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Rotigotine transdermal system for the management of motor function and sleep disturbances in Parkinson's disease: Results from a 1-year, open-label extension of the RECOVER study

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ABSTRACT

In RECOVER, a multinational, double-blind, placebo-controlled trial, continuous 24-h transdermal delivery of rotigotine resulted in significant improvements in early-morning motor function and nocturnal sleep disturbances in subjects with idiopathic Parkinson's disease (PD). On completion of RECOVER, subjects were eligible to enter a 1-year, open-label extension in which they received rotigotine (2–16 mg/24 h) for a 10-month maintenance period. Safety and tolerability were assessed by monitoring adverse events, changes in vital signs, physical and neurological findings, ECGs, and clinical laboratory values. The primary efficacy measure was the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Motor Examination) with the modified Parkinson's Disease Sleep Scale (PDSS-2) as a co-primary measure. Of 84 subjects from RECOVER who enrolled, 79% completed 1 year of open-label treatment. Rotigotine was well tolerated; the most common adverse events (AEs; open-label phase) were application site reactions (ASRs; 24%); somnolence and hallucinations (13% each); nausea and fall (12% each); and dizziness and dyskinesia (11% each). Most were mild or moderate in intensity and had resolved at the end of the trial. Twelve subjects (14%) discontinued due to AEs, most commonly ASRs (5 subjects) and peripheral edema (2 subjects). At end of maintenance, the mean UPDRS Part III score was improved by 5.8 (±9.4) points relative to open-label baseline and 10.9 (±10.7) points relative to double-blind baseline and the mean PDSS-2 score by 5.8 (±7.8) points relative to double-blind baseline. Hence, the beneficial effects of rotigotine transdermal system on motor function and sleep disturbances were sustained for up to 1 year.

Introduction

While the defining feature of Parkinson's disease (PD) is motor impairment, leading to symptoms such as tremor, bradykinesia, and gait disturbances, sleep disorders are also common and significantly impact the quality of life of PD patients [1–3]. Nonetheless, only a small number of published trials have prospectively examined the effects of treatment on sleep in PD [4–9]. One such study is RECOVER (Randomized Evaluation of the 24-h COVerage: Efficacy of Rotigotine; NCT00474058 [10]), a multinational, double-blind, placebo-controlled trial of the non-ergoline dopamine agonist (DA), rotigotine (2–16 mg/24 h administered once daily using a transdermal patch for up to 12 weeks), the first large,

Abbreviations: AE, adverse event; ASR, application site reaction; BDI-II, Beck Depression Inventory; DA, dopamine agonist; NADCS, Nocturnal Akinesia, Dystonia and Cramps score; NMSS, non-motor symptoms scale; PD, Parkinson's disease; PDSS-2, modified Parkinson's Disease Sleep Scale; PDQ-8, short-form Parkinson's disease questionnaire; RECOVER, Randomized Evaluation of the 24-h COVerage: Efficacy of Rotigotine; SD, standard deviation; UPDRS, unified Parkinson's disease rating scale.

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placebo-controlled trial in PD to assess nocturnal sleep disturbance as a co-primary outcome measure along with motor function. The RECOVER study demonstrated that 24-h transdermal delivery of rotigotine to PD patients with early-morning motor dysfunction resulted in significant benefits in control of both early-morning motor function and nocturnal sleep disturbances over a 12-week period. While it is known from previous open-label trials [11–13], that rotigotine results in sustained improvement in motor function, there have been no studies of rotigotine or, indeed, of any non-ergoline DA, to include as a co-primary outcome measure, effects on sleep over an extended period of time. The study described here (SP915; NCT00519532) is a one-year, open-label extension of RECOVER, conducted to assess the long-term effects of rotigotine on motor function, sleep and the non-motor symptoms of PD.

Material and methods

Subjects

As subjects were eligible to enter this extension upon completion of the preceding RECOVER study, its inclusion criteria are identical to those described previously [10]. Subjects were men and women (aged $\geqslant$18 years) with PD (Hoehn and Yahr Stage I-IV) and unsatisfactory control of early-morning motor function as determined by the investigator. In addition, it was required that the subject be willing and able to comply with all trial requirements and be expected to benefit from long-term treatment with rotigotine, in the opinion of the investigator. Any subjects who were experiencing any ongoing serious adverse events (AEs) that were assessed as related to study medication were not permitted to enroll in the open-label extension.

