Rotigotine is a nonergoline dopamine receptor agonist with structural similarity to dopamine. Rotigotine binds to the D_1 through D_3 dopamine receptors, having several times more affinity than dopamine does to the D_2 and D_3 receptors. Although rotigotine was demonstrated to restore locomotor activity in animal models of Parkinson’s disease (PD), the rapid metabolism of rotigotine limited the development of an orally administered formulation. Rotigotine’s high lipid solubility and extended duration of action when applied to the skin in experimental models of PD suggested that rotigotine was a candidate for transdermal application. The constant transdermal delivery of rotigotine over 24 h is hypothesized to approximate continuous agonist–receptor stimulation, which conceptually more closely mimics physiologic striatal dopamine receptor function. Randomized clinical studies have demonstrated rotigotine’s efficacy, safety, and tolerability in patients with early- and advanced-stage PD, including improvements in motor symptoms and off-time. Although the etiology is unknown, restless legs syndrome (RLS) is thought to involve dopaminergic dysregulation. Randomized clinical studies also have demonstrated the efficacy of rotigotine in improving the symptoms of moderate-to-severe primary RLS. This review examines rotigotine’s developmental history for transdermal administration leading to its approval for the treatment of early- and advanced-stage PD and moderate-to-severe primary RLS.

**Keywords:** dopamine agonists; neurodegenerative disease; Parkinson’s disease; restless legs syndrome; rotigotine

**Introduction**

Parkinson’s disease (PD) and restless legs syndrome (RLS) are regarded as progressive and chronic neurological disorders, respectively, that may be treated with dopaminergic agents, depending on patient characteristics. In the United States, an estimated 630,000 to 1 million people were diagnosed with PD in 2010. With approximately 50,000 new cases diagnosed each year, recent estimates project that the number of people diagnosed with PD in the United States will double by the year 2040 compared to 2010. The incidence of PD increases after age 60 and is higher in men than in women. Approximately 5 million suffer from RLS in the United States. The prevalence rates for RLS in North America and Western European countries range from 4% to 29% with 3% experiencing moderately to severely distressing symptoms at least twice weekly, increases with age, and is higher amongst women than men. Although the symptoms of PD and RLS both respond to dopaminergic agents, the pathological processes of these two disorders differ.

The nonergoline dopamine receptor agonist Neupro® (UCB Inc, Smyrna, GA), a transdermal patch containing rotigotine, was developed for the treatment of early- and advanced-stage PD and moderate-to-severe RLS. The rotigotine transdermal system attempted to achieve sustained administration of the drug to address some of the limitations of short-acting and pulsatile dopaminergic PD
and RLS treatments by providing stable 24-h steady-state plasma concentrations of rotigotine. This review discusses the pharmacokinetic and clinical development of the rotigotine transdermal system for the treatment of signs and symptoms of early- and advanced-stage PD and moderate-to-severe primary RLS and other relevant long-term treatment results.

**PD, RLS: basic concepts**

The pathological hallmark of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in decreased dopaminergic neurotransmission in the basal ganglia. The cardinal clinical manifestations of PD include motor symptoms of resting tremor, rigidity, bradykinesia (slowness of movement), postural instability, and gait disturbances. PD is a complex disorder, and many patients also experience some form of nonmotor symptoms at various stages of the disease. Nonmotor symptoms can involve autonomic dysfunction, neuropsychiatric features (e.g., depression, apathy, anhedonia, anxiety), sleep disorders, fatigue, gastrointestinal (GI) dysfunction, and pain. GI disorders, including dysphagia (difficulty swallowing), gastroparesis (delayed gastric emptying), and bowel dysfunction, are some of the most commonly encountered and distressing nonmotor symptoms, with incidences reported to be as high as 80%. Nonmotor symptoms become increasingly prevalent over time and result in substantial impairment to a patient's quality of life (QoL). Therefore, there is a significant need for continued development of effective therapies for treating both the motor and nonmotor symptoms.

In PD, levodopa is considered the gold standard for dopaminergic treatment of the motor symptoms. However, in the majority of patients, chronic levodopa therapy is associated with the development of motor complications, including dyskinesias (involuntary movements) and motor fluctuations. While not completely understood, pulsatile stimulation of the striatal dopamine receptors is thought to be a major contributor in levodopa-induced dyskinesias. Animal models and clinical studies using continuous intravenous or subcutaneous administration of dopaminergic agents that more closely mimic physiologic striatal dopamine receptor stimulation support this hypothesis, but these routes of administration are not ideal for routine outpatient clinical use.

Unlike PD, the etiology of RLS is not well understood. RLS is a chronic neurological sensorimotor disorder where patients experience an irresistible urge to move their legs, usually associated with unpleasant, uncomfortable, or painful leg sensations, particularly at rest or during inactivity. Most symptoms follow a circadian pattern with predominant symptoms occurring in the evening and often interfering with sleep. While it is a common neurological disorder, RLS is frequently underdiagnosed or misdiagnosed. As the disease progresses, daytime or breakthrough symptoms commonly appear. RLS may be idiopathic (primary) or may be related to a secondary cause such as iron deficiency, pregnancy, or renal impairment. Despite the unknown etiology of RLS, improvements in RLS symptoms following dopaminergic therapy suggest a dopaminergic component to the disease. Additionally, studies in animals and humans led to the suggestion of impairment in brain iron metabolism and/or changes in dopaminergic function in the disease. Population studies also have observed a strong hereditary component, and several genes have been associated with RLS.

Like PD, RLS can negatively affect QoL. In fact, the negative effect of RLS on patient QoL has been found to be comparable to other chronic medical conditions, such as type 2 diabetes mellitus, depression and anxiety, and osteoarthritis with hypertension. In addition, a growing body of evidence suggests a strong association between RLS and increased cardiovascular disease (CVD) risk, including hypertension, and CVD and cerebrovascular disease. These data emphasize the seriousness of RLS as a chronic disease and the importance of appropriate diagnosis and treatment.

**History of rotigotine development**

Rotigotine is a nonergoline dopamine agonist with a structural resemblance to dopamine. The compound N-0434 was identified to be a potent dopamine D2 receptor agonist. Chemical modification of N-0434 enhanced the potency and duration of action, resulting in N-0437. While there were two isomers (or positive and negative enantiomers) of N-0437, only the negative isomer demonstrated presynaptic and postsynaptic agonistic...
activity. In behavioral models with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesion primates, intramuscular injections of (−)-N-0437 induced contralateral rotation. In addition, subcutaneous administration of (−)-N-0437 induced contralateral rotation in unilaterally 6-hydroxydopamine–lesioned rats. These results led to the continued investigation of (−)-N-0437, later known as N-0923 and finally as rotigotine, for the treatment of PD.

Rotigotine binds to several dopamine receptors, with the highest affinity at the D1 receptor (inhibition constant (K): 0.71 nM), followed by the D4, 2 (K: 3.9 nM), D3 (K: 5.4 nM), D4, 7 (K: 5.9 nM), D2 (K: 13.5 nM), D4, 4 (K: 15 nM), and D1 (K: 83 nM) receptors. Functional reporter gene assays established rotigotine to be 2600, 53, and 4.4 times more potent than dopamine at the D3, D2, and D1 receptors, respectively. The D1, D2, and D3 receptors are located in areas of the brain implicated in motor control such as the striatum, an area important in fine-motor control. Therefore, restoring dopaminergic stimulation to these areas is key to alleviating disruptions in fine-motor control that defines the clinical presentation of PD symptomology. Activation of the D1 receptor is unique to rotigotine among the nonergot–derived dopamine receptor agonists; pramipexole and ropinirole do not display activity at D1, but only at D2 and D3. It should be noted, however, that the mechanisms by which rotigotine’s action on these receptor subtypes results in modifications of the motor and nonmotor symptoms of PD remain unknown. Additional characterization of rotigotine detected some agonist activity at the 5HT1A receptor and antagonist activity at the α1-adrenergic α2B receptor. Although the clinical significance of rotigotine’s action at the 5HT1A and adrenergic α2B receptors is unknown, dysfunction of the serotonergic and adrenergic pathways in the brain are hypothesized to contribute to nonmotor symptoms of PD, including depression. Thus, the clinical significance of these findings to humans has not been fully elucidated.

During development, it was found that oral rotigotine undergoes extensive first-pass metabolism and has low bioavailability. Studies in animals suggested that rotigotine, with its high lipid solubility, may be suitable for transdermal applications. Dermal application of an alcohol-based rotigotine solution to the skin of MPTP-treated marmosets improved locomotor deficits caused by the lesion for up to 48 h, whereas oral and intraperitoneal formulations were effective for only approximately 2 hours. Similarly, subcutaneous injections of a slow-release rotigotine formulation improved motor deficits in 6-hydroxydopamine–lesioned rats and MPTP-lesioned marmosets. Thus, the improvement in motor deficits in dopamine-depleted animals following dermal rotigotine application suggested the compound may be an appropriate candidate for transdermal application.

Rotigotine was first approved in the European Union in 2006 for early-stage PD. The rotigotine transdermal system is a thin, matrix-type system composed of three layers (Fig. S1). Rotigotine is included in a self-adhesive drug matrix layer allowing constant delivery over 24 hours. In 2008, the rotigotine patch was voluntarily withdrawn from the U.S. market owing to the discovery of rotigotine crystals within the patch. European regulatory authorities allowed the rotigotine patch to remain available following modification of the production process and implementation of a cold-chain storage and distribution system, which were necessary to prevent rotigotine crystallization. The U.S. Food and Drug Administration (FDA), however, required the reformulation of rotigotine to a room-temperature formulation free from crystallization. The reformulated room-temperature stable patch has the same qualitative, but slightly different quantitative, composition as the original patch. Clinical studies demonstrated bioequivalence and similar adhesion characteristics between the room-temperature stable patch and the original and cold-chain patches. The reformulated room temperature rotigotine patch was approved by the FDA in April 2012, along with additional indications for advanced-stage PD and moderate-to-severe primary RLS.

Pharmacokinetic profile for PD and RLS

Approximately 45% of rotigotine is released from the patch within 24 h (0.2 mg/cm2). Thus, a patch containing 4.5 mg of rotigotine (10 cm2 patch size) equates to a nominal dose of 2 mg/24 h. The absolute bioavailability of rotigotine with transdermal application is approximately 37% of the applied dose. Maximum plasma concentrations of rotigotine are achieved within 16–20 h after patch application (Fig. 1). The majority of rotigotine is excreted as inactive metabolites through the urine.
Development of rotigotine for PD and RLS Benitez et al.

Figure 1. Mean plasma concentration time profile of unconjugated rotigotine at steady state following 8 mg/24 h dose in patients with early-stage idiopathic PD. PD, Parkinson’s disease.

(71%) within 96 h of patch application, with the remainder eliminated in the feces (24%). Plasma concentrations of rotigotine decrease once the patch is removed, with a mean terminal half-life of 5–7 hours. Dose proportionality was demonstrated in patients with early-stage PD over the therapeutic dose range of 2–8 mg/24 h. Dose proportionality also has been demonstrated in patients with advanced PD in doses up to 24 mg/24 h, which is higher than the recommended maximum 8 mg/24 h dose in the United States and 16 mg/24 h dose in the European Union for patients with advanced disease. Mean rotigotine plasma concentrations are comparable between different applications sites (shoulder, upper arm, hip, flank, abdomen, and thigh), although some variability was shown between sites, with shoulder application showing higher bioavailability.

Drug–drug interactions
It is likely that patients with PD or RLS will require medications for other medical conditions, particularly older patients. Therefore it is important to consider the potential drug–drug interactions between rotigotine and other drug classes. Because multiple CYP isoforms can metabolize rotigotine, other CYP enzymes may catalyze rotigotine metabolism if one isoform becomes inhibited. Studies in healthy volunteers established that rotigotine is extensively metabolized by conjugation and N-dealkylation. Rotigotine is enzymatically metabolized by multiple CYP isoenzymes, sulfotransferases, and two uridine 5′-diphosphoglucuronosyltransferases (UDP-glucuronosyltransferases). Following intravenous administration, sulfate conjugates and glucuronide conjugates of rotigotine, and sulfate conjugates of the N-despropyl-rotigotine and conjugates of N-desthienylethyl-rotigotine are the predominant metabolites in human plasma. Coadministration of the CYP inhibitors cimidine or omeprazole in healthy subjects does not change the pharmacokinetics of rotigotine. The coadministration of rotigotine and the dopamine receptor antagonist domperidone, which undergoes extensive CYP enzymatic metabolism, also had no effect on the pharmacokinetics of rotigotine in healthy subjects. Finally, coadministration of rotigotine and levodopa/carbidopa has no effect on the steady-state pharmacokinetic parameters of either medication.

Rotigotine in special populations
Patients with PD or RLS may suffer from renal or hepatic impairment. Indeed, up to 25% of patients with renal impairment, particularly those on dialysis, also have RLS. In a study comparing the pharmacokinetics of rotigotine in healthy subjects and those with different stages of renal disease, rotigotine bioavailability and plasma concentrations were not affected by renal insufficiency or dialysis. In subjects with moderate hepatic impairment, the time to maximal plasma concentration and half-life of rotigotine were lower, the renal clearance was unaffected and overall clearance was higher. Thus, the pharmacokinetics of rotigotine...
are largely unaffected by moderate hepatic impairment. As such, dosing adjustments for rotigotine are not needed in patients with renal insufficiency or moderate hepatic impairment.

As mentioned, RLS has a higher prevalence in women, and it is possible some women within childbearing age may require dopamine agonists for RLS. Because the oral contraceptive ethinyl estradiol and rotigotine are metabolized by CYP3A4, Braun et al. examined the potential interactions between rotigotine and an oral contraceptive containing ethinyl estradiol and levonorgestrel in healthy women volunteers. Coadministration of rotigotine and an oral contraceptive did not affect the efficacy of the contraceptive. These results suggest that rotigotine should not affect oral contraceptive efficacy with drug products containing ethinyl estradiol and levonorgestrel.

**Clinical studies**

**Parkinson's disease**

Rotigotine is indicated for the treatment of the signs and symptoms of idiopathic PD. In patients with early-stage PD, rotigotine dosing is suggested to start at 2 mg/24 h, and in patients with advanced-stage PD dosing is suggested to start at 4 mg/24 h. Rotigotine may be increased weekly by 2 mg/24 h depending on tolerability and treatment response. In the United States, the highest recommended dose of rotigotine in early-stage PD is 6 mg/24 h and in advanced-stage PD is 8 mg/24 h; the maximum recommended dose in the European Union is 8 mg/24 h for early-stage PD and 16 mg/24 h for advanced-stage PD. Results of the key rotigotine trials in early- and advanced-stage patients are briefly summarized below.

**Early-stage PD.** The efficacy, safety, and tolerability of rotigotine in patients with early-stage PD has been demonstrated in three phase III, double-blind, placebo-controlled clinical studies (Table 1). It is important to note that that none of the patients with early-stage PD was receiving concomitant levodopa. The first study was a randomized, multinational double-blind, placebo-controlled dose-ranging study in 316 patients with early-stage PD (SP506), which established the dose–response relationship between escalating doses of rotigotine (2, 4, 6, and 8 mg/24 h) and improvements in the Unified Parkinson's Disease Rating Scale (UPDRS). Changes from baseline to end of maintenance (EoM) in UPDRS II + III scores was the primary efficacy variable, and changes in UPDRS II (activities of daily living) and III (motor examination) scores were assessed as secondary efficacy variables. Statistically significant mean changes from baseline to EoM were observed in the intent-to-treat population for UPDRS II + III scores demonstrating dose-related improvements for the 4, 6, and 8 mg/24 h dose groups. The effect of the 6 mg/24 h and 8 mg/24 h dose groups were similar. In a subanalysis reporting the results from the North American cohort of SP506 (n = 242), significant mean rotigotine–placebo treatment difference (95% confidence interval (CI)) changes from baseline to EoM on the UPDRS II + III were observed in the intent-to-treat population for the 6 mg/24 h (−4.83 (−7.68, −1.97); P = 0.001) and 8 mg/24 h (−5.23 (−8.02, −2.44); P < 0.001) dose groups versus placebo. The most common adverse events (AEs; reported by ≥ 10% of subjects randomized to rotigotine (total group) and greater than placebo) included nausea (47%), application-site reactions (ASRs; 39%) (ASRs are discussed in more detail in section "Application-site reactions", below), somnolence (22%), vomiting (16%), and fatigue (15%). ASRs were cited as the reason for study discontinuation in eight patients, four of which were in the 8 mg/24 h dose group.

The clinical efficacy and safety of rotigotine in patients with early-stage PD was further established by two randomized, double-blind, placebo-controlled clinical studies (SP512 and SP513). These were flexible-dosed studies in which participants randomized to active treatment received increasing doses of rotigotine until the optimal or maximum allowed dose was achieved. The optimal effective dose was defined as the dose resulting in maximum reduction in PD symptoms without intolerable side effects. In SP512, patients were randomized to receive a dose of 2–6 mg/24 h of rotigotine (n = 181) or placebo (n = 96); the mean (standard deviation (SD)) rotigotine dose was 5.7 (0.84) mg/24 h; the majority of patients (115/181 patients (64%)) received 6 mg/24 h for the duration of the maintenance period; 6% received 4 mg/24 h, and 3% received 2 mg/24 h. Most enrolled patients (≥ 81%) completed the full treatment period (rotigotine 78%, placebo 84%). The primary efficacy variable was the change from baseline to EoM in

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**Table 1**

| Study Design | Population | Results |
|-------------|------------|---------|
| SP506       | Early-stage PD | Dose ranging 2–6 mg/24 h, established dose–response relationship |
| SP512       | Early-stage PD | Randomized, double-blind, placebo-controlled, flexible-dosed study |
| SP513       | Advanced-stage PD | Randomized, double-blind, placebo-controlled, flexible-dosed study |

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Table 1. Summary of key rotigotine clinical trials in Parkinson’s disease

| Study     | Design                                                                 | Number of randomized patients | Inclusion criteria                                                                 | Study completers n (%) | Treatment duration | Rotigotine dose Mean (SD) mg/24 h | Rotigotine dosing |
|-----------|------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------|-------------------------|------------------|---------------------------------|------------------|
| **Phase III efficacy and safety studies in patients with early-stage PD** |                                                                       |                               |                                                                                    |                         |                                |                   |                  |
| SP506     | Randomized, multicenter, double-blind, placebo-controlled, two-arm, parallel group, dose-ranging study | 242                           | Aged > 30 years, idiopathic PD, H&Y ≤ 3                                           | Placebo: 40/47 (85) Rotigotine: 166/195 (85) | Titration: up to 4 weeks Maintenance: 7 weeks | NA Fixed dose rotigotine, 2, 4, 6, and 8 mg/24 h |                   |
| SP512     | Randomized, multicenter, double-blind, placebo-controlled, two-arm, parallel group, optimized dosing study | 277                           | Aged ≥ 30 years, idiopathic PD diagnosed ≤ 5 years, UPDRS pt III ≥ 10 H&Y ≤ 3   | Placebo: 81/96 (84) Rotigotine: 142/181 (78) | Titration: 3 weeks Maintenance: 24 weeks | 5.7 (0.84) Optimal dose rotigotine 2–6 mg/24 h |                   |
| SP513     | Randomized, multicenter, double-blind, double-dummy, placebo-and ropinirole-controlled, three-arm, parallel group, optimized-dosing study | 561                           | Aged ≥ 30 years, idiopathic PD diagnosed ≤ 3 years, UPDRS pt III ≥ 10 H&Y ≤ 3 | Placebo: 84/118 (71) Rotigotine: 151/215 (70) Ropinirole: 174/228 (76) | Titration: up to 4 weeks Maintenance: 33 weeks | NA Optimal dose rotigotine 2–8 mg/24 h |                   |
| **Open-label extension studies** |                                                                       |                               |                                                                                    |                         |                                |                   |                  |
| SP512     | Prospective, multicenter, single-arm, open-label extension study of SP512 | 217                           | Completion of SP512                                                                  | 102/217 (47) still in study at time of closure | Up to 6 years | 7.2 (3.4) Optimal dose rotigotine 2–6 mg/24 h the first year and up to 16 mg/24 h thereafter |                   |
| SP513     | Prospective, multicenter, single-arm, open-label extension study of SP513 | 381                           | Completion of SP513                                                                  | 197/381 (52) still in study at time of closure | Up to 6 years | 8.2 (3.8) Optimal dose rotigotine 2–8 mg/24 h for the first year and up to 16 mg/24 h thereafter |                   |
| **Phase III efficacy and safety studies in patients with advanced-stage PD** |                                                                       |                               |                                                                                    |                         |                                |                   |                  |
| SP515     | Randomized, multicenter, double-blind, double-dummy, placebo-and pramipexole-controlled, three-arm, parallel-group study | 506                           | Aged ≥ 30 years, idiopathic PD diagnosed ≥ 5 years, H&Y 2–4 Stable levodopa “Off-time” ≥ 2.5 h/day | Placebo: 75/101 (74) Rotigotine: 181/204 (89) Pramipexole: 171/201 (85) | Titration: Up to 7 weeks Maintenance: 16 weeks | 12.95 (3.54) Optimal dose rotigotine 4–16 mg/24 h |                   |
| SP650     | Randomized, multicenter, double-blind, placebo-controlled, two-arm, parallel-group study | 351                           | Aged ≥ 30 years, idiopathic PD diagnosed ≥ 3 years, H&Y 2–4 Stable levodopa “Off-time” ≥ 2.5 h/day | Placebo: 92/120 (77) Rotigotine 8 mg/24 h: 87/120 (73) Rotigotine 12 mg/24 h: 81/111 (73) | Titration: 5 weeks Maintenance: 24 weeks | 8 mg/24 h group: 7.16 (range: 4.00–7.73) 12 mg/24 h group: 9.51 (range: 4.00–11.16) Fixed dose rotigotine 8 and 12 mg/24 h |                   |
| **Open label extension studies** |                                                                       |                               |                                                                                    |                         |                                |                   |                  |
| SP515     | Prospective, multicenter, single-arm, open-label extension study of SP515 | 395                           | Completion of SP515                                                                  | 189/395 (48) still in study at time of closure | Up to 4 years | 11.6 (3.2) Optimal dose rotigotine 4–16 mg/24 h |                   |

