for 14 patients, but none of these were in the 8 mg/24 h rotigotine group (Supplemental Table 3). Most SAEs were considered 'not related to the study drug' by the investigator. Two deaths occurred during the study: one patient randomized to rotigotine 2 mg/24 h experienced pneumonia aspiration, iron deficiency anemia, candidiasis, and decreased hemoglobin that led to

death. The other patient randomized to 6 mg/24 h rotigotine experienced head injury and intracranial hemorrhage that led to death. These deaths were considered either 'not to be related' or 'unlikely to be related' to the study drug.

There were no clinically relevant changes in laboratory parameters, vital signs, ECGs, or physical and neurological examinations in any treatment group.

Other outcomes

There were no apparent differences between treatment groups in CGI total scores, duration of sleep, PDSS, or ESS. There was a trend towards an improvement in the total NADCS in rotigotine-treated patients (Supplemental Table 4).

DISCUSSION

In this study, rotigotine transdermal system at 8 mg/24 h was the minimally effective dose to significantly reduce 'off' time compared with placebo in patients with advanced PD not adequately controlled on levodopa. There was a dose-dependent trend of reduction in absolute 'off' time with rotigotine doses of 2–6 mg/24 h, suggesting that lower doses may also be beneficial in individual patients, and supporting the common practice of starting at a low dose and gradually titrating to clinical effectiveness. However, if the present study indicates that the minimal, statistically significant, effective dose of rotigotine in advanced PD patients on levodopa is 8 mg/24 h, this suggests that some PD patients may benefit from this higher dose, if lower doses are not fully adequate, before contemplating switching to another dopamine agent.

The effects on absolute 'off' time were similar to those observed in double-blind, controlled studies of the immediate-release or once-daily formulations of the oral dopamine receptor agonists ropinirole and pramipexole in subjects with advanced PD [15–17]. However, due to differences in study design and doses used, direct comparisons between these studies cannot be made.

Following 3 months maintenance, the mean reduction in absolute 'off' time was 2.4 h/day with rotigotine 8 mg/24 h versus 1.5 h/day with placebo. The average treatment effect in the 8 mg/24 h group compared with placebo was −0.85 h/day. The reduction in absolute 'off' time observed in the current study, using 8 mg/24 h as the highest dose, is similar to that seen in two other studies investigating the efficacy of rotigotine in patients with advanced PD. The 6-month CLEOPATRA-PD study employed an optimal dose design up to 16 mg/24 h of rotigotine (mean dose 12.95 mg/24 h) and showed a mean reduction in absolute 'off' time of 2.5 h/day, which corresponded to a 1.6 h/day reduction compared with placebo [10]. In the 6-month PREFER study, a reduction of 2.7 h/day was seen with 8 mg/24 h of rotigotine and 2.1 h/day with 12 mg/24 h of rotigotine, corresponding to a 1.8 and 1.2 h/day reduction compared with placebo [11]. The observed reduction in 'off' time with placebo in the current study appeared greater than in these previous rotigotine studies (placebo reduction in absolute 'off' time of 1.5 h/day in this study versus 0.9 h/day placebo reduction in the PREFER and CLEOPATRA-PD studies) [10, 11]. The reasons for this are unclear, but may be due, at least in part, to the longer duration of PREFER and CLEOPATRA-PD (6-month vs. 3-month current study); in PREFER, the placebo effect for change in 'off' time was similar to the current study at the 3 month time point, but appeared to diminish after this. However, despite the relatively large placebo effect observed in the current study, the reduction in 'off' time was greater across all rotigotine treatment groups (2–8 mg/24 h) as compared with placebo-treated patients.

Secondary efficacy analyses generally supported the findings of the primary analysis. For example, mean changes in the percentage of time spent 'off' were higher for all rotigotine groups than with placebo. 'Off' time reductions with rotigotine corresponded with gains in absolute time spent 'on'. Rotigotine increased absolute time spent 'on' compared with placebo from doses as low as 4 mg/24 h.