This study was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice requirements, the Declaration of Helsinki and the local laws of the countries involved. The study protocol and amendments were approved by a national, regional, or Independent Ethics Committee or Institutional Review Board. All subjects provided written, informed consent before study participation.

Study design

At the end of the double-blind trial all subjects had their dose de-escalated in a blinded fashion in 2 mg/24 h steps over a period of up to 14 days. Within 2 days of the end of de-escalation those subjects entering the Phase IIIb, multicenter, multinational, open-label extension started a dose titration period (lasting up to 8 weeks) in which their dose of transdermal rotigotine increased in increments of 2 mg/24 h per week from a starting dose of 2 mg/24 h in week 1 until the optimal dose was reached (based on discussion between patient and investigator and up to a maximum of 16 mg/24 h). There was no additional wash-out period between the end of RECOVER and the start of its open-label extension. The optimal dose was maintained for a 10-month maintenance period. Subjects who did not continue on commercially available rotigotine then had their dose de-escalated over a 14-day period in 2 mg/24 h increments every other day.

Clinic visits occurred weekly during dose titration; at the start of the maintenance period; 4 weeks later (to confirm optimal dose); and at 13-week intervals thereafter. An end-of-treatment visit occurred at the end of the maintenance period or upon premature discontinuation with a safety follow-up visit 28 days later. A subject's rotigotine dose could be increased or decreased as required to maintain an optimal dose during the maintenance period.

Permitted concomitant medications were: L-dopa (in combination with benserazide or carbidopa); MAO-B inhibitors; anticholinergic agents; NMDA antagonists; entacapone; certain atypical neuroleptics and modafinil. In addition, antiemetics without central antidopaminergic activity were permitted during the trial to treat nausea and vomiting.

Outcome measures

Safety and tolerability were assessed throughout the study and up to 30 days after treatment discontinuation by monitoring the frequency and severity of AEs, and any changes in vital signs, physical and neurological findings, ECGs, and clinical laboratory values. Application and instillation site reactions (MedDRA high-level term, referred to as application site reactions [ASRs]) are known to occur with the rotigotine patch and so are of particular interest; they comprise application site hypersensitivity, pruritus, erythema, reaction, irritation, inflammation, rash, eczema, and vesicles. Slight reddening of the skin upon patch removal does not constitute an ASR.

The primary efficacy outcome measure was the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Motor Examination) [14] with the modified Parkinson's Disease Sleep Scale (PDSS-2) [15] as a co-primary measure. UPDRS Part III was assessed at every titration visit; at maintenance visits 2, 3, and 4; at the end-of-treatment visit; and the safety follow-up visit, while the subject was in the "on" state. The self-administered PDSS-2 questionnaire was completed at all visits during the maintenance period and at end-of-treatment.

Secondary efficacy outcome measures were the Nocturnal Akinesia, Dystonia, and Cramps Score (NADCS) [2] and number of nocturias. Exploratory outcome measures were the short-form Parkinson's Disease Questionnaire (PDQ-8) [16]; UPDRS Part II (Activities of Daily Living) score; Beck Depression Inventory (BDI-II) [17]; PD Non-Motor Symptom Scale (NMSS) [18]; and an 11-point Likert Pain Scale. In addition, the UPDRS Part IV was used to assess complications of therapy–dyskinesias (duration, disability, pain and presence of early morning dystonia), clinical fluctuations (off periods) and other complications (anorexia, nausea, vomiting, insomnia, hypersomnolence or symptomatic orthostasis).

Statistical analysis

Efficacy analyses were performed on the full analysis set – all subjects who received at least one dose of trial medication, had a valid baseline assessment for the primary and co-primary efficacy variables, and at least one valid post-baseline measurement during the titration or maintenance periods. Safety analyses were performed on the safety set (all subjects who received at least one rotigotine patch). Descriptive statistics for the sum scores in all outcome measures were provided as the respective change from baseline by visit. Because there was no washout period between studies, meaning that subjects are unlikely to have returned to an un-medicated state at baseline of the open label extension study, visit 2 of the double-blind (RECOVER) study was defined as baseline in reporting efficacy results, except for UPDRS for which baseline was defined as the first titration visit of the open-label phase; this was because of a difference in the administration of UPDRS between RECOVER and its open-label extension – UPDRS was measured in the early morning in RECOVER but could be measured at any time of the day during the open-label extension. In a post-hoc analysis, mean change in UPDRS Part III scores from double-blind baseline were also calculated. End of maintenance was defined as the last available post-baseline value until the end of the maintenance period.