Continued
Table 1. Continued

| Study                     | Design                                      | Number of randomized patients | Inclusion criteria | Study completers n (%) | Treatment duration | Rotigotine dose (SD) mg/24 h | Rotigotine dosing       |
|---------------------------|---------------------------------------------|-------------------------------|--------------------|------------------------|---------------------|-------------------------------|--------------------------|
| SP715                     | Prospective, multicenter, single-arm, open-label extension study of SP650 | 258 enrolled                 | Completion of SP650 | 115/258 (45) still in study at time of closure | Up to 6 years       | 10.1 (3.4)                   | Optimal dose rotigotine 4–12 mg/24 h for the first year and up to 16 mg/24 h thereafter |
| Other phase III studies    |                                             |                               |                     |                        |                     |                               |                          |
| SP889 (RECOVER; NCT00474058) | Phase IIIb, randomized, double-blind, placebo-controlled, parallel-group two-arm study | 287                           | Aged ≥18 years PD and unsatisfactory control early morning motor symptoms Not taking levodopa or stable levodopa | Placebo: 80/97 (82) Rotigotine: 166/190 (87) | Titration: 1–8 weeks Maintenance: 4 weeks | NA The mean rotigotine dose during the RECOVER trial maintenance period was 11.2 ± 4.47 mg/24 h (n = 178). | Optimal dose rotigotine 2–16 mg/24 h |
| SP915                     | Prospective, multicenter, single-arm, open-label extension study of SP889 | 84 enrolled                  | Completion of SP889 | 66/84 (79)             | 1 year              | 11.5 (3.8) (over maintenance) | Optimal dose rotigotine 2–16 mg/24 h |

aRotigotine dose at end of maintenance.

bStudy initiation predates 2005 ClinicalTrial.gov requirement.

cSP513 also included a ropinirole comparison arm (n = 228 randomized patients).

dSP515 also included a pramipexole comparison arm (n = 201 randomized patients).

eMean dose in patients entering maintenance phase.

CLEOPATRA-PD: Clinical Efficacy of Pramipexole and Transdermal Rotigotine in Advanced PD; H&Y: Hoehn and Yahr; NA: Not available; PREFER: Prospective Randomized Evaluation of a new Formulation: Efficacy of Rotigotine; RECOVER: Randomized Evaluation of the 24-Hour Coverage: Efficacy of Rotigotine; SD: standard deviation.

mean UPDRS II + III score. The mean (SD) change from baseline to EoM in UPDRS II + III scores for the rotigotine-treated patients was −3.98 (0.707) compared to +1.31 (0.956) for placebo; resulting in a mean (SD) treatment difference of −5.28 (1.18; P < 0.0001).

Study SP513 randomized patients to placebo (n = 118), rotigotine (n = 215), and ropinirole (n = 228) treatment groups. In SP513, patients were randomized to receive a dose of 2–8 mg/24 h rotigotine, up to 24 mg/24 h of oral ropinirole administered three times daily, or placebo; the mean daily rotigotine dose was just less than 8 mg/24 h and the median ropinirole dose was 14.1 mg/day. Approximately 73% of patients completed the study (rotigotine 70%, ropinirole 76%, placebo 71%). A secondary outcome for SP513, the mean (SD) change in UPDRS II + III scores from baseline to EoM for rotigotine was −7.2 (9.9) and −2.2 (10.2) for patients receiving placebo (P < 0.0001; Fig. 2A). The mean (SD) change in UPDRS II + III scores from baseline to EoM for ropinirole was −11.0 (10.5; P < 0.001 vs. placebo). Both studies reported a significantly higher proportion of rotigotine patients experiencing a greater than 20% UPDRS II + III improvement compared to placebo (Fig. 2B). In the SP513 study, 52% of the rotigotine patients and 68% of the ropinirole-treated patients achieved >20% improvement compared to 30% of patients randomized to placebo. Although rotigotine and ropinirole both showed significant improvements in motor symptoms compared with
Development of rotigotine for PD and RLS

Benitez et al.

Placebo
Rotigotine
2-6mg/24 h
Placebo
Rotigotine
2-8mg/24 h
Ropinirole

Mean Change from Baseline

Figure 2. (A) Mean change from baseline to EoM in UPDRS II + III (ITT population) in patients with early-stage PD. (B) Responder rates at EoM (ITT population) from studies SP512 and SP513 in patients with early-stage PD. Treatment comparisons and results (i.e., P values) were based on an analysis of covariance.76,84 EoM, end of maintenance; ITT, intent-to-treat; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

Placebo, rotigotine noninferiority with ropinirole was not demonstrated. The study, however, was not powered to demonstrate superiority. Moreover, the authors noted that the rotigotine-treated patients may have been underdosed; rotigotine-treated patients were titrated to the maximum permitted rotigotine dose whereas patients in the ropinirole group were treated with a considerable wide range of ropinirole doses (range 0.75–24 mg/day).76 This difference in dosing may account for, at least in part, some of the differences in results between rotigotine and ropinirole.

The most commonly reported AEs (≥10%) in rotigotine treated patients for studies SP512 (safety set n = 181) and SP513 (safety set n = 215) were nausea (41% and 29%, respectively), ASRs (44% and 38%), dizziness (19%, 14%), and somnolence (33%, 23%). ASRs were more common with rotigotine compared with placebo (SP512: 12%; SP513: 11%) and were the most common AEs leading to treatment discontinuation.76,84 AEs led to early discontinuation of 14% of rotigotine-treated patients and 6% of patients given placebo in SP512. In SP513, 17% of rotigotine-treated and 13% of
ropinirole-treated patients, and 5% of patients given placebo had AEs leading to discontinuation. ASRs were the most common AE that led to discontinuation of rotigotine-treated patients in both trials (SP512: 5%; SP513: 8%).

Two open-label extension studies of up to 6 years, SP702 (SP512) and SP716 (SP513), evaluated the long-term safety and tolerability of rotigotine in patients with early-stage PD (Table 1). In both studies, patients completing the maintenance period of the randomized, double-blind, placebo-controlled studies were offered enrollment into the open-label extension. At the end of each initial study, rotigotine treatment was deescalated to a minimum dose of 2 mg/24 h over 4 (SP702) or 12 days (SP716). The rotigotine dose was then uptitrated to an optimally effective dose; the maximum dose was 6 mg/24 h in study SP702 and 8 mg/24 h in study SP716. After the first year of open-label maintenance, up titration to a maximum of 16 mg/24 h rotigotine was permitted. In study SP702, the mean (SD) rotigotine dose at the end of treatment was 7.2 (3.4) mg/24 h, and was 8.2 (3.8) mg/24 h in study SP716. The most common AEs reported in SP702 (safety set \( n = 216 \)) and SP716 (safety set \( n = 380 \)) included somnolence (54% and 38%, respectively), falls (33% and 12%), peripheral edema (37% and 19%), ASRs (32% and 31%), and nausea (31% and 19%). ASRs were the most common AE resulting in discontinuation (SP702: 3%, SP716: 7%). In each study, the majority of patients (SP702: 74%, SP716: 69%) began adjunctive levodopa therapy. Of the patients who reported dyskinesias (SP702: 25%; SP716: 17%), the majority of the dyskinesias began after the initiation of adjunctive levodopa therapy. Of the patients who reported dyskinesias (SP702: 25%; SP716: 17%), the majority of the dyskinesias began after the initiation of adjunctive levodopa therapy (SP702: 83%; SP716: 72%). In the open-label studies, UPDRS II + III scores gradually declined toward the double-blind baseline values, remaining within four points of the double-blind baseline value until the end of the 6-year maintenance period.

Advanced-stage PD. The efficacy, safety, and tolerability of rotigotine in patients with advanced-stage PD (i.e., on treatment with levodopa) who were experiencing fluctuations were evaluated in two phase III randomized, double-blind, placebo-controlled studies (SP515 and SP650). In SP515 (CLEOPATRA-PD, Clinical Efficacy of Pramipexole and Transdermal Rotigotine in Advanced PD), rotigotine was administered (\( n = 204 \)) to optimal response or maximum dose of 16 mg/24 h. SP515 also included a group randomized to pramipexole (\( n = 201 \)) up to a maximum dose of 4.5 mg/day given three times daily to optimal response. SP650 (PREFER, Prospective Randomized Evaluation of a new Formulation: Efficacy of Rotigotine) was a fixed-dose study; patients were randomized to target doses of 8 mg/24 h (\( n = 120 \)) or 12 mg/24 h (\( n = 111 \)). Adjunctive rotigotine resulted in significant improvement in absolute mean change in daily off time from baseline to EoM compared to placebo. Overall, 74% patients completed SP650 and 84% completed SP515. In SP515, the difference in the mean (95% CI) change from baseline to EoM in daily off time between rotigotine and placebo was \(-1.58 \text{ h} \) \((-2.27, -0.90; P < 0.0001)\); this difference was \(-1.94 \text{ h} \) \((-2.63, -0.90; P < 0.0001)\) for the comparison between pramipexole and placebo (Fig. 3). Rotigotine was determined to be noninferior to pramipexole in the absolute off time (\( P = 0.003 \)) but was not noninferior to pramipexole in the responder rate (\(-7.3\% \) \((-16.7, 2.1); P = 0.108\)). The mean (SD) dose of rotigotine in patients entering the maintenance phase was 12.95 (3.54) mg/24 h and 3.1 (1.24) mg/day for the patients randomized to pramipexole. Similar differences from baseline to EoM in off time between rotigotine and placebo were reported in SP650 (Fig. 3). Both studies also reported responder rates (defined as a \( \geq 30\% \) decrease in the absolute off time) that were at least 20% greater with patients receiving rotigotine (or pramipexole in SP515) than those given placebo. Thus, in patients with advanced stage PD, rotigotine treatment results in clinically relevant reductions in off time. In SP515, the most common AEs (\( \geq 10\% \)) in rotigotine treated patients (\( n = 204 \)) were nausea (17%), somnolence (12%), and dyskinesia (12%). The most common AEs (\( \geq 10\% \)) in SP650 (8 mg/24 h: \( n = 118 \); 12 mg/24 h: \( n = 111 \)) were ASRs (8 mg/24 h: 36%; 12 mg/24 h: 46%), somnolence (32%, 32%), nausea and vomiting (28%, 24%), dizziness (23%, 15%), dyskinesia (14%, 17%), and headache (10%, 8%). ASRs resulted in the greatest number of discontinuations in SP515 (2.9%) and in 1.7% of patients in SP650. Patients who completed the double-blind phases of studies SP650 and SP515 were eligible for participation in open-label extension studies (SP715 (\( n = 258 \)) and SP516 (\( n = 395 \)), respectively).
Figure 3. Mean change from baseline to EoM in off time (ITT population) in patients with advanced-stage PD. Treatment comparisons and results (i.e., \(P\) values) were based on an analysis of covariance. \(\text{SP513}\) optimal dosing: rotigotine 4–16 mg/24 h (mean dose was 12.95 mg/24 h), pramipexole 0.375–4.5 mg/day (mean dose was 3.1 mg/day).\(^b\) Mean dose of rotigotine and pramipexole; \(^c\) \(P = 0.003\) 12 mg/24 h rotigotine versus placebo; \(^d\) \(P < 0.0001\) rotigotine or pramipexole versus placebo. CI, confidence interval; EoM, end of maintenance; ITT, intent-to-treat; PD, Parkinson’s disease.

Following dose de-escalation to 4 mg/24 h, rotigotine was titrated to optimal doses to a maximum of 16 mg/24 h (in \(\text{SP715}\) the maximum rotigotine dose was 12 mg/24 h for year 1).\(^78\) AEs were generally mild to moderate in intensity. The most commonly reported AEs (≥10%) in \(\text{SP516}\) (safety set \(n = 395\)) and \(\text{SP715}\) (safety set \(n = 258\)) included somnolence (34% and 58%, respectively), ASRs (26%, 33%), falls (16%, 40%), nausea (14%, 24%), insomnia (11%, 22%), back pain (12%, 21%), and hallucinations (9%, 23%). ASRs led to the most discontinuations in \(\text{SP516}\) (3.5%) and hallucinations resulted in most discontinuations in \(\text{SP715}\) (2.3%). Similar to patients with early-stage PD, UPDRS scores receded from their initial improvements from baseline during the double-blind maintenance period. UPDRS III (motor) scores remained below baseline values, whereas UPDRS II (ADL) scores did not. At the end of the studies, 36% and 24% of patients were classified as treatment responders on the UPDRS II + III sum score, for \(\text{SP516}\) and \(\text{SP715}\), respectively.\(^78\)

A retrospective, post hoc analysis of data from the studies in patients with early-stage (\(\text{SP512}\) and \(\text{SP513}\)) and advanced-stage PD (\(\text{SP515}\) and \(\text{SP650}\)) compared the safety and tolerability of rotigotine in younger and older patients.\(^86\) The data from the early-stage and advanced-stage studies were pooled separately. The incidence of AEs was stratified by two separate age groups: <65-year old (\(\text{SP512/SP513}: n = 343; \text{SP515/SP650}: n = 286\)) and ≥65-year old (\(n = 266; n = 367\)), and <75-year old (\(n = 555; n = 543\)) and ≥75-year old (\(n = 54; n = 110\)).\(^86\) In the patients with early-stage disease, a ≥5% difference between the patients aged <65 years and patients aged ≥65 years was found for nausea (37.6% vs. 30.1%, respectively) and headache (15.3% vs. 9.0%); constipation was greater among the patients aged ≥65 years than for the younger patients (10.8% vs. 3.5%). A ≥10% difference was noted in the <75-year age group versus the ≥75 year age group for nausea (35.5% vs. 20.7%); dizziness was reported more frequently in the ≥75 year age group (27.6% vs. 15.0%).\(^86\) In patients with advanced-stage disease, only the incidence of falls occurred with a ≥5% difference in incidence between patients <65 years and patients aged ≥65 years (5.6% vs. 11.0%). Nausea was the only AE that occurred with a
difference of >5% between the <75-year age group and the ≥75-year age group (23.1% vs. 11.4%).

Thus, for the most part, the results from this post hoc analysis of clinical study data suggests that rotigotine is generally well tolerated irrespective of patient age. A similar evaluation of the differences in the efficacy of rotigotine in younger and older patients with early- or advanced-stage disease is currently ongoing.

**Early-morning symptoms.** The motor symptoms of PD can lead to nocturnal and early-morning dystonia and akinesia, as well as nonmotor symptoms such as sleep disruption. Study SP889 (RECOVER, Randomized Evaluation of the 24-Hour Coverage: Efficacy of Rotigotine) was a phase IIIIB, randomized, double-blind, placebo-controlled, parallel-group, two-arm study in 287 patients with PD and unsatisfactory control of early-morning symptoms. Patients on stable doses of levodopa for at least 28 days as well as patients not taking levodopa could be included. Study SP889 evaluated the effect of rotigotine in patients with PD on early-morning motor function and nocturnal sleep disturbances (Table 1). Rotigotine was titrated over 1–8 weeks starting at 2 mg/24 h to an optimal dose or up to a maximum of 16 mg/24 h, and maintained for 4 weeks. Before application of a new patch in the morning, early-morning motor function was assessed with the UPDRS III (motor) scale, and sleep and nocturnal sleep disturbances were evaluated with the modified Parkinson’s Disease Sleep Scale (PDSS-2). Rotigotine treatment resulted in significant improvements from baseline to EoM in early morning UPDRS III scores compared to placebo (least square (LS) mean (95% CI) treatment difference: −3.55 (−5.37, −1.73; P = 0.0002) and PDSS-2 scores (−4.26 (−6.08, −2.45); P < 0.0001). AEs (safety set n = 191) were similar with previous rotigotine studies and included nausea (21%), ASRs (15%), dizziness (10%), dyskinesia (8%), and headache (7%). ASRs led to discontinuation in 3% (5/191) of rotigotine-treated patients. At the end of a 1-year open-label extension (SP915; Table 1), mean (SD) UPDRS III scores were 10.9 (10.7) points lower relative to the double-blind baseline and 5.8 (9.4) points lower than the open-label baseline. Similar improvements in PDSS-2 scores relative to double-blind baseline were maintained for the open-label period. Thus, motor and sleep improvements with rotigotine were maintained for up to 1 year of continued open-label treatment.

Behavioral side effects of rotigotine include impulse-control disorders (ICDs; discussed in more detail below in the “Impulse-control disorders” section) excessive daytime sleepiness (EDS) and sleep attacks (defined as a sudden and overwhelming onset of sleep without warning). EDS and sleep attacks also have been reported to occur with dopamine agonist treatment. In the North American cohort of SP506, one case each of sudden sleep onset (6 mg/24 h) and a brief loss of consciousness while driving (8 mg/24 h) were reported. Sleep attacks were reported by 3% of rotigotine-treated patients with early-stage PD in study SP513. In SP702 the 6-year open-label extension study in patients with early PD, five patients reported sleep attacks (2.3% of 216 patients), two of which were serious. Two subjects treated with rotigotine in SP889 reported experiencing sleep attacks.

Patients with early- and advanced-stage PD treated with rotigotine have reported falling asleep while engaging in activities of daily living including driving, which has resulted in accidents. Many of these patients have reported somnolence, a common AE reported by patients being treated for symptoms of PD (and RLS) with rotigotine. The data in post-marketing surveillance is consistent with the published reports of somnolence. Because patients may not acknowledge increased somnolence or drowsiness until questioned, clinicians should directly evaluate patients for sleepiness or drowsiness.

**Restless legs syndrome**

Rotigotine is indicated for the treatment of moderate-to-severe symptoms of primary RLS. Rotigotine should be initiated at 1 mg/24 h and then increased as needed weekly by 1 mg/24 h, up to a maximum dose of 3 mg/24 hours. Clinical studies in RLS have used the International Restless Legs Study Group rating scale (IRLS) and Clinical Global Impression (CGI) scale to evaluate the efficacy of rotigotine.

**Primary RLS.** Two 6-month, randomized, double-blind, placebo-controlled studies evaluated the efficacy of rotigotine for idiopathic RLS, SP790, and SP792 (Table 2). Patients with RLS were randomized to placebo or rotigotine in doses of 0.5 (SP792 only), 1, 2, or 3 mg/24 hours. The coprimary
| Study | Design | Number of subjects | Inclusion criteria | Study completers\(^a\) (% | Treatment duration | Rotigotine dose\(^b\) | Mean (SD) mg/24 h | Rotigotine dosing |
|------|--------|-------------------|--------------------|--------------------------|---------------------|-------------------|-----------------|-----------------|
| **Phase III efficacy and safety studies** | | | | | | | | |
| SP709 (NCT00243217)\(^4\) | Randomized, double-blind, placebo-controlled dose-finding study | 341 | Aged 18–75 years IRLSSG RLS diagnosis No previous RLS treatment | 263/286 (92) | Titration: 2 weeks Maintenance: 4 weeks | NA | | Fixed-dose rotigotine 0.5, 1, 2, 3, or 4 mg/24 h |
| SP790 (NCT00136045)\(^6\) | Randomized, multinational, double-blind, placebo-controlled, four-arm study | 458 | Aged 18–75 years IRLSSG RLS diagnosis Baseline IRLS ≥ 15 | 245/341 (72) | Titration: 3 weeks Maintenance: 24 weeks | NA | | Fixed-dose rotigotine 1, 2, and 3 mg/24 h |
| SP792 (NCT00135993)\(^9\) | Randomized, multicenter (U.S. only), double-blind, placebo-controlled, five-arm study | 505 | Aged 18–75 years IRLSSG RLS diagnosis Baseline IRLS ≥ 15 | 253/405 (62) | Titration: 4 weeks Maintenance: 24 weeks | NA | | Fixed-dose rotigotine 0.5, 1, 2 and 3 mg/24 h |
| SP794 (NCT00275236)\(^9\) | Randomized, double-blind, placebo-controlled, parallel-group, polysomnographic study | 67 | Aged 18–75 years IRLSSG RLS diagnosis Baseline IRLS ≥ 15 | 41/46 (89) | Titration: 3 weeks Maintenance: 4 weeks | 2.09 (0.78) | | Optimal dose rotigotine 1–3 mg/24 h |
| **Open-label extension studies** | | | | | | | | |
| SP710 (NCT00498186)\(^9\,\(^2\,\(^3\)) | Prospective, multicenter, single-arm, open-label extension study of SP709 | 295 | Completion of SP709 | 126/295 (43)\(^a\) | 5 years | 3.09 (1.07) | | Optimal dose rotigotine 0.5–4 mg/24 h |
| SP791 (NCT00498108)\(^9\) | Open-label extension of European studies (SP790 and SP794) | 341 | Completion of SP790 and SP794 | NA | 1 year | NA | | Optimal dose rotigotine 1–3 mg/24 h |
| SP793 (NCT00263068)\(^9\) | Open-label extension of a 6-month, U.S., double-blind, placebo-controlled trial (SP792) | 279 | Completion of SP792 | NA | 1 year | NA | | Optimal dose rotigotine 0.5–3 mg/24 h |
| **Phase IV studies** | | | | | | | | |
| SP0977 (NCT01435012)\(^9\) | Phase IV, randomized, double-blind, placebo-controlled, parallel-group, two-arm, multicenter, sleep-lab study | 81 | NA | NA | Titration: 3 weeks Maintenance: 4 weeks | NA | | Optimal dose rotigotine 1–3 mg/24 h |

\(^a\)Patients randomized to rotigotine treatment, unless otherwise noted.

\(^b\)Rotigotine dose at end of maintenance.

\(^c\)Completers at the end of the 5-year study.

IRLSSG, International Restless Legs Syndrome Study Group; RLS, restless legs syndrome; SD, standard deviation.
variables in both studies were the absolute change from baseline to EoM in the IRLS sum score and in the CGI item 1 (severity of symptoms) score; secondary endpoints included the proportion of IRLS and CGI treatment responders (≥50% improvement from baseline to EoM in IRLS or CGI item-1 scores). In SP790, 68% of the patients completed the study (313/458 randomized patients). Rotigotine treatment resulted in statistically significant improvement from baseline to EoM in both coprimary endpoints for all treatment groups (1–3 mg/24 h) compared to placebo (Table S1). In SP792, 63% (320/505) of randomized subjects completed the study. Improvements were statistically significant only for rotigotine 2 and 3 mg/24 h dose groups (Table S1). In both studies, >50% of rotigotine-treated patients were IRLS responders (Fig. 4). In addition, the percentage of patients rated as IRLS remitters (IRLS sum score ≤10) and complete remitters (IRLS sum score = 0) generally increased with increasing rotigotine doses (Fig. 4), which suggests a reduction of RLS symptoms in some patients to subclinical levels or a complete absence of symptoms with continued treatment.

The most common (≥5%) AEs reported among the rotigotine dose groups (safety set; SP790: 1 mg/24 h: n = 115; 2 mg/24 h: n = 112; 3 mg/24 h: n = 114; SP792: 0.5 mg/24 h: n = 99; 1 mg/24 h: n = 100; 2 mg/24 h: n = 99; 3 mg/24 h: n = 106) were ASRs (range among all dose groups SP70: 35–52%; SP792: 17–34%; ASRs are discussed in more detail in section “Application-site reactions,” below), nausea (SP790: 9–21%; SP792: 13–21%), headache (SP790: 10–16%; SP792: 10–14%), and fatigue (SP790: 7–15%; SP792: 3–10%). In SP790, rotigotine-related reasons for discontinuations included ASRs (n = 35), nausea (n = 4), vomiting (n = 3), and pruritus (n = 3). ASRs and dizziness were the most common reasons for study discontinuation in SP792 (4.7% and 1.7% of patients treated with rotigotine, respectively). The long-term safety and efficacy of rotigotine for primary RLS was evaluated in a 5-year open-label study (SP710; Table 2). Subjects were participants from an earlier 6-week, randomized, double-blind, placebo-controlled dose-finding study (SP709, rotigotine doses 0.5–4 mg/24 h). Of the 295 patients entering the open-label extension, 126 patients (43%) completed the 5-year study.
The mean (SD) dose at EoM was 3.09 (1.07) mg/24 h; 49% of the patients received 4 mg/24 h, 20% received 2 mg/24 h or 3 mg/24 h, 7% received 1 mg/24 h, and 5% received 0.5 mg/24 h of rotigotine. During open-label treatment, the most common (≥10%) AEs (safety set: n = 295) were ASRs (58%), nasopharyngitis (19%), back pain (14%), nausea (12%), and fatigue (11%). The incidence of AEs was greatest during the first year (220/290 (76%)), declined in years 3 (134/220 (61%)) and 2 (103/191 (54%)), and remained stable through years 4 (93/159 (58%)) and 5 (91/147 (62%)). The most common AEs resulting in discontinuation were ASRs (56 patients (19%)). Augmentation resulted in discontinuation in 12 patients (4%); see below). Patients who entered the open-label phase of the study maintained overall improvements in IRLS total scores; of the patients who completed the study, 67% were considered responders, 59% considered remitters, and 39% were considered complete remitters (IRLS score of 0) at the EoM.3 A post hoc analysis of patients in the open-label study receiving only the FDA-approved dosages of rotigotine (1–3 mg/24 h) reported that the proportion of treatment responders was maintained over the 5 years of open-label treatment (Fig. 4).2 Thus, treatment with rotigotine was generally well tolerated and provided sustained efficacy in patients with moderate- to-severe primary RLS.2,3

An important dopaminergic-associated RLS treatment complication is augmentation. Augmentation is a worsening of RLS symptoms during treatment, leading to an increase in overall symptom severity compared to before treatment was initiated and is considered a consequence of long-term treatment.3 Augmentation can lead to dose adjustments or change in pharmacologic therapy.4 In a retrospective analysis including data from SP700 and SP792, the rate of clinically relevant augmentation ranged from 1.5% after 6 months to 2.9% of rotigotine-treated patients after 1 year. In the 5-year open-label study (SP710), clinically relevant augmentation was observed in 11.9% (15/126) of patients treated with the approved 1–3 mg/24 h rotigotine doses and 19% (24/126) of patients treated with 4 mg/24 h rotigotine.5 A total of 12 (4%) patients (1–3 mg/24 h, n = 4 (1%); 4 mg/24 h, n = 8 (3%)) discontinued treatment in the 5-year open-label study owing to clinically significant augmentation.5

**RLS and CVD.** The prevalence of hypertension and CVD (including stroke) has been shown to be higher in patients with RLS and periodic leg movements during sleep (PLMS).7,8 The ENCORE study (SP0977: Effects of Neupro on Cardiovascular Observations in Patients with Restless Legs Syndrome) was a preliminary study designed to determine whether rotigotine would decrease the number of elevations in nocturnal systolic blood pressure (SBP) associated with PLMS in patients with RLS. At baseline, patients randomized to placebo or rotigotine had approximately 300 nocturnal SBP elevations associated with PLMS. Treatment with rotigotine resulted in significantly greater reductions from baseline to EoM in PLMS-associated SBP elevations (LS mean (95% CI) change: –239.95 (–275.34, –204.56)) compared with placebo (–79.61 (–119.25, –39.97); treatment difference: –160.34 nocturnal SBP elevations (–213.23, –107.45); P < 0.0001 vs. placebo).9 Although these results suggest that reducing PLMS may have an effect on CVD variables, such as nocturnal SBP, the relationship between RLS/PLMS and CVD risk is complex.

**Application-site reactions**

ASRs are common and dose-dependent AEs associated with the rotigotine transdermal system. In the initial dose-finding study in patients with early PD (SP506; n = 330), the incidences of ASRs were 19% for placebo, and 24%, 21%, 34%, and 46% for rotigotine 2, 4, 6, and 8 mg/24 h, respectively.5 In the open-label extension studies (SP702 and SP716) of up to 6 years each in patients with early-stage PD treatment (n = 217 and n = 380, respectively, up to 16 mg/24 h), the incidence of ASRs was highest during the first year and then decreased over long-term treatment.7,7 Overall, 32% and 31% of patients reported ASRs in SP702 and SP716, respectively. Most cases were mild to moderate (SP702: 94%; SP716: 92%) in intensity. In SP702 and SP716, the median (range) time for the development of ASRs was 78 (1–1771) days and 55 (1–1869) days, respectively.7,7 In patients with advanced PD (n = 349), the incidences of ASRs were 13% for placebo, and 36% and 46% for rotigotine 8 and 12 mg/24 h, respectively.5 In the open-label studies in advanced-stage PD patients (SP516 and SP715), most ASRs (72% to 83%) resolved by study completion, and the majority of ASRs were mild to moderate in intensity.7 The mean (SD) time from start of treatment to the first
onset of an ASR was 110 (158) days (SP716) and 228 (370) days (SP715).78

Dose-dependent ASR rates also were observed in the two RLS double-blind, placebo-controlled, dose-response studies (SP790 and SP792; \( n = 962 \), duration 6 months); ASRs were observed in 23%, 27%, 38%, and 43% of patients with RLS treated with 0.5 mg, 1 mg, 2 mg, and 3 mg/24 h rotigotine, respectively, versus 4% for placebo.57 In the 5-year open-label extension study (SP710), the incidence of ASRs was 37% of patients treated with rotigotine during year 1, 17% in year 2, 14% in year 3, and 5% in years 4 and 5.93 Most patients (67%) recovered without requiring dose reduction or dose decrease. The median duration of ASR was 160 days (range 1–1810) with a median of 94 days/year of exposure.93

In general, ASRs take the form of localized erythema, edema, or pruritus limited to the patch area and usually did not lead to dose reduction. Generalized skin reactions (i.e., allergic rash, including erythematous, macular–papular rash, or pruritus), have been reported at lower rates than ASRs during the development of rotigotine.57 In a clinical study in 221 healthy subjects designed to investigate the cumulative skin irritation of rotigotine, daily rotation of rotigotine application sites reduced ASR incidence compared to repetitive application to the same site.57 Thus, daily rotation of the application site may reduce the incidence of ASRs. The same site should not be used more than once every 14 days. Also, to reduce the possibility of ASRs, patients should wash the application site after patch removal with soap and water to remove any drug or adhesive. Baby or mineral oil may be used to remove any excess residue. Alcohol and other solvents (such as nail polish remover) may cause skin irritation and should not be used. Direct sunlight on the area where a skin rash or irritation develops should be avoided until the skin heals because this exposure could lead to a change of skin color.57

**Impulse-control disorders**

Impulse-control disorders (ICDs) such as pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating may occur with dopamine agonists, including rotigotine, in patients treated for PD or RLS.99–105 ICDs were identified in the long-term, open-label extension studies in patients with early-(SP702 and SP716) and advanced-stage (SP516 and SP715) PD treated with rotigotine. In SP702, compulsive behaviors were reported by 8% (18/216) of rotigotine-treated patients, with the majority (86%) being mild to moderate in intensity.75 In SP716, 37 AEs indicative of an ICD were reported in 7% (25/380) of rotigotine-treated patients.77 These ICDs included hypersexuality/compulsive sexual behavior/increased libido in 8 (2%) patients, pathological gambling in 6 (2%) patients, compulsive eating in 5 (1%) patients, and punding in 5 (1%) patients. Most (28/37 (76%)) of the ICDs occurred after levodopa initiation; nine ICDs occurred with rotigotine monotherapy.77 In the long-term extension studies in patients with advanced-stage PD (SP516 and SP715), 42 AEs reported by 6% (22/395) of patients and 28 AEs reported by 8% (21/258) of patients, respectively, were indicative of ICDs.78 ICDs were thought to be related to rotigotine treatment in 4% of patients.78,80 A retrospective analysis of the rotigotine clinical program identified three patients with advanced-stage PD (all receiving levodopa) who developed ICD symptoms while receiving rotigotine 8 mg/24 h (\( n = 2 \)) or 10 mg/24 h (\( n = 1 \)).106 ICDs included hypersexuality (\( n = 1 \)), pathological gambling (\( n = 1 \)), and a combination of hypersexuality, punding, and pathological gambling (\( n = 1 \)). Symptoms occurred during an increase in dose (\( n = 2 \)) or at the initiation of rotigotine therapy (\( n = 1 \)). The rotigotine dose was either reduced (\( n = 1 \)) or discontinued (\( n = 2 \), one patient also reduced selegiline and levodopa doses).106

Garcia-Ruiz et al. evaluated the presence of ICDs in 233 patients with PD (62% male; mean (SD) age 66 (9.7) years) treated for >6 months with a single nonergoline dopamine agonist (ropinirole, pramipexole, or rotigotine).104 The mean (SD) exposure times per DA were 6.4 (4.2) years for pramipexole, 6 (4.3) years for ropinirole, and 4.3 (2.6) years for rotigotine. Many of the patients (81.2%) were taking the extended-release formulations of pramipexole or ropinirole. The incidence of ICDs was 42% with ropinirole, 43% for pramipexole, and 19% with rotigotine (combined ropinirole and pramipexole vs. rotigotine: \( P = 0.0317 \)). Using multivariate analysis, the odds of developing an ICD associated with treatment with ropinirole or pramipexole was more than threefold greater than with rotigotine (odds ratio 3.14 (95% CI: 1.26, 7.83); \( P = 0.014 \)).104
ICDs also can occur in patients with RLS treated with levodopa and dopamine agonists. In patients with RLS treated with pramipexole (average daily dose 1.25 mg (range 0.5–2.0 mg) or ropinirole (average daily dose 3.6 mg (range 0.5–6.0 mg). ICDs have been reported to occur in up to 17% of patients. Although there were no reports of ICDs in the two randomized double-blind, 6-month clinical studies in patients with RLS (SP790: n = 458; SP792: n = 505), there was one recorded ICD case in the 5-year open-label extension study (SP710: n = 295). There have been other postmarketing reports of ICDs in patients with RLS treated with rotigotine. Thus, patients and their caregivers should be asked specifically about the development of new or increased impulse-control or compulsive behaviors while being treated for RLS with rotigotine; a dose reduction or discontinuation of rotigotine should be considered if such urges develop.

Switching patients to rotigotine therapy

The prescribing information for rotigotine contains no information regarding switching from another dopamine agonist to rotigotine and a search of the published medical literature does not identify U.S. guidelines for switching from one dopamine agonist to another. However, two studies have addressed the issue of switching from one dopamine agonist to rotigotine in patients with PD. LeWitt et al. conducted an open-label multicenter study assessing an overnight switch from oral pramipexole (up to 2 mg/day), ropinirole (up to 9 mg/day), or cabergoline (up to 3 mg/day) to rotigotine in a total of 116 early-stage patients with PD (77 male; mean (SD) age 62.8 (±9.9) years) whose symptoms were not adequately controlled. Patients had a mean (SD) disease duration of 5.0 (4.4) years, and 63% were receiving levodopa. A total of 104 patients completed the 28-day rotigotine treatment. After switching to rotigotine, one-step (2 mg/24 h) dose adjustment was needed in 15 (13%) patients: 12 increases (two ropinirole, six pramipexole, four cabergoline) and three decreases (one in each dopamine agonist group). The most common AEs (≥5% incidence) were ASRs (n = 10), nausea (n = 7), and somnolence (n = 7). Although the study was designed to evaluate safety and tolerability, not efficacy, improvements in UPDRS II and III and CGI scores were observed following the switch from the oral dopamine agonists to rotigotine treatment. Similar results were observed in a study in Korean patients with PD treated with ropinirole and switched to rotigotine therapy. In this open-label study with 116 patients with early-stage PD (99 patients (85%) completed), a one-step (2 mg/24 h) dose adjustment was needed in 11 (9%) patients (one decrease, 10 increases). The most common AEs (≥5% incidence and considered clinically relevant) were dizziness (n = 7), tremor (n = 7), dyskinesia (n = 6), and asthenia (n = 6). Based on the data from these two studies in patients with early-stage PD, an overnight switch from oral dopamine agonists to the rotigotine transdermal patch was well tolerated with no loss in efficacy. To date, no studies have been published evaluating switching from oral dopamine agonists to rotigotine in patients with advanced-stage PD.

In 684 patients with moderate-to-severe RLS (72% female; mean age 65.6 years), Stiasny-Kolster et al. evaluated rotigotine treatment in a routine clinical practice setting in Germany over 3 months. In this clinical-practice study, 55% of patients (233/424) were switched directly or overnight to rotigotine monotherapy from previous monotherapy with levodopa (50.1% (202/403)), pramipexole (23.8% (96/403)), or ropinirole (10.2% (41/403)) without downtitration. More patients who were switched to rotigotine 1 mg/24 h had their dose adjusted during the first 4 weeks of rotigotine treatment than did patients started on 2 mg/24 hours. AEs were not reported by the investigators.

Discussion

Rotigotine has had an interesting history, as reflected in the drug’s development. The identification of rotigotine for its potent D2 receptor binding affinity led to further development of the molecule for possible application in PD. Continued investigation revealed that rotigotine also had high affinity for the D3 and D1 receptors, as well as the 5HT1A and adrenergic α2B receptors, which also may play an important role in PD. The limitation of extensive first-pass metabolism of rotigotine was overcome in large part by the molecule’s suitability for transdermal application. Transdermal application avoids first-pass metabolism and provides steady plasma concentrations of rotigotine over 24 h. This is an important concept in PD, as pulsatile stimulation of dopaminergic receptors is thought...
to contribute to the induction of dyskinesias and loss of treatment effectiveness, or “off time.”

The clinical studies of rotigotine in patients with early- and advanced-stage PD demonstrate that transdermal application of rotigotine effectively reduces the cardinal motor symptoms of the disease and decreases the emergence of early-morning motor symptoms. Clinical studies also have demonstrated the efficacy of rotigotine in treating the symptoms of RLS.

Continuous stimulation of dopaminergic receptors through continuous dopaminergic delivery is thought to more closely reflect the normal physiological state in which these receptors function. Largely developed with primate and rodent models involving chemical denervation of the dopaminergic systems (via MPTP and 6-OHDA), the continuous dopaminergic stimulation (CDS) theory suggests that the motor complications of PD result from intermittent or pulsatile stimulation of dopamine receptors, which causes intracellular changes and alterations in striatal neuron firing patterns. The concept is predicated on the assumption that a steady plasma profile of a dopaminergic agent will provide continuous dopaminergic receptor stimulation consistent with the normal basal state in humans. The concept of CDS, however, has its limitations. Although dopamine agonist formulations that provide a continuous delivery of the drug to the patient show reductions in off time, there currently is no published evidence demonstrating that a steady plasma profile of a dopaminergic agent leads to continuous receptor occupancy. In addition, the CDS animal model was in large part developed to explain the onset of dyskinesias in PD resulting from perturbations in the dopaminergic system. Clinically, PD is a much more complicated neurodegenerative disease involving Lewy body pathology resulting in motor and nonmotor complications. Given these limitations, however, the concept of CDS in the animal models has led to a better understanding of the underlying dynamics of the dopaminergic system that may lead to motor complications of PD and its treatment, and how to overcome these complications.

Clinical and pathological studies examining dopaminergic neurons and the responsiveness of RLS symptoms to dopamine agonists suggest an underlying central nervous system dopaminergic dysregulation in the underlying etiology of RLS. While symptoms of RLS mostly occur at night, patients with more severe disease may experience daytime or breakthrough symptoms, resulting in daytime sleepiness and fatigue. The clinical studies with rotigotine in patients with moderate-to-severe RLS established the effectiveness of rotigotine in treating the symptoms of the disease. Additionally, long-acting or continuously delivered agents providing stable plasma concentrations may play a relevant role in the treatment of unpredictable onset and severity of symptoms, daytime occurrence, and breakthrough symptoms.

The clinical studies for rotigotine, both in patients with PD and those with RLS, have suggested a favorable safety and tolerability profile. The most common AEs throughout the clinical studies in PD and RLS included nausea, somnolence, dizziness, and fatigue. ASRs are an AE specific to the rotigotine transdermal system and can be managed by regularly rotating the site of patch application. ICDS can also be a concern with rotigotine, as with all dopamine agonists, and patients should be evaluated regularly to assess the status of these disorders; dose reduction or stopping rotigotine should be considered if ICDS develop during rotigotine therapy. Postmarketing surveillance information on the total amount (mg) of rotigotine distributed is available from January 1, 2007 through January 31, 2014. In order to estimate cumulative patient exposure, three assumptions were made: the patients were fully compliant, the daily drug delivery was 6 mg/day, and that a year corresponded to 365.25 days. A total of 896,468,787 mg of rotigotine was distributed worldwide during the period from January 1, 2007 to January 31, 2014, representing 409,066 patient-years. During this period, the rotigotine transdermal system has shown a favorable benefit–risk balance. The safety profile of rotigotine remains consistent with the safety profile of currently marketed dopamine agonists and transdermal therapeutic systems. Based on the efficacy, safety profile, and data available during the review period, the benefit–risk balance of rotigotine transdermal patch for the treatment of signs and symptoms of idiopathic PD and for the symptomatic treatment of moderate-to-severe idiopathic RLS in adults remains favorable.

The early investigation of the biochemical and pharmacokinetic characteristics of rotigotine were, in large part, validated with the results of the
clinical studies in patients with PD or RLS. Overall, the transdermal route of administration was an innovative way to reach and maintain stable plasma levels and provide once-daily continuous stable delivery of rotigotine, avoiding pulsatile stimulation of dopamine receptors. However, no long-term, prospective, active comparator-controlled studies specifically designed to evaluate whether the continuous, stable plasma profile of rotigotine versus the pulsatile stimulation of dopaminergic receptors with levodopa or the oral dopamine agonists have been conducted. Studies such as these would enable a better understanding of the differences in motor outcomes or treatment-related AE profiles between these two drug delivery systems. This is particularly true when considering the long-term effects of treatment. A limitation of the rotigotine extension studies is that selection into long-term extension studies typically includes patients who have tolerated the treatment. Thus, the long-term studies with rotigotine in patients with PD and RLS may have been subject to selection bias for patients who tolerated rotigotine and/or the transdermal patch better than patients who discontinued use of the agent. In addition, because clinical studies provide an idealized treatment environment, more real-world, pragmatic studies in patients with early- and advanced-stage PD or RLS may offer better insights into the advantages and disadvantages of rotigotine transdermal treatment over other dopaminergic agents. Continuing basic and clinical research with rotigotine will provide a better understanding of PD and RLS and identify new therapeutic targets or treatment modalities to best benefit patients.

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Conflicts of interest

Arturo Benitez is an employee of UCB Inc., Smyrna, GA, and holds stock options from this employment. Heather Edens is an employee of UCB Inc., Smyrna, GA and reports no other conflicts of interest. Jesse Fishman is an employee of UCB Inc., Smyrna, GA and reports no other conflicts of interest. Kimberly Moran is an employee of UCB Inc., Smyrna, GA, and holds stock options from this employment. Mahnaz Asgharnejad is an employee of UCB Inc., Raleigh, NC, and holds stock options from this employment.

Supporting Information

Additional supporting information may be found in the online version of this article.

Figure S1. Overview of the chemical structure, composition, and application of the rotigotine transdermal patch. The * designates the chiral center.

Table S1. Summary of primary efficacy outcomes in rotigotine clinical studies for RLS.

References

1. Trenkwalder, C. & W. Paulus. 2010. Restless legs syndrome: pathophysiology, clinical presentation and management. Nat. Rev. Neuro. 6: 337–346.
2. Lees, A.J. et al. 2009. Parkinson’s disease. Lancet 373: 2055–2066.
3. Kowal, S.L. et al. 2013. The current and projected economic burden of Parkinson’s disease in the United States. Mov. Disord. 28: 311–318.
4. Olanow, C.W. et al. 2009. The scientific and clinical basis for the treatment of Parkinson disease (2009). Neurology 72: S1–S136.
5. National Institute of Neurological Disorders and Stroke. 2004. Parkinson’s disease backgrounder. March 25, 2014.http://www.ninds.nih.gov/disorders/parkinsons_disease/parkinsons_disease_backgrounder.htm.
6. Wirdefeldt, K. et al. 2011. Epidemiology and etiology of Parkinson’s disease: a review of the evidence. Eur. J. Epidemiol. 26(Suppl 1): S1–S38.
7. National Institute of Neurological Disorders and Stroke. 2010. Restless legs syndrome fact sheet. March 25, 2014. http://www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm.
8. Innes, K.E. et al. 2011. Prevalence of restless legs syndrome in North American and Western European populations: a systematic review. Sleep Med. 12: 623–634.
9. Ohayon, M.M. et al. 2012. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Med. Rev. 16: 283–295.
10. Allen, R.P. et al. 2005. Restless legs syndrome prevalence and impact: REST general population study. Arch. Intern. Med. 165: 1286–1292.
11. Antonini, A. et al. 2010. Rotigotine transdermal patch in the management of Parkinson’s disease (PD) and its nighttime use for PD-related sleep disorders. Funct. Neurol. 25: 21–25.
12. Elshoff, J.P. et al. 2012. Steady-state plasma concentration profile of transdermal rotigotine: an integrated analysis of three, open-label, randomized, phase I multiple dose studies. Clin. Ther. 34: 966–978.
13. Barone, P. et al. 2009. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson’s disease. Mov. Disord. 24: 1641–1649.
14. Rana, A.Q. et al. 2013. A cross-sectional study investigating clinical predictors and physical experiences of pain in Parkinson’s disease. *Funct. Neurol.* 28: 297–304.
15. Seppi, K. et al. 2011. The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson’s disease. *Mov. Disord.* 26(Suppl 3): S42–S80.
16. Pfeiffer, R.F. 2011. Gastrointestinal dysfunction in Parkinson’s disease. *Parkinsonism Relat. Disord.* 17: 10–15.
17. Antonini, A. et al. 2012. The progression of non-motor symptoms in Parkinson’s disease and their contribution to motor disability and quality of life. *J. Neurol.* 259: 2621–2631.
18. Breen, K.C. & G. Druyte. 2013. Non-motor symptoms of Parkinson’s disease: the patient’s perspective. *J. Neural Transm.* 120: 531–535.
19. Duncan, G.W. et al. 2014. Health-related quality of life in early Parkinson’s disease: the impact of nonmotor symptoms. *Mov. Disord.* 29: 195–202.
20. Martinez-Martin, P. et al. 2011. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson’s disease. *Mov. Disord.* 26: 399–406.
21. Santos-Garcia, D. & R. de la Fuente-Fernández. 2013. Impact of non-motor symptoms on health-related and perceived quality of life in Parkinson’s disease. *J. Neurol. Sci.* 332: 136–140.
22. Song, W. et al. 2014. The impact of non-motor symptoms on the health-related Quality of Life of Parkinson’s disease patients from Southwest China. *Parkinsonism Relat. Disord.* 20: 149–152.
23. Weerkamp, N.J. et al. 2013. Nonmotor symptoms in nursing home residents with Parkinson’s disease: prevalence and effect on quality of life. *J. Am. Geriatr. Soc.* 61: 1714–1721.
24. Jenner, P. et al. 2011. Continuous drug delivery in early- and late-stage Parkinson’s disease as a strategy for avoiding dyskinesia induction and expression. *J. Neural Transm.* 118: 1691–1702.
25. Lv, Q. & B. Zhang. 2013. Application of the concept of continuous dopaminergic stimulation for the management of Parkinson’s disease. *Neurosci. Bull.* 29: 661–669.
26. International Restless Legs Syndrome Study Group. 2012. 2012 Revised ILSSG diagnostic criteria for RLS. Accessed March 25, 2014. http://irlssg.org/diagnostic-criteria/.
27. Hening, W. et al. 2004. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. *Sleep Med.* 5: 237–246.
28. Tzonova, D. et al. 2012. Breakthrough symptoms during the daytime in patients with restless legs syndrome (Willis-Ekbom disease). *Sleep Med.* 13: 151–155.
29. Giannaki, C.D. et al. 2013. Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review. *Kidney Int.* 85: 1275–1282.
30. Allen, R.P. & C.J. Earley. 2007. The role of iron in restless legs syndrome. *Mov. Disord.* 22(Suppl 18): S440–S448.
31. Brandl, S. et al. 2013. Patients suffering from restless legs syndrome have low internal locus of control and poor psychological functioning compared to healthy controls. *Neuropsychobiology* 68: 51–58.
32. Cho, Y.W. et al. 2012. Assessing health-related quality of life in patients with restless legs syndrome in Korea: comparison with other chronic medical diseases. *Sleep Med.* 13: 1158–1163.
33. Dodel, R. et al. 2010. Health economic burden of patients with restless legs syndrome in a German ambulatory setting. *PharmacoEconomics* 28: 381–393.
34. Salas, R.E. & A.B. Kwan. 2012. The real burden of restless legs syndrome: clinical and economic outcomes. *Am. J. Manag. Care* 18: S207–212.
35. Scholz, H. et al. 2011. Psychological distress of patients suffering from restless legs syndrome: a cross-sectional study. *Health Qual. Life Outcomes* 9: 73.
36. Weström, J. et al. 2010. Health-related quality of life and restless legs syndrome among women in Sweden. *Psychiatry Clin. Neurosci.* 64: 574–579.
37. Ferini-Strambi, L. et al. 2013. The relationship among restless legs syndrome (Willis-Ekbom Disease), hypertension, cardiovascular disease, and cerebrovascular disease. *J. Neurol.* 261: 1051–1068.
38. Siddiqui, F. et al. 2007. Rise of blood pressure with periodic limb movements in sleep and wakefulness. *Clin. Neurophysiol.* 118: 1923–1930.
39. Jenner, P. 2005. A novel dopamine agonist for the transdermal treatment of Parkinson’s disease. *Neurology* 65(Suppl 1): S3–S5.
40. Horn, A.S. et al. 1984. N-0434, a very potent and specific new D-2 dopamine receptor agonist. *Eur. J. Pharmacol.* 99: 125–126.
41. Van der Weide, J. et al. 1986. Pharmacological profiles of three new, potent and selective dopamine receptor agonists: N-0434, N-0437 and N-0734. *Eur. J. Pharmacol.* 125: 273–282.
42. Belluzzi, J.D. et al. 1994. N-0923, a selective dopamine D2 receptor agonist, is efficacious in rat and monkey models of Parkinson’s disease. *Mov. Disord.* 9: 147–154.
43. Loschmann, P.A. et al. 1989. Stereoselective reversal of MPTP-induced parkinsonism in the marmoset after dermal application of N-0437. *Eur. J. Pharmacol.* 166: 373–380.
44. Scheller, D. et al. 2009. The in vitro receptor profile of rotigotine: a new agent for the treatment of Parkinson’s disease. *Naunyn. Schmiedebergs Arch. Pharmacol.* 379: 73–86.
45. Waters, C. 2013. The development of the rotigotine transdermal patch: a historical perspective. *Neuro. Clin.* 31: S37–50.
46. Millan, M.J. et al. 2002. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. *J. Pharmacol. Exp. Ther.* 303: 791–804.
47. Nicholson, S.L. & J.M. Brotchie. 2002. 5-hydroxytryptamine (5-HT, serotonin) and Parkinson’s disease—opportunities for novel therapeutics to reduce the problems of levodopa therapy. *Eur. J. Neurol.* 9(Suppl 3): 1–6.
48. Ohno, Y. 2011. Therapeutic role of 5-HT1A receptors in the treatment of schizophrenia and Parkinson’s disease. *CNS Neurosci. Ther.* 17: 58–65.
Development of rotigotine for PD and RLS
Benitez et al.

49. Chaudhuri, K.R. & A.H. Schapira. 2009. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 8: 464–474.

50. Barone, P. 2010. Neurotransmission in Parkinson's disease: beyond dopamine. Eur. J. Neurol. 17: 364–376.

51. Fox, S.H. et al. 2008. Non-dopaminergic treatments in development for Parkinson's disease. Lancet Neurol. 7: 927–938.

52. Remy, P. et al. 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128: 1314–1322.

53. Swart, P.J. & R.A. de Zeeuw. 1992. Extensive gastrointestinal metabolic conversion limits the oral bioavailability of the dopamine D2 agonist N-0923 in freely moving rats. Pharmazie 47: 613–615.

54. Swart, P.J. & R.A. de Zeeuw. 1993. Pharmacokinetics of the dopamine D2 agonist S(-)-2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin in freely moving rats. J. Pharm. Sci. 82: 200–203.

55. Schmidt, W.I. et al. 2008. Continuous versus pulsatile administration of rotigotine in 6-OHDA-lesioned rats: contralateral rotations and abnormal involuntary movements. J. Neural Transm. 115: 1385–1392.

56. Stockwell, K.A. et al. 2009. Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction. Exp. Neurol. 219: 533–542.

57. UCB Pharma. 2013. Neupro® (rotigotine transdermal system) (U.S. prescribing information). March 25, 2014. Revised 2013. www.accessdata.fda.gov/drugsatfda_docs/label/.../021829s002lbl.pdf.

58. Chaudhuri, K.R. 2008. Crystallisation within transdermal rotigotine patch: is there cause for concern? Expert Opin. Drug Deliv. 5: 1169–1171.

59. Elshoff, J.P. et al. 2013. Comparison of the bioavailability and adhesiveness of different rotigotine transdermal patch formulations. Curr. Med. Res. Opin. 29: 1657–1662.

60. UCB Pharma. 2013. Annex 1: Summary of Product Characteristics (Neupro® (rotigotine transdermal patch)). March 25, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000626/WC500026397.pdf.

61. Cawello, W. et al. 2009. Absorption, disposition, metabolic fate, and elimination of the dopamine agonist rotigotine in man: administration by intravenous infusion or transdermal delivery. Drug Metab. Dispos. 37: 2055–2060.

62. Cawello, W. et al. 2007. Transdermal administration of radiolabelled (14C)rotigotine by a patch formulation: a mass balance trial. Clin. Pharmacokinet. 46: 851–857.

63. Malik, M. et al. 2008. Thorough QT/QTc study in patients with advanced Parkinson's disease: cardiac safety of rotigotine. Clin. Pharmacol. Ther. 84: 595–603.

64. Hansen, K. et al. 2005. Low drug–drug interaction potential of rotigotine. J. Clin. Pharmacol. 45: 1091.

65. Elshoff, J. et al. 2014. No influence on the CYP2C19-selective inhibitor omeprazole on the pharmacokinetics of the dopamine receptor agonist rotigotine. Clin. Pharmacol. Drug Dev. 3: 187–193.

66. Braun, M. et al. 2009. Influence of domperidone on pharmacokinetics, safety and tolerability of the dopamine agonist rotigotine. Br. J. Clin. Pharmacol. 67: 209–215.

67. Braun, M. et al. 2009. Lack of pharmacokinetic interactions between transdermal rotigotine and oral levodopa/carbidopa. J. Clin. Pharmacol. 49: 1047–1055.

68. Araujo, S.M. et al. 2010. Restless legs syndrome in end-stage renal disease: clinical characteristics and associated comorbidities. Sleep Med. 11: 785–790.

69. Gigli, G.L. et al. 2004. Restless legs syndrome in end-stage renal disease. Sleep Med. 5: 309–315.

70. Lin, C.H. et al. 2013. Restless legs syndrome in end-stage renal disease: a multicenter study in Taiwan. Eur. J. Neurol. 20: 1025–1031.

71. Takaki, J. et al. 2003. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. Am. J. Kidney Dis. 41: 833–839.

72. Cawello, W. et al. 2012. Single dose pharmacokinetics of the transdermal rotigotine patch in patients with impaired renal function. Br. J. Clin. Pharmacol. 73: 46–54.

73. Cawello, W. et al. 2013. Influence of hepatic impairment on the pharmacokinetics of the dopamine agonist rotigotine. Eur. J. Drug Metab. Pharmacokinet. Sep 20. (Epub ahead of print).

74. Braun, M. et al. 2009. Influence of transdermal rotigotine on ovulation suppression by a combined oral contraceptive. Br. J. Clin. Pharmacol. 68: 386–394.

75. Elmer, L.W. et al. 2012. Long-term safety and tolerability of rotigotine transdermal system in patients with early-stage idiopathic Parkinson’s disease: a prospective, open-label extension study. Parkinsonism Relat. Disord. 18: 488–493.

76. Giladi, N. et al. 2007. Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. Mov. Disord. 22: 2398–2404.

77. Giladi, N. et al. 2013. The safety and tolerability of rotigotine transdermal system over a 6-year period in patients with early-stage Parkinson's disease. J. Neural Transm. 120: 1321–1329.

78. LeWitt, P.A. et al. 2012. Rotigotine transdermal system for long-term treatment of patients with advanced Parkinson’s disease: results of two open-label extension studies, CLEOPATRA-PD and PREFER. J. Neural Transm. 120: 1069–1081.

79. LeWitt, P.A. et al. 2007. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology 68: 1262–1267.

80. Poewe, W.H. et al. 2007. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol. 6: 513–520.

81. The Parkinson Study Group. 2003. A controlled trial of rotigotine monotherapy in early Parkinson's disease. Arch. Neurol. 60: 1721–1728.

82. Tenkwalder, C. et al. 2012. Rotigotine transdermal system for the management of motor function and sleep disturbances in Parkinson's disease: Results from a 1-year,
Development of rotigotine for PD and RLS

open-label extension of the RECOVER study. *Basal Ganglia* 2: 79–85.

83. Trenkwalder, C. et al. 2011. Rotigotine effects on early morning motor function and sleep in Parkinson’s disease: a double-blind, randomized, placebo-controlled study (RECOVER). *Mov. Disord.* 26: 90–99.

84. Watts, R.L. et al. 2007. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology* 68: 272–276.

85. Pham D.Q. & A. Nogid. 2008. Rotigotine transdermal system for the treatment of Parkinson’s disease. *Clin. Ther.* 30: 813–824.

86. Oertel, W. et al. 2013. Treatment of patients with early and advanced Parkinson’s disease with rotigotine transdermal system: age-relationship to safety and tolerability. *Parkinsonism Relat. Disord.* 19: 37–42.

87. Trenkwalder, C. et al. 2011. Parkinson’s disease sleep scale—validation of the revised version PDSS-2. *Mov. Disord.* 26: 644–652.

88. Trenkwalder, C. et al. 2008. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 7: 595–604.

89. Hening, W.A. et al. 2010. Rotigotine improves restless legs syndrome: a 6-month randomized, double-blind, placebo-controlled trial in the United States. *Mov. Disord.* 25: 1675–1683.

90. Bauer, A. et al. 2013. The effect of rotigotine transdermal system on nocturnal systolic blood pressure elevations associated with periodic leg movements in patients with restless legs syndrome (abstract). *J. Clin. Hyperten.* 15(Suppl 1): 12.

91. Benes, H. et al. 2012. Augmentation in the treatment of restless legs syndrome with transdermal rotigotine. *Sleep Med.* 13: 589–597.

92. Dohin, E. et al. 2013. Safety and efficacy of rotigotine transdermal patch in patients with restless legs syndrome: a post-hoc analysis of patients taking 1–3 mg/24 h for up to 5 years. *Expert Opin. Pharmacother.* 14: 15–25.

93. Oertel, W. et al. 2011. Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study. *Lancet Neurol.* 10: 710–720.

94. Oertel, W.H. et al. 2008. Efficacy of rotigotine transdermal system in severe restless legs syndrome: a randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. *Sleep Med.* 9: 228–239.

95. Oertel, W.H. et al. 2010. Rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome: a randomized, placebo-controlled polysomnographic study. *Sleep Med.* 11: 848–856.

96. García-Borreguero, D. & A.M. Williams. 2010. Dopaminergic augmentation of restless legs syndrome. *Sleep Med. Rev.* 14: 339–346.

97. García-Borreguero, D. et al. 2007. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. *Sleep Med.* 8: 520–530.

98. Innes, K.E. et al. 2011. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. *Sleep Med. Rev.* 16: 309–339.

99. Hassan, A. et al. 2011. Dopamine agonist-triggered pathological behaviors: surveillance in the PD clinic reveals high frequencies. *Parkinsonism Relat. Disord.* 17: 260–264.

100. Kelley, B.J. et al. 2012. Dopamine agonists and pathologic behaviors. *Parkinsons Dis.* 2012: 603631.

101. Voon, V. & S.H. Fox. 2007. Medication-related impulse control and repetitive behaviors in Parkinson disease. *Arch. Neurol.* 64: 1089–1096.

102. Weintraub, D. et al. 2010. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch. Neurol.* 67: 589–595.

103. Zesiewicz, T.A. & P. Martinez-Martin. 2013. Effects of rotigotine transdermal system on non-motor symptoms in Parkinson’s disease: an overview. *Expert Rev. Neurother.* 13: 1329–1342.

104. García-Ruiz, P.J. et al. 2014. Impulse control disorder in patients with Parkinson’s disease under dopamine agonist therapy: a multicentre study. *J. Neurol. Neurosurg. Psychiatry.*

105. Voon, V. et al. 2011. Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome. *BMC Neurol.* 11: 117.

106. Wingo, T.S. et al. 2009. Impulse control disorders arising in 3 patients treated with rotigotine. *Clin. Neuropharmacol.* 32: 59–62.

107. Cornelius, J.R. et al. 2010. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. *Sleep* 33: 81–87.

108. Schreglmann, S.R. et al. 2012. Transdermal rotigotine causes impulse control disorders in patients with restless legs syndrome. *Parkinsonism Relat. Disord.* 18: 207–209.

109. LeWitt, P.A. et al. 2007. Overnight switch from oral dopaminergic agonists to transdermal rotigotine patch in subjects with Parkinson disease. *Clin. Neuropharmacol.* 30: 256–265.

110. Kim, H.J. et al. 2011. Overnight switch from ropinirole to transdermal rotigotine patch in patients with Parkinson disease. *BMC Neurol.* 11: 100.

111. Stiasny-Kolster, K. et al. 2013. Effectiveness and tolerability of rotigotine transdermal patch for the treatment of restless legs syndrome in a routine clinical practice setting in Germany. *Sleep Med.* 14: 475–481.

112. Senek, M. & D. Nyholm. 2014. Continuous drug delivery system for the treatment of restless legs syndrome. *CNS Drugs* 28: 19–27.

113. Jenner, P. 2004. Avoidance of dyskinesia: preclinical evidence for continuous dopaminergic stimulation. *Neurology* 62: S47–55.

114. Chaudhuri, K.R. et al. 2013. Motor and nonmotor complications in Parkinson’s disease: an argument
Development of rotigotine for PD and RLS

for continuous drug delivery? *J. Neural Transm.* **120**: 1305–1320.

115. Ahlskog, J.E. 2007. Beating a dead horse: dopamine and Parkinson disease. *Neurology* **69**: 1701–1711.

116. Jenner, P. 2009. From the MPTP-treated primate to the treatment of motor complications in Parkinson’s disease. *Parkinsonism Relat. Disord.* **15**(Suppl 4): S18–23.

117. Rascol, O. & S. Perez-Lloret. 2009. Rotigotine transdermal delivery for the treatment of Parkinson’s disease. *Expert Opin. Pharmacother.* **10**: 677–691.

118. Ghys, L. *et al.* 2011. Effect of rotigotine on sleep and quality of life in Parkinson’s disease patients: post hoc analysis of RECOVER patients who were symptomatic at baseline. *Expert Opin. Pharmacother.* **12**: 1985–1998.