Rotigotine was well tolerated, with lower discontinuation rates due to AEs across all doses compared with placebo. In fact, the highest dose of rotigotine (8 mg/24 h) resulted in the fewest withdrawals. The proportion of rotigotine-treated patients who withdrew due to AEs was similar to that observed in randomized controlled trials of patients with advanced PD receiving immediate-release or once-daily formulations of pramipexole [17] or ropinirole [15, 16]. However, in those studies, the proportion of patients treated with these dopamine agonists who discontinued due to AEs was equivalent or higher than in their respective placebo groups [15, 17]. The AE profile of rotigotine was similar to previous 6-month studies in patients with advanced PD, with typical dopaminergic side effects and ASRs [10, 11]. Of clinical interest, across all doses of rotigotine, the incidence of somnolence and orthostatic hypotension (common features of PD

and/or dopaminergic treatment) was either equivalent to or lower than those with placebo, and there was no apparent worsening of daytime sleepiness (as measured using the ESS). Impulse control disorders are often reported in PD; in a large cross-sectional population study of patients with PD, patients treated with dopamine receptor agonists had a higher frequency of impulse control disorders compared with those not treated with agonists (17.1% vs. 6.9%, $p < 0.001$)[18]. In the current placebo-controlled clinical study, five patients (1%) treated with rotigotine reported AEs indicative of impulsive behaviour compared to no patients in the placebo (no dopamine receptor agonist) group. Although dyskinesia was one of the most commonly reported AEs in rotigotine-treated patients, incidence of dyskinesia at the end of the study, according to the UPDRS IV item 32, was not different between placebo- and rotigotine-treated patients, and generally did not present severe disability. Furthermore, the rotigotine AE profile appeared relatively unaffected by increasing age, in line with other rotigotine studies [19]. As a result, these data suggest that rotigotine should be considered as an adjunct therapy in elderly patients with PD, in contrast with the conventional belief that the use of dopamine agonists in general should be avoided in these individuals due to the increased potential for cognitive and behavioral side effects [20].

Despite these interesting findings, there are potential limitations to consider. For example, while the minimal effective dose of rotigotine transdermal system has been identified in this study in patients with advanced PD, we cannot conclude whether doses higher than 8 mg/24 h may also show a dose-dependent and statistically significant benefit in decreasing 'off' time, as other rotigotine studies have suggested [10, 11]. Secondly, restrictions on levodopa dose changes in the study make it difficult to reach a conclusion on the benefits of rotigotine in facilitating a substantial reduction of levodopa dose in advanced PD. Finally, the ability to generalize the results of this study is limited to patients with advanced PD not adequately controlled on levodopa with an average of at least 2.5 hours spent 'off' per day.

In summary, the results of this study provide evidence that the minimal effective dose of rotigotine transdermal system to significantly reduce absolute 'off' time in patients with advanced PD is 8 mg/24 h. Viewed together with the favorable tolerability and safety profile, rotigotine, at a dose of 8 mg/24 h, represents an effective treatment option in patients with advanced PD not adequately controlled with levodopa.

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CONFLICT OF INTEREST

Anthony P. Nicholas, Rupam Borgohain, Pedro Chaná, and Lawrence W. Elmer received grant payments from UCB Pharma for enrolling patients into the study. Anthony P. Nicholas has served as a paid consultant for Ipsen and UCB Pharma; has been hired by Ipsen on an *ad hoc* basis to provide comprehensive botulinum toxin injection training for physicians; and receives ongoing research support from UCB Pharma and Merz. Rupam Borgohain attended an advisory board meeting of Newron/Neuronova. Pedro Chaná has been a participant in the speaker's bureaus of UCB Pharma, Ipsen, GSK, and Boehringer-Ingelheim. Erwin Surmann is an employee of UCB Pharma, Monheim am Rhein, Germany. Emily L. Thompson provided writing and editorial assistance towards the development of the manuscript, which was contracted by UCB Pharma, Brussels, Belgium. Lars Bauer is an employee of UCB Pharma, Monheim am Rhein, Germany, and holds stock options from this employment. John Whitesides is an employee of UCB Pharma, Raleigh, NC, USA, and holds stock options from this employment. Lawrence W. Elmer has received honoraria for speaking engagements from Lundbeck,

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Supplemental Table 1
Secondary outcomes: status upon waking, and UPDRS II, III, and IV (FAS)

	Placebo ($n = 105$)	Rotigotine 2 mg/24 h ($n = 99$)	Rotigotine 4 mg/24 h ($n = 103$)	Rotigotine 6 mg/24 h ($n = 101$)	Rotigotine 8 mg/24 h ($n = 94$)
Status Upon Waking – 'On' Without Troublesome Dyskinesias (% of status)[a]					
Change from baseline to EoM, mean ± SD	19.7 ± 41.9 ($n = 81$)	23.7 ± 41.6 ($n = 80$)	24.6 ± 43.0 ($n = 82$)	20.9 ± 42.1 ($n = 82$)	21.1 ± 45.6 ($n = 80$)
LS mean [95% CI] treatment difference; p value	–	3.24 [−9.35, 15.82]; $p = 0.614$	2.23 [−10.31, 14.77]; $p = 0.727$	−1.23 [13.79, 11.32]; $p = 0.847$	2.00 [−10.62, 14.61]; $p = 0.756$
Status Upon Waking – 'On' With Troublesome Dyskinesias (% of status)[a]					
Change from baseline to EoM, mean ± SD	−0.2 ± 8.9 ($n = 81$)	−0.7 ± 18.9 ($n = 80$)	−0.8 ± 12.8 ($n = 82$)	1.6 ± 23.7 ($n = 82$)	1.7 ± 13.4 ($n = 80$)
LS mean [95% CI] treatment difference; p value	–	1.42 [−2.99, 5.83]; $p = 0.528$	0.42 [−3.96, 4.80]; $p = 0.850$	3.63 [−0.76, 8.02]; $p = 0.105$	1.68 [−2.73, 6.09]; $p = 0.454$
Status Upon Waking – 'Off' (% of status)[a]					
Change from baseline to EoM, mean ± SD	−19.5 ± 43.3 ($n = 81$)	−23.0 ± 40.7 ($n = 80$)	−23.8 ± 43.2 ($n = 82$)	−22.6 ± 40.5 ($n = 82$)	−22.8 ± 47.2 ($n = 80$)
LS mean [95% CI] treatment difference; p value	–	−3.85 [−16.38, 8.67]; $p = 0.546$	−2.21 [−14.68, 10.26]; $p = 0.728$	−1.63 [−14.10, 10.85]; $p = 0.798$	−3.62 [−16.17, 8.94]; $p = 0.572$
UPDRS II[b]					
Change from baseline to EoM, mean ± SD	−0.9 ± 3.7	−2.1 ± 4.3[c]	−2.2 ± 3.9[d]	−1.5 ± 4.7[d]	−2.1 ± 4.6
UPDRS III[b]					
Change from baseline to EoM, mean ± SD	−2.5 ± 8.2	−3.4 ± 7.6[c]	−4.5 ± 7.5[e]	−3.5 ± 8.9[d]	−5.9 ± 7.6
UPDRS IV[b]					
Incidence of early morning dystonia at EoM (item 35), *n* (%)	26 (25)	24 (24)[c]	19 (19)[d]	25 (26)[e]	18 (19)
Incidence of dyskinesia at EoM (score > 0 item 32), *n* (%)	46 (44)	51 (52)[c]	39 (39)[d]	45 (46)[e]	46 (49)
Disabling dyskinesia at EoM (score >0 item 33), *n* (%)	29 (28)	24 (24)[c]	20 (20)[d]	18 (18)[e]	19 (20)

[a]Data are presented for the FAS, observed cases. [b]Data are presented for the FAS, LOCF: data missing (total score) from [c]1 patient, [d]2 patients, [e]3 patients.

Supplemental Table 2
Adverse events by age category, safety set (*n* %)

Preferred term	<75 years Placebo (*n* = 88)	≥75 years Placebo (*n* = 20)	<75 years Rotigotine overall (*n* = 337)	≥75 years Rotigotine overall (*n* = 69)
Any AE	62 (70)	16 (80)	240 (71)	55 (80)
Application site reactions[a]	8 (9)	0	52 (15)	8 (12)
Nausea	8 (9)	0	43 (13)	7 (10)
Dyskinesia	3 (3)	0	29 (9)	5 (7)
Dizziness	6 (7)	3 (15)	21 (6)	11 (16)
Headache	12 (14)	0	30 (9)	2 (3)
Insomnia	7 (8)	0	22 (7)	4 (6)
Fall	2 (2)	5 (25)	14 (4)	11 (16)
Somnolence	5 (6)	4 (20)	20 (6)	5 (7)
Fatigue	5 (6)	1 (5)	12 (4)	6 (9)
Dry mouth	0	0	19 (6)	3 (4)
Constipation	6 (7)	2 (10)	16 (5)	1 (1)
Tremor	2 (2)	1 (5)	14 (4)	0
Confusional state	1 (1)	1 (5)	10 (3)	4 (6)
Arthralgia	2 (2)	1 (5)	11 (3)	1 (1)
Back pain	5 (6)	0 (0)	11 (3)	2 (3)
Urinary tract infection	2 (2)	2 (10)	7 (2)	5 (7)
Upper respiratory tract infection	4 (5)	0	9 (3)	3 (4)
Orthostatic hypotension	5 (6)	2 (10)	4 (1)	2 (3)
Hallucination	0	1 (5)	8 (2)	2 (3)
Impulse control disorders[b]	0	0	2 (1)	3 (4)
Peripheral edema	0	3 (15)	8 (2)	3 (4)

[a]MedDRA (Version 9.1) high-level term "application and instillation site reactions". [b]MedDRA high-level term.

Supplemental Table 3
Serious adverse events:[a] safety set

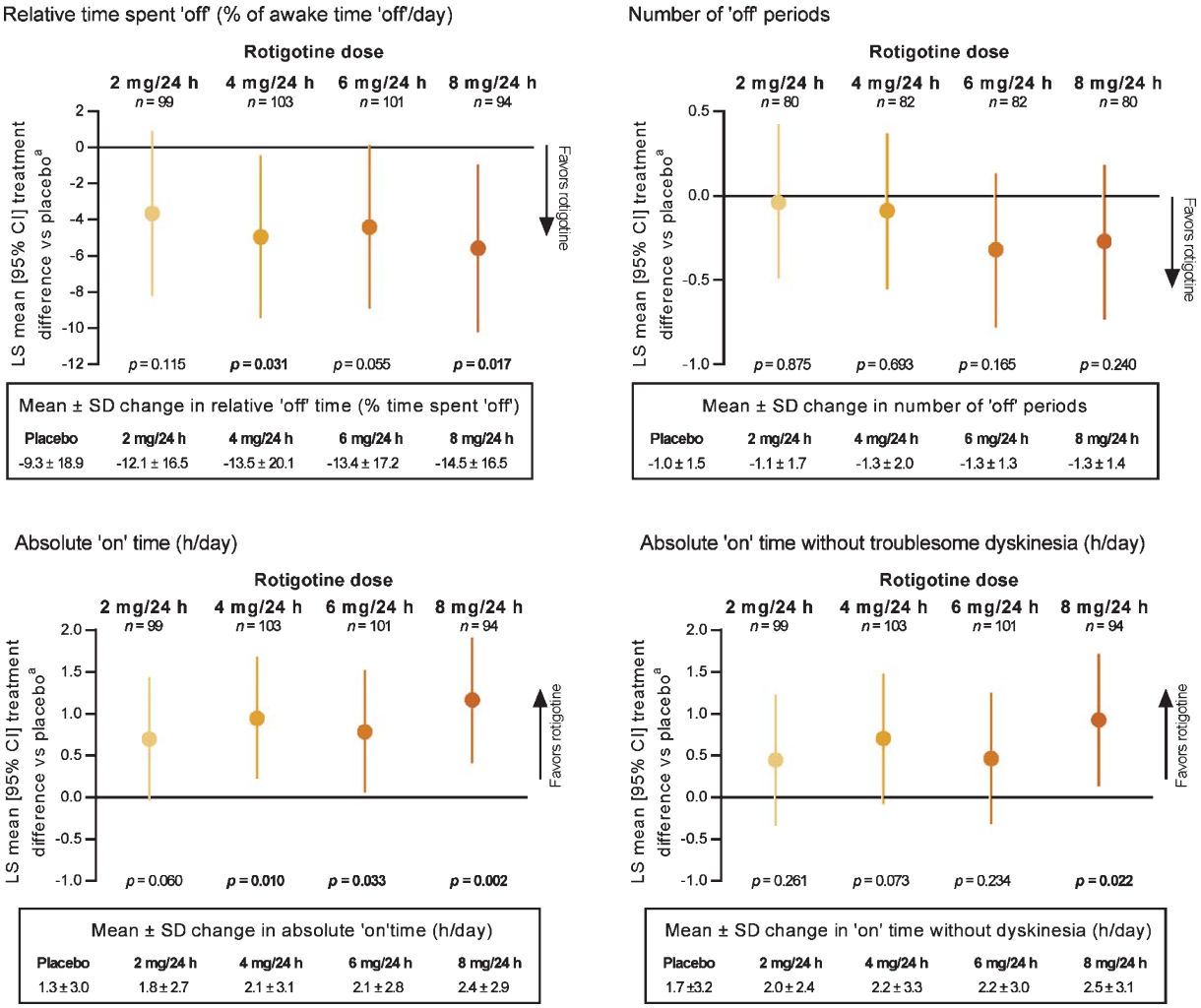
Placebo (*n* = 108)	Rotigotine 2 mg/24 h (*n* = 101)	Rotigotine 4 mg/24 h (*n* = 107)	Rotigotine 6 mg/24 h (*n* = 104)	Rotigotine 8 mg/24 h (*n* = 94)
5 Patients (5 SAEs):	4 Patients (7 SAEs):	3 Patients (5 SAEs):	2 Patients (8 SAEs):	0 SAEs
1. Myocardial infarction	1. Bundle branch block left	1. Mallory-Weiss syndrome	1. Transient ischemic attack	
2. Gastro-esophageal reflux disease	2. Orchitis	2. Fall, lumbar vertebral fracture	2. Fall (2), brain herniation, head injury, skull fracture, hemorrhage intracranial (2)	
3. Cerebral hemorrhage	3. Pneumonia aspiration	3. Joint injury, rotator cuff syndrome		
4. Cerebrovascular accident	4. Gastrointestinal hemorrhage, acetabulum fracture, pubic rami fracture, mental status changes			
5. Sleep attacks				

[a]MedDRA (Version 9.1) preferred term.

Supplemental Table 4
Summary of other outcomes: change from baseline to end of treatment[a]

Outcome	Placebo (*n* = 108)	Rotigotine 2 mg/24 h (*n* = 101)	Rotigotine 4 mg/24 h (*n* = 107)	Rotigotine 6 mg/24 h (*n* = 104)	Rotigotine 8 mg/24 h (*n* = 94)
CGI total score	−0.2 ± 0.8 (*n* = 104)	−0.5 ± 0.9 (*n* = 97)	−0.4 ± 0.8 (*n* = 99)	−0.4 ± 0.7 (*n* = 96)	−0.5 ± 1.0 (*n* = 93)
Duration of sleep, h	0.2 ± 1.2 (*n* = 95)	0.2 ± 0.9 (*n* = 95)	−0.1 ± 1.2 (*n* = 90)	0.0 ± 1.2 (*n* = 90)	0.0 ± 1.3 (*n* = 87)
PDSS-2 total score	−1.9 ± 9.9 (*n* = 102)	−1.1 ± 9.8 (*n* = 94)	−1.0 ± 7.3 (*n* = 99)	−2.6 ± 8.6 (*n* = 94)	−2.4 ± 8.0 (*n* = 92)
ESS total score	−0.9 ± 3.5 (*n* = 104)	−0.1 ± 3.5 (*n* = 95)	−0.1 ± 3.5 (*n* = 99)	−1.4 ± 3.4 (*n* = 95)	−0.2 ± 3.4 (*n* = 93)
NADCS total score	−0.2 ± 2.1 (*n* = 103)	−0.3 ± 2.0 (*n* = 97)	−0.7 ± 1.9 (*n* = 98)	−0.7 ± 2.1 (*n* = 94)	−1.0 ± 2.3 (*n* = 92)

[a]Data are mean ± SD change from baseline to end of treatment, using data as observed. End of treatment is the last available value during the entire treatment period (maintenance visit and early withdrawal visit combined). Data are presented for the FAS.



Supplemental Figure 1. Secondary outcomes. Relative time spent 'off' (FAS, LOCF); number of 'off' periods (FAS, observed cases); absolute 'on' time (FAS, LOCF); absolute 'on' time without troublesome dyskinesia (FAS, LOCF). [a]ANCOVA model with treatment and pooled site as factors and baseline value as covariate.