Common Drug Review

Clinical Review Report (Resubmission)

November 2015

Drug	Rotigotine (Neupro)
Indication	Treatment of the signs and symptoms of idiopathic Parkinson's disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Listing request	As adjunctive therapy to levodopa for the treatment of patients with advanced Parkinson's disease.
Manufacturer	UCB Canada Inc.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
APD	advanced Parkinson's disease
CDR	Common Drug Review
CDEC	Canadian Drug Expert Committee
CGI	Clinical Global Impression
COMT	catechol-O-methyl transferase
CI	confidence interval
DA	dopamine agonist
DB	double-blind
EPD	early Parkinson's Disease
EMA	European Medicines Agency
ER	extended release
FAS	full analysis set
HRQoL	health-related quality of life
IR	immediate release
LOCF	last observation carried forward
MAO-B	monoamine oxidase B
MTC	multiple treatment comparison
MCID	minimal clinically important difference
NMA	network meta-analysis
NMDA	N-methyl-D-aspartate
ONW	*on* without dyskinesia
ONT	*on* with troublesome dyskinesia
PPS	per-protocol set
PD	Parkinson's disease
PDHD	Parkinson's Disease Home Diaries
PDQ	Parkinson's Disease Questionnaire
PDSS	Parkinson's Disease Sleep Scale
PSC	Parkinson Society Canada
QoL	quality of life
RCT	randomized controlled trial
RLS	restless legs syndrome
SAE	serious adverse event
TEAE	treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Idiopathic Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by the loss of dopaminergic nerve cells in the substantia nigra (midbrain). This results in a deficiency of the neurotransmitter dopamine in the striatum, a portion of the brain involved in coordinating body movement. Clinical hallmarks of the disease are postural instability, tremor, rigidity, and bradykinesia, or slowness of movement. There are a wide range of non-motor features associated with PD, including cognitive impairment and dementia, autonomic dysfunction (e.g., orthostatic hypotension), and nocturnal sleep disturbances. Rotigotine is a non-ergolinic dopamine agonist (DA) with an approved indication in Canada for the treatment of signs and symptoms of idiopathic PD in adults, both as monotherapy in early Parkinson's disease (EPD) and as an adjunct to levodopa in advanced Parkinson's disease (APD).[1] Rotigotine is also approved in Canada for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS) in adults.[1]

Rotigotine is formulated as 5 cm^2, 10 cm^2, 15 cm^2, 20 cm^2, 30 cm^2, and 40 cm^2 transdermal patches, which contain nominal doses of 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, and 8 mg of rotigotine. The recommended starting dose for PD is 2 mg/24 h, and the maximum dose for EPD is 8 mg/24 h; for APD, it is 16 mg/24 h. Multiple patches are used to achieve doses higher than 8 mg/24 h.

Indication under review
Treatment of the signs and symptoms of idiopathic Parkinson's disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Listing criteria requested by sponsor
Use of rotigotine as adjunctive therapy to levodopa for the treatment of patients with advanced Parkinson's disease.

An initial submission for the treatment of idiopathic PD was considered by the Canadian Drug Expert Committee (CDEC) in February 2014, and reconsidered in May 2014, with a recommendation of "do not list".[2] The reason for the recommendation was the uncertain comparative clinical benefit of rotigotine versus other, less costly non-ergolinic DAs, i.e., immediate release (IR) oral formulations of ropinirole and pramipexole. Two phase 3 randomized controlled trials (RCTs), one in EPD (SP513) and one in APD (SP515), failed to demonstrate consistently that rotigotine was non-inferior to ropinirole (SP513)[3] or pramipexole (SP515).[4] In the EPD trial, rotigotine failed to show non-inferiority against ropinirole for improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (activities of daily living [ADL]) + Part III (motor function) subtotal score and for the number of responders achieving at least a 20% reduction in the subtotal score.[4] In the APD trial, non-inferiority against pramipexole was demonstrated for the absolute reduction in time spent *off* but not for the number of responders achieving a 30% or more reduction in *off* time. ("*On*" time for Parkinson's patients refers to times when medications are working and symptoms are controlled; "*off*" time refers to periods when patients experience more symptoms, i.e., a state of decreased mobility.) CDEC noted there were insufficient data to confirm the benefit of transdermal administration compared with oral administration with respect to patient adherence and clinical end points, and that application site reactions were the most commonly reported adverse events (AEs) leading to discontinuation by rotigotine-treated patients in both SP512

(5%) and SP513 (8%). CDEC also noted there was insufficient evidence about the long-term efficacy of rotigotine.

The basis of the manufacturer's resubmission is new clinical information: specifically, two RCTs in the subgroup of patients with APD, including one active comparator trial, and a change in price for the incremental doses of rotigotine ([redacted]).[5] There is also a change in the manufacturer's requested listing, which is restricted to the use of rotigotine as adjunctive therapy to levodopa for the treatment of patients with APD.

The objective of this report is to update the original CADTH Common Drug Review (CDR) by conducting a systematic review of the new clinical evidence on the beneficial and harmful effects of rotigotine for the signs and symptoms of idiopathic PD. Although the manufacturer has requested a listing restricted to APD, both EPD and APD are included in this review because the Health Canada–approved indication is for both subgroups of patients.

The only substantive change to the review protocol, compared with the protocol for the prior CDR review, is the removal of a restriction to RCTs of ≥ 16 weeks in duration; CDR review protocols no longer exclude studies based on duration. Studies included in the previous CDR review are excluded from this review, which focuses on new information only. However, because of the removal of the restriction on trial length, the excluded trials from the original review were reassessed to determine their eligibility for this review.

Results and Interpretation

Included Studies

Three published, parallel-group, double-blind (DB) RCTs met the inclusion criteria for this review: two trials that enrolled patients with APD,[6-9] and a third trial involving patients with PD of all stages, but predominantly APD (mixed population).[10-14] The latter trial had been excluded from the prior CDR review on the basis of duration. Only one trial, Mizuno 2014, was an active comparator trial.[6,7] The three trials were of ≤ 16 weeks' duration and were of similar overall design, with a titration phase of eight to 12 weeks, depending on the trial, followed by a maintenance phase of four weeks during which the test drug dose could not be changed. Rotigotine was initiated at 2 mg/24 h and titrated up on the basis of symptom control and tolerability to a maximum of 16 mg/24 h.

Mizuno 2014 (N = 420) was a 16-week, three-group, phase 3 trial conducted in Japan that compared rotigotine with placebo and ropinirole as adjunct therapy to levodopa in APD.[6] The dose of ropinirole was up to a maximum of 15 mg/day, less than the allowable maximum dose of 24 mg/day in Canada. The dose of up to 15 mg/day is consistent with usual clinical practice, according to the clinical expert involved in this review. All patients were experiencing levodopa-associated issues such as *off* time (68%), dyskinesia (6% to 14%), and early morning dystonia (15%). The study was designed to demonstrate superiority to placebo and non-inferiority to ropinirole in a hierarchical manner for the primary outcome, the UPDRS Part III sum score. The UPDRS Part III is a widely used, clinician-assessed score evaluating various aspects of motor function, including speech, limb function, postural instability, and gait.

The other two trials were placebo-controlled only. Nomoto 2014 (N = 174), also conducted in Japan, was a two-group, phase 3 trial of 12 to 14 weeks' duration. It enrolled a population similar to that enrolled in Mizuno 2014, i.e., patients with APD who were experiencing issues with levodopa.[8] Rotigotine as adjunct therapy was compared with placebo for improvement in the same primary outcome, the UPDRS

Part III sum score. The third trial, SP889 (N = 336), a two-group, phase 3 trial of 12 weeks' duration, enrolled patients who had investigator-defined unsatisfactory control of early morning symptoms and PD of any stage.[10] Although the use of levodopa was not a requirement for enrolment in SP889, the majority of patients had APD, and approximately 80% were on levodopa. SP889 evaluated two co-primary outcomes: UPDRS Part III sum score in the early morning period before re-application of a transdermal patch; and nocturnal sleep disturbances as measured by a modified version of the Parkinson's Disease Sleep Score (PDSS-2).

Several key limitations or features of the trials' methods are worth noting. The two trials conducted in Japan used a dynamic allocation process for randomization that could potentially compromise the concealment of allocation, particularly in Mizuno 2014, which sought to balance groups on a number of factors.[6,8] SP889 stratified randomization by site and did not report sufficient information on the generation of the computerized randomization sequence to assess potential for risk of bias. The high incidence of application site reactions may have compromised blinding, particularly for Mizuno 2014[6] and Nomoto 2014.[8] SP889 had early termination of recruitment because of a manufacturing change in rotigotine, which reduced the power of the trial but still provided an acceptable probability of a type II error.[10] [redacted][7] [redacted].[15] [redacted] In SP889, the potential interdependence of the primary outcomes was not addressed. The Japanese trials[6,8] enrolled more females than males, and used lower average doses of levodopa than might be encountered in North American populations — features that could limit the trials' applicability to usual clinical practice in Canada. In Mizuno 2014, there is uncertainty about whether rotigotine and ropinirole were administered at clinically equivalent doses; a higher average dose of rotigotine was used.

Efficacy

For efficacy outcomes reported as continuous measures, a negative value for the mean difference in the change from baseline between groups indicates a result in favour of rotigotine. The primary pre-specified analyses for continuous measures were identified as adjusted means in Mizuno 2014[6] and SP889,[10] and unadjusted means in Nomoto 2014.[8] For dichotomous outcomes (responders), a positive value indicates there were more responders in the rotigotine group compared with the control.

For the comparison of rotigotine versus ropinirole, Mizuno 2014 demonstrated non-inferiority of rotigotine for motor function as measured by the UPDRS Part III sum score using a preset non-inferiority margin of 2.5 points for the upper boundary of the 95% confidence interval [CI] (Table 1). The non-inferiority margin appears reasonable, taking into account the available minimal clinically important difference (MCID) of 6.5 points, according to the clinical expert involved in this review. In a per-protocol analysis, the between-group adjusted mean difference in change from baseline was [redacted] (95% CI, [redacted]). Because the upper limit of the 95% CI did not cross the preset non-inferiority margin of 2.5, rotigotine was shown to be non-inferior to ropinirole. An analysis using the full analysis set (FAS) with last observation carried forward (LOCF) was consistent with the per-protocol analysis. Although 11% (95% CI, 2% to 21%) more patients on rotigotine achieved a 20% reduction in UPDRS Part III sum scores compared with ropinirole, this percentage reduction from baseline corresponds to a change of approximately five points, which is an amount less than the published MCID of 6.5 points. The proportion of patients who responded to treatment with a 30% reduction in UPDRS Part III, corresponding to an amount that exceeds the MCID, was not statistically significantly different between rotigotine and ropinirole. Ropinirole reduced *off* time by 0.5 hours more than rotigotine, but the

difference was not statistically significant and is less than the range of values reported as MCIDs (1.3 to 1.9 hours). There was no statistically significant between-group difference in the adjusted mean change from baseline in nocturnal sleep disturbance as measured by PDSS-2 scores: –0.7 points (95% CI, –1.9 to 0.6). For PDSS-2, a published MCID is not available to help interpret the clinical relevance of these findings.

For the comparison of rotigotine versus placebo, in the APD trials,[6,8] rotigotine was statistically significantly superior to placebo for improvement in the UPDRS Part III sum score from baseline to the end of the maintenance period. At the end of the maintenance phase, in Mizuno 2014, the between-group adjusted mean difference from baseline was –6.4 points (95% CI, –8.7 to –4.1), an amount that approximates the MCID (6.5 points). In the smaller phase 2 trial, Nomoto 2014, there was a between-group unadjusted mean difference of similar magnitude, –5.7 points (95% CI, –8.2 to –3.2), which was slightly less than the MCID. In Mizuno 2014, rotigotine statistically significantly reduced *off* time to a greater extent than placebo by an adjusted mean difference of 1.1 hours, an amount close to the lower limit of the range of published MCIDs (1.3 hours to 1.9 hours). In Nomoto 2014, the unadjusted mean difference in *off* time was similar in magnitude: 1.4 hours (95% CI, –2.5 to –0.3). Numerically more patients treated with rotigotine achieved a ≥ 30% reduction in time spent *off* compared with placebo in both trials, but the between-group difference for each trial was not statistically significant. There was a statistically significant difference between rotigotine and placebo for the adjusted mean difference in PDSS-2 scores in Mizuno 2014: –2.6 points (95% CI, –4.1 to –1.1). However, it was noted that the unadjusted mean difference in PDSS-2 scores [redacted](95% CI, [redacted]) [redacted]. In the absence of published MCID values for the PDSS-2, interpretation of these findings is limited. Overall, the efficacy treatment effect sizes versus placebo were consistent with findings reported in the prior CDR review for SP515[4] and SP650.[16]

Neither of the two APD trials included a measure of patient-reported health-related quality of life (HRQoL) or patient and caregiver satisfaction with treatment. Adherence was high in both trials, but not reported separately by treatment group for Mizuno 2014. There were no patients who had < 85% adherence in Nomoto 2014, except for three patients with < 14 days adherence — one in the rotigotine group and two in the placebo group. They were excluded from analysis altogether.

In the mixed population trial, SP889, rotigotine was statistically significantly superior to placebo in reducing the early morning UPDRS Part III sum score, with an adjusted between-group mean difference of –3.6 points (95% CI, –5.4 to –1.7). An MCID is not available for this specific time period (an *off* state). The trial used a practical definition of *off* time (i.e., early morning), and did not report the proportion of patients experiencing *off* time throughout the day, or absolute change in *off* time. For the co-primary outcome — nocturnal sleep disturbance, as assessed by PDSS-2 scores — there was a statistically significant between-group adjusted mean difference of –4.3 points (95% CI, –6.1 to –2.5). In the absence of published MCID values for the PDSS-2, interpretation of these findings is limited.

A short form of the Parkinson's Disease Questionnaire, PDQ-8, was used to assess patient-reported quality of life (QoL) and was considered an exploratory outcome only. A between-group adjusted mean difference in the change from baseline in PDQ-8 was –5.7 points (95% CI, –8.7 to –2.8). For PDQ-8, published MCID values for health status worsening "only a little bit" ranged from 5.8 to 7.4 points, although it is unclear if these values directly apply to improvement in health status rather than worsening. Adherence was defined by the use of > 85% to < 115% of medication and assessed by returned medication; 83% of the rotigotine group and 76% of the placebo group were adherent. The

method used to assess adherence may not be the most accurate approach, as medication that was not returned may not have been used.

The prior CDR review included one 23-week trial in APD patients that failed to demonstrate consistent non-inferiority of rotigotine versus another non-ergolinic DA, pramipexole. There were two primary outcomes tested for non-inferiority because of the different regulatory requirements of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These were tested in a stepped procedure. In that trial, non-inferiority was demonstrated on the basis of reduced absolute time spent *off* (the primary outcome for the US FDA), but not for the proportion of responders achieving a 30% or more reduction in *off* time (the primary outcome for the EMA). Mizuno 2014 is the second non-inferiority trial for use of rotigotine as adjunct therapy in patients with APD, and demonstrates non-inferiority for a different efficacy outcome (UPDRS Part III motor sum score) against a different comparator (ropinirole).

Harms

The overall frequency of treatment-emergent adverse events (TEAEs) was generally high across treatment groups in all three studies (Table 1 and Table 2). In the APD studies, the proportion of patients experiencing one or more AEs was 89%, 78%, and 69% in the rotigotine, ropinirole, and placebo groups, respectively, in Mizuno 2014, and 94% and 89% in the rotigotine and placebo groups, respectively, in Nomoto 2014. In SP889, 72% and 62% of patients in the rotigotine and placebo groups, respectively, experienced one or more AE. Withdrawals due to adverse events (WDAEs) (6% to 10%) and serious adverse events (SAEs) (3% to 7%) were similar in frequency across treatment groups within the trials.

In the one active comparator trial, 11% more patients experienced one or more AEs in the rotigotine group compared with ropinirole.[6] The AE profiles of rotigotine and ropinirole were similar except for the higher frequency of application site reactions associated with rotigotine, occurring in 58% and 19% of patients in the rotigotine and ropinirole treatment groups respectively. Dyskinesia was experienced by 16% of patients treated with rotigotine and 14% of patients treated with ropinirole. Somnolence was reported in 7% of patients treated with rotigotine and 5% of patients treated with ropinirole. There was a similar frequency of vomiting (7% in each treatment group) and perception disturbances (10% in each treatment group, mainly hallucinations of any type). There were no deaths in the active drug groups, and the frequency of discontinuations due to AEs (8% in each group) and non-fatal SAEs (3% to 4%) were similar. One patient in each active drug group (0.6%) had sudden onset of sleep (sleep attacks). For obsessive-compulsive disorders (OCDs), no events were reported as clinical AEs. However, on the screening interview for impulse control disorders, 4.2% of patients in the rotigotine group and 6.6% of patients in the ropinirole treatment group had positive findings on a gateway question with or without affirmative responses on the remaining questions. There were no events of valvulopathy. Three patients in the rotigotine group (1.8%) and no patients in the ropinirole group (0%) experienced syncope. [redacted].[7] The trial was limited in its ability to capture uncommon events because of sample size.

The AE profile for the comparison of rotigotine versus placebo was similar to that previously reported; application site reactions were the most common rotigotine-associated AE, with more dyskinesia, nausea, perception disturbances or hallucination, vomiting, and somnolence also associated with rotigotine. In Nomoto 2014, 66% of patients in the rotigotine group had application site reactions compared with 25% in the placebo group. In Study SP889, 15% and 4% of participants in the rotigotine and placebo groups had application site reactions, respectively. The lower incidence of application site

reactions in SP889 appeared less typical, and may have reflected a lower average dose of rotigotine and/or a shorter duration of exposure overall. Other AEs that differed between rotigotine and placebo in Nomoto 2014 were constipation, postural dizziness, and anorexia.
The included trials were relatively short (12 weeks to 16 weeks) and do not provide information on the longer-term efficacy or AEs of rotigotine. This may be particularly important given the changes in neuromodulation that occur with disease progression and/or with medication use.

A manufacturer-sponsored network meta-analysis (NMA) combined direct and indirect RCT evidence to compare non-ergolinic DAs as adjunct therapies in APD and as monotherapies in EPD. This study was summarized on the basis of its study report as supplemental information in the prior CDR review and has since been published. When pramipexole, ropinirole, and rotigotine were compared with each other, their effect estimates were similar and did not reach statistical significance in EPD or APD. AEs were not incorporated into the NMA. A systematic review by Zhou et al. compared the efficacy, tolerability, and safety of long-acting non-ergolinic DAs (i.e., pramipexole extended release [ER], ropinirole prolonged release, or rotigotine transdermal patch) with standard release pramipexole or ropinirole in patients with EPD and APD. Eight DB RCTs of up to 37 weeks' duration were included, with four studies each in patients with EPD and APD. Individual drugs were pooled within each category and no information was provided on drug dosages. The only included rotigotine trials were Giladi et al. 2007 in EPD (comparator: ropinirole IR)[3] and Poewe et al. 2007 in APD (comparator: pramipexole IR).[4]
Tolerability was similar among long- and short-acting DAs, with no statistically significant differences detected in overall withdrawals, WDAEs, withdrawals due to lack of efficacy, SAEs, or common AEs. These data are limited, and are insufficient to assess or draw conclusions about the comparative risks of rotigotine versus other non-ergolinic DAs, because the trials pooled rotigotine with other long-acting drugs.

Comparative RCT data are sparse. There are no comparative RCTs that have assessed the role of rotigotine in patients who might be intolerant of other non-ergolinic DAs or in those who have gastrointestinal problems (e.g., dysphagia, gastroparesis). A transdermal application system may be perceived as a useful alternative to oral drugs in patients who have severe gastrointestinal problems (e.g., dysphagia, gastroparesis) — issues that occur more commonly in APD. However, it is not known whether rotigotine is as efficacious as the short-acting oral formulations of ropinirole and pramipexole because the only available trials were designed as non-inferiority trials. For APD, there are no long-term efficacy comparative data, as the trial in this review was 16 weeks long, and in the prior review, 23 weeks long. Therefore, it is not known whether a long-acting formulation with continuous exposure to a drug offers any advantage, in the long term, for control of motor symptoms when used on a chronic basis. There is also insufficient evidence to conclude that rotigotine has an advantage over short-acting, oral, non-ergolinic DAs to control non-motor symptoms, such as sleep disturbances, or to improve HRQoL. No comparative long-term safety data are available that assess the comparative risk of serious but relatively uncommon events, including arrhythmias and sudden death. There are also no long-term comparative efficacy data.

Based on differences in recommended dose, concomitant medications, and disease features, the findings in this review cannot be generalized to the use of rotigotine monotherapy in EPD, Thus, this review provides no additional comparative evidence to support the use of rotigotine in EPD.

Supplementary Information on Harms
In open-label extension studies [redacted]

[redacted][17-19].
Interpretation of these data is limited because of the uncontrolled nature of the data and the highly selected population: the majority had previously demonstrated they could tolerate a non-ergolinic DA. Among the most common AEs reported were application site reactions, dyskinesia, somnolence, hallucinations and delusions, nausea, falls, dizziness, and (in one study) feeling abnormal. The number of patients experiencing SAEs ranged from 6% to 19%, and 13% to 19% withdrew because of AEs. Gastric ulcer hemorrhage occurred as an SAE in three patients (0.9% of the total study population) in the largest study (N = 321 patients with APD), which was conducted in Japan, a region that has a higher incidence of gastric ulcers than Western countries.[20] In the three open-label extension phases, the frequency of sudden onset of sleep ranged from 0.8% to 3.6%; syncope from 0% to 1.2% (two studies); impulse control disorder from 0.8% to 1.2%; and arrhythmias from 0% to 0.3% (two studies). There were no valvulopathy events reported in any of the extension studies.

There was one sudden death in each of the open-label extension studies (incidence ranging from 0.3% to 1.9%). Two of the patients had underlying cardiovascular disease; therefore, the relation of the sudden deaths to rotigotine is uncertain, particularly in the absence of autopsy information about any other acute cardiovascular event. One death was reported to be unrelated to rotigotine; another was evaluated as related to rotigotine; and the relationship of the third death to rotigotine could not be ascertained in the absence of a translated clinical study report.

The only new supplementary information on rotigotine use in patients with EPD was a pooled post hoc analysis of the incidence of dyskinesia in two open-label extension studies of up to six years' duration. In the pooled population (N = 596), 19% of patients developed dyskinesia.[21] Of the patients who were not taking levodopa (N = 173), approximately 15% developed dyskinesia, with a median onset approximately 2.5 years earlier than those who developed dyskinesia on levodopa. It is unknown whether these patients have any distinguishing clinical characteristics that confer susceptibility to dyskinesia. Dyskinesia in the absence of levodopa has also been reported for pramipexole and ropinirole.[22,23] This study, which is exploratory only, does not provide comparative data with which to evaluate whether any particular DA is associated with less dyskinesia.

Supplementary Information on Efficacy

In the uncontrolled, open-label, single-group studies Mizuno 2014 and SP889, the observed improvement in efficacy slightly diminished over the one-year period, but no statistical analysis was performed. It is not possible to distinguish whether this might represent disease progression or tolerance; therefore, conclusions cannot be drawn from these data.

Potential Place in Therapy[1]

Dysphagia is one of the many problems faced by patients (and their caregivers) with advancing PD. In addition to its impact on feeding and on increasing the risk of aspiration pneumonia, dysphagia can become an important barrier to the reliable administration of oral antiparkinsonian medications. Currently in Canada, all approved antiparkinsonian medications are administered only by mouth. A drug that could be given by a non-oral route would be potentially useful in APD.

[1] Based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The evidence from the clinical trial considered in this review suggests that transdermal rotigotine has efficacy that is non-inferior to ropinirole in APD. In the original review, one trial in patients with EPD failed to demonstrate non-inferior efficacy of rotigotine to ropinirole; one trial in APD showed inconsistent non-inferiority to pramipexole. Rotigotine might be an alternative to ropinirole or pramipexole for the treatment of APD, but not EPD. Transdermal rotigotine may find a niche in APD patients whose oropharyngeal dysfunction interferes significantly with taking pills orally; a once daily rotigotine skin patch could replace oral ropinirole three times daily, or pramipexole, in this specific population. Such patients would be readily identified at follow-up clinic visits by asking the patient or caregiver whether there are any difficulties taking medicines by mouth. No special testing, imaging, or other investigations would be needed.

Conclusions

Based on two DB RCTs in patients with APD, rotigotine adjunct therapy resulted in statistically significant and clinically meaningful improvements in UPDRS Part III motor function and time spent *off* compared with placebo. An additional DB RCT in a mixed but predominately APD population showed statistically significant improvement in early morning UPDRS Part III motor function and nocturnal sleep disturbance compared with placebo. The AE profile compared with placebo was similar to that previously identified.

Based on one RCT, rotigotine was non-inferior to ropinirole adjunct therapy for improvement in UPDRS Part III motor function in patients with APD. Rotigotine use was associated with a higher proportion of patients experiencing one or more AEs. This was likely driven by a high frequency of application site reactions not experienced with oral DAs. WDAEs and SAEs were similar among active drug groups. The incidence of AEs such as arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy was low, and generally appeared to be similar between rotigotine and ropinirole, but the trial was not designed to detect differences in these events. For all three trials, the ability to capture uncommon events could be limited by the sample size.

TABLE 1: SUMMARY OF RESULTS FOR ADVANCED PARKINSON'S DISEASE STUDIES

Outcome	Mizuno 2014 (16 weeks)			Nomoto 2014 (12 weeks)	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
UPDRS Part III ("On" State) Sum Score Mean Change from Baseline to End of Maintenance Period					
Baseline mean (SD)	25.8 (10.6)	25.8 (11.0)	25.6 (10.4)	28.1 (12.2)	26.2 (10.4)
Mean change (SD) from baseline to end point	[redacted]	[redacted]	[redacted]	–10.1 (9.0)	–4.4 (7.4)
Rotigotine – placebo difference (95% CI)	[redacted]			–5.7 points (–8.2 to –3.2)	
Rotigotine – ropinirole difference (95% CI)	[redacted]			NA	
LS mean change (SE) from baseline to end point	–10.9 (0.6)	–9.5 (0.6)	–4.5 (0.9)	NR	NR
Rotigotine – placebo difference in adjusted mean (95% CI)	–6.4 points (–8.6 to –4.2)			[redacted]	
Rotigotine – ropinirole difference in adjusted mean[a]	–1.4 points[a] (–3.2 to 0.4)			NA	

Outcome	Mizuno 2014 (16 weeks)			Nomoto 2014 (12 weeks)	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
(95% CI)					
UPDRS Part III ("On" State) Sum Score Mean Change from Baseline to End of Maintenance Period, Per-protocol Analysis					
LS mean change (SE) from baseline to end point	[redacted]	[redacted]	[redacted]	NA	NA
Rotigotine – placebo difference in adjusted mean (95% CI)	[redacted]			NA	
Rotigotine – ropinirole difference in adjusted mean[a] (95% CI)	[redacted]			NA	
Responders Achieving ≥ 20% Reduction in UPDRS Part III ("On" State)					
Responder rate, n (%)	132 (80.5)	114 (69.1)	47 (56.6)	(73.3)	(43.0)
Rotigotine – placebo difference (95% CI)	23.9% (11.6 to 36.1)			30.2% (16.2 to 44.3)	
Rotigotine – ropinirole difference (95% CI)	11.4% (2.1 to 20.7)			NA	
Absolute Off Time (Hours/day), Mean Change from Baseline to End of Maintenance Phase					
Baseline mean (SD)	4.5 (3.4)	5.0 (3.6)	4.9 (3.0)	6.6 (3.5)	6.0 (3.4)
	N = 111	N = 113	N = 57	N = 54	N = 56
Mean change (SD)	[redacted]	[redacted]	[redacted]	–2.1 (3.1)	–0.7 (2.8)
Rotigotine – placebo difference (95% CI)	[redacted]			–1.4 hours (–2.5 to –0.3)	
Rotigotine – ropinirole difference (95% CI)	[redacted]			NA	
LS mean change (SE) from baseline to end point	–1.4 (0.2)	–1.9 (0.2)	–0.4 (0.3)	NR	NR
	N = 110	N = 113	N = 57		
Rotigotine – placebo difference in adjusted mean (95% CI)	–1.1 hours (–1.9 to –0.3)			NR	
Rotigotine – ropinirole difference in adjusted mean[a] (95% CI)	0.5 hours (–0.2 to 1.2)			NA	
Responders Achieving ≥ 30% Reduction in Off Time (%)					
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]		
Rotigotine – placebo difference (95% CI)	[redacted]			[redacted]	
Rotigotine – ropinirole difference (95% CI)	[redacted]			NA	
Nocturnal Sleep — PDSS-2 Sum Score, Mean Change from Baseline to End of Maintenance Phase					
Baseline mean (SD)	12.3 (8.9) N = 162	14.3 (9.2) N = 165	15.0 (9.2) N = 81	NR	NR

Outcome	Mizuno 2014 (16 weeks)			Nomoto 2014 (12 weeks)	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
Mean change (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Rotigotine – placebo difference (95% CI)	[redacted]				
Rotigotine – ropinirole difference (95% CI)	[redacted]			NA	
LS mean change (SE) from baseline to end point	–3.7 (NR)	–3.0 (NR)	–1.1 (NR)	NR	NR
Rotigotine – placebo difference in adjusted mean (95% CI)	–2.6 points (–4.1 to –1.1)			NR	
Rotigotine – ropinirole difference in adjusted mean (95% CI)	–0.7 points (–1.9 to 0.6)			NA	
AEs					
n (%)	149 (88.7)	130 (77.8)	59 (69.4)	82 (94.3)	77 (88.5)
SAEs					
n (%)	7 (4.2)	5 (3.0)	6 (7.1)	3 (3.5)	3 (3.5)
WDAEs					
n (%)	13 (7.7)	13 (7.8)	8 (9.4)	9 (10.3)	7 (8.1)
Notable Harms					
Sudden onset of sleep, n (%)	1 (0.6)	1 (0.6)	0	0	0
Syncope, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICD – clinical AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICD – identified on mMIDI[b], n (%)	[redacted]	11 (6.6)	3 (3.5)	NR	NR
Valvulopathy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arrhythmias, n (%)	[redacted][c]	[redacted][c]	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; ICD = impulse control disorder; LS = least squares; mMIDI = modified Minnesota Impulsive Disorder Interview; NA = not applicable; NR = not reported; PDSS = Parkinson's Disease Sleep Scale; SAE = serious adverse events; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

[a] Test of non-inferiority with a pre-defined non-inferiority margin of 2.5 points.

[b] The reported patients had a positive finding on mMIDI, defined as an affirmative response on a gateway question with or without affirmative responses on remaining questions.

[c] For rotigotine, these were [redacted]; of these, [redacted] was identified with [redacted] and [redacted] with [redacted]; for ropinirole, [redacted] had [redacted].[7]

Note: Adjusted means for Mizuno 2014 are from an analysis of covariance (ANCOVA) model with baseline value as a covariate.[6] Full analysis set (FAS) with data imputed by last observation carried forward (LOCF) method provided for efficacy outcomes. [redacted].[24]

TABLE 2: SUMMARY OF RESULTS FOR MIXED POPULATION (ADVANCED AND EARLY PARKINSON'S DISEASE) STUDIES

SP889 (12 weeks)		
Outcome	**Placebo N = 89**	**Rotigotine N = 178**
UPDRS Part III Sum Score in Early Morning Period, Mean Change from Baseline		
Baseline, mean (SD)	31.8 (13.6)	29.7 (12.4)
Mean change (SD)	–3.9 (7.3)	-7.0 (7.6)
Rotigotine – placebo difference in adjusted mean[a] (95% CI)	–3.6points (–5.4 to –1.7)	
Nocturnal Sleep (PDSS-2 Total Score), Mean Change from Baseline to End of Maintenance Period		
Baseline mean (SD)	20.3 (10.2)	19.3 (9.2)
Mean change (SD)	–1.9 (8.2)	–5.9 (7.6)
Rotigotine – placebo difference in adjusted mean[a] (95% CI)	–4.3 points (–6.1 to –2.5)	
UPDRS Part II Sum Score in Early Morning Period, Mean Change from Baseline		
Baseline mean (SD)	13.5 (6.3)	12.7 (5.6)
Mean change (SD)	–1.5 (3.5)	–2.8 (3.6)
Rotigotine – placebo difference in adjusted mean[a] (95% CI)	–1.5 points[a] (–2.3 to –0.7)	
Quality of Life — PDQ-8 Score, Mean Change from Baseline to End of Maintenance Period		
Baseline mean (SD)	31.1 (17.0)	30.8 (18.2)
Mean change (SD)	–2.3 (13.8)	–7.4 (11.9)
Rotigotine – placebo difference in adjusted mean[a] (95% CI)	–5.7 points[b] (–8.7 to –2.8)	
Compliance		
Compliant n (%) (≥ 85% and < 115 % compliant)	73 (76.0)	158 (82.7)
AEs		
n (%)	54 (56.3)	137 (71.7)
SAEs		
n (%)	5 (5.2)	10 (5.2)[c]
WDAEs		
n (%)	6 (6.3)	12 (6.3)
Notable Harms		
Sudden onset of sleep, n (%)	0	2 (1.1)
Syncope, n (%)	0	[redacted][d]
ICD – clinical AE, n (%)	0	0

SP889 (12 weeks)		
Outcome	**Placebo N = 89**	**Rotigotine N = 178**
ICD – identified on mMIDI, n (%)	8 (4.2)[e]	2 (2.1)
Valvulopathy, n (%)	[redacted]	[redacted]
Arrhythmias, n (%)	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; ICD = impulse control disorder; NR = not reported; mMIDI = modified Minnesota Impulsive Disorder Interview; PDQ-8 = Parkinson's Disease Questionnaire; PDSS = Parkinson's Disease Sleep Scale; SAE = serious adverse event; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale; WDAE = withdrawal due to adverse event.

[a] Adjusted least squares means are presented from analysis of covariance (ANCOVA) with treatment and regions as factors and baseline value as covariate.

[b] Difference is considered exploratory.

[c] Includes two deaths.

[d] One additional case of vasovagal syncope was reported separately in the rotigotine group; it is unclear whether this event overlaps with events in the category syncope.

[e] One patient had a positive finding on a structured psychiatric interview, and seven had positive findings in at least one module of the mMIDI.

Note: Full analysis set (FAS) with data imputed by last observation carried forward (LOCF) method provided for UPDRS Part III and PDSS-2; FAS (observed cases) provided for UPDRS Part II (N = 78 for placebo, N = 163 for rotigotine) and PDQ-8 (N = 78 for placebo, N = 161 for rotigotine).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Idiopathic Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder characterized by the loss of dopaminergic nerve cells in the substantia nigra (midbrain). This results in a deficiency of the neurotransmitter dopamine in the striatum, a portion of the brain involved in coordinating body movement and motivation. Nerve synaptic dysfunction related to the aggregation of alpha-synuclein (a presynaptic protein) and several additional neurotransmitter pathways also plays a role in the pathogenesis of PD.[25,26]

The average age of onset of PD is about 60 years, and diagnosis is mainly based on history of symptoms and neurologic examination. Hallmark clinical manifestations are postural instability, tremor, rigidity, and slowness of movement (bradykinesia). Although PD is predominantly a movement disorder, non-motor features are also associated with PD, and include neuropsychiatric disorders (psychosis, depression, anxiety), cognitive impairment and dementia, autonomic dysfunction (e.g., orthostatic hypotension), sleep disturbances (e.g., insomnia, sleep fragmentation, and rapid eye movement behaviour disorder), and sensory disorders. A systematic review of the prevalence of oropharyngeal dysphagia estimated that about a third of community-dwelling patients with PD have subjective dysphagia, with higher prevalence in more severe disease;[27] other gastrointestinal problems, such as gastroparesis and malabsorption, can also occur.[28]

Data from the 2010/2011 Canadian Community Health Survey provide an estimated population prevalence of PD in the community of 0.2%. Among the community-dwelling population, 79% of people with PD were 65 years of age or older. In addition, 4.9% of long-term care facility residents (N = 12,500) — almost all of whom are older than age 65 — have a diagnosis of PD.[29]

1.2 Standards of Therapy

All available treatments for PD are aimed at ameliorating symptoms; there is no established disease-modifying or neuroprotective pharmacological treatment. Drug treatments aim to restore the dopaminergic deficit, either with levodopa (a precursor to dopamine) or with dopamine receptor agonists (DAs). A complementary approach is to restore the balance between cholinergic and dopaminergic inputs on the basal ganglia using anticholinergic drugs.[26] However, anticholinergic drugs are generally not a first-choice monotherapy for early Parkinson's disease (EPD).[30]

Levodopa is the mainstay of treatment for PD.[30] It has a short plasma half-life, 1.5 hours, in the presence of a peripheral decarboxylase inhibitor (e.g., carbidopa).[31] Peripheral decarboxylase inhibitors reduce conversion to dopamine in the periphery and increase the amount of available drug in the brain. Levodopa's effect initially lasts three to four hours but diminishes over time. Approximately 50% of patients with PD who have received levodopa for more than five years will develop motor complications. These complications include involuntary movements (dyskinesia, dystonia) and complex motor fluctuations (known as "wearing-off" phenomenon).[32,33]

Direct agonists of dopamine do not require conversion in the brain, and may compensate for the progressive neurotransmitter shortfall, although they are not as effective as levodopa in ameliorating motor signs and symptoms.[30] DAs available in Canada include the non-ergolinic DAs pramipexole, ropinirole, and rotigotine, and the ergot-derived DA, bromocriptine. Because there is a greater risk of pleuropulmonary and cardiac valve fibrosis with ergot-derived agonists, non-ergolinic DAs are

preferred.[30] DAs require slow up-titration because of early adverse events (AEs) such as nausea, dizziness, somnolence, and hallucinations.[30] The Canadian Guidelines on Parkinson's Disease suggest DAs should be used with caution in patients over the age of 70, if not avoided, because they are less effective than levodopa, are associated with more AEs, and are more expensive.[30] Younger age of onset is a risk factor for dyskinesia; DAs may be introduced as initial treatment for patients younger than 60 years.[34] Increasing evidence, however, suggests that the early advantage of DA monotherapy over levodopa diminishes over time.[34]

For the treatment of EPD, there is no universal first-choice drug; individualized decision-making requires consideration of the known short- and long-term benefits and risks of the available drugs, the severity of symptoms, and the patient's lifestyle.[30,35-37] First-line monotherapy options include levodopa, DAs, and monoamine oxidase B (MAO-B) inhibitors (e.g., selegiline or rasagiline). Amantadine, a nonselective N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that also has anticholinergic properties, can be used but is not considered a first-line treatment.[30] Anticholinergic drugs are also not a first choice due to limited efficacy and neuropsychiatric AEs.[30]

For the treatment of advanced Parkinson's disease (APD), management strategies include increasing the dosage of dopaminergic medication, modifying the levodopa dosing regimen (using smaller, more frequent doses), adding another dopaminergic drug, or adding a MAO-B inhibitor or a catechol-o-methyltransferase (COMT) inhibitor to inhibit the breakdown of dopamine and levodopa. Anticholinergic drugs are also used as add-on treatments. There are few trials that directly compare these options in APD.[34] Adding drugs in combination with levodopa can reduce both *off* time and the levodopa dose with the aim of reducing motor complications.[30,38] Patients may prefer being in the *on* state with dyskinesia rather than in the *off* state without dyskinesia, so management is individualized for the type of motor complication and its timing in relation to levodopa administration.[37] Controlled release oral formulations of levodopa can be used for overnight wearing-off, but are not first choice to treat motor fluctuations.[30] Continuous intraduodenal infusion of levodopa via a percutaneous tube can also be used, but is not commonly available.[30] Amantadine reduces dyskinesia, and subcutaneous or continuous infusion apomorphine is an option for sudden unresponsive *off* periods but has restricted use in Canada.[30,39] Combinations of three or four drugs may be required to manage levodopa-related wearing-off motor fluctuations.[34]

Surgical treatment (e.g., deep brain stimulation of the subthalamic nucleus) may be an option for APD when optimized medical treatment has failed to ameliorate motor complications.[40] A variety of other drugs are used for the symptomatic treatment of non-motor symptoms.

1.3 Drug

Rotigotine is a non-ergolinic DA with an approved indication in Canada for the treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used both as monotherapy in the treatment of EPD and as an adjunct to levodopa in the treatment of APD. Rotigotine is also approved in Canada for the symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS) in adults.[1]

Rotigotine is formulated as 5 cm^2, 10 cm^2, 15 cm^2, 20 cm^2, 30 cm^2, and 40 cm^2 transdermal patches, which respectively contain 2.25 mg, 4.5 mg, 6.75 mg, 9.0 mg, 13.5 mg, and 18.0 mg of rotigotine (total dose). These doses correspond to nominal or apparent doses of 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, and 8 mg of rotigotine per 24 hours. Transdermal patches providing nominal doses of 1 mg and 3 mg per 24 hours are used for idiopathic RLS, whereas the other doses, as detailed below, are approved for PD.

Throughout this review, nominal doses are used and are converted, if necessary, from total doses using Table 3.

TABLE 3: NOMINAL DOSES OF ROTIGOTINE TO TREAT PARKINSON'S DISEASE

Rotigotine Total Dose per 24 Hours	Rotigotine Nominal Dose per 24 Hours
4.5 mg	2 mg
9.0 mg	4 mg
13.5 mg	6 mg
18.0 mg	8 mg
22.5 mg	10 mg
27.0 mg	12 mg
31.5 mg	14 mg
36.0mg	16 mg

Rotigotine is applied once a day, and should remain on the skin for 24 hours. In Canada, the recommended starting dose for PD is 2 mg/24 h. Recommended increments are 2 mg/24 h weekly, and the maximum approved dose is 8 mg/24 h for EPD and 16 mg/24 h for APD. Multiple patches may be used to achieve doses higher than 8 mg/24 h. Rotation of application sites is recommended (abdomen, flank, upper arm, shoulder, thigh, and hip). In patients with EPD, the equivalence of six application sites was not demonstrated, but was regarded as sufficiently similar to support the rotation of application sites (95% confidence intervals [CIs] for the ratio between different application sites ranged from 0.72% to 1.41%).[41]

Although the exact mechanism of action of rotigotine for the treatment of PD is unknown, it is believed to increase activity of D1, D2, and D3 dopamine receptors in the caudate putamen in the brain.

Indication under review
Treatment of the signs and symptoms of idiopathic Parkinson's disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Listing criteria requested by sponsor
As adjunctive therapy to levodopa for the treatment of patients with advanced Parkinson's disease.

TABLE 4: KEY CHARACTERISTICS OF DRUGS USED IN EARLY AND ADVANCED PARKINSON'S DISEASE STUDIES (MODIFIED FROM ORIGINAL REVIEW)

	Rotigotine	Ropinirole	Pramipexole	Levodopa/Carbidopa	Levodopa/Benserazide
Mechanism of Action	Non-ergolinic DA; believed to reduce the symptoms of PD by increasing the activities of the D3, D2, and D1 receptors of the caudate putamen in the brain, but is an agonist for D1 to D5 receptors.	Non-ergolinic DA that activates post-synaptic dopamine receptors.	Non-ergolinic DA with high in vitro specificity at the D2 subfamily of dopamine receptors.	Levodopa crosses the blood-brain barrier and is converted to dopamine in the basal ganglia. Carbidopa is a decarboxylase inhibitor limited to peripheral tissues. It makes more levodopa available for transport to the brain.	Levodopa crosses the blood-brain barrier and is converted to dopamine in the basal ganglia. Benserazide is a decarboxylase inhibitor limited to peripheral tissues. It makes more levodopa available for transport to the brain.
Indication[a]	Treatment of the signs and symptoms of idiopathic PD. Rotigotine may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.	Treatment of the signs and symptoms of idiopathic Parkinson's disease. Can be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.	Treatment of the signs and symptoms of idiopathic PD. Can be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.	Treatment of Parkinson's disease.	Treatment of Parkinson's disease with the exception of drug-induced parkinsonism.
Route of Administration	Transdermal	Oral			
Recommended Dose	Transdermal system: 2 mg/24 h, 4 mg/24 h, 6 mg/24 h, 8 mg/24 h rotigotine.[b] The recommended starting dose for PD is 2 mg/24 h, with increases in 2 mg increments per week as needed; maximal dose is 8 mg/24 h for EPD and 16 mg/24 h for APD.	Tablets: 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, 4.0 mg, 5.0 mg. The recommended maximum dose is not explicitly identified under dosage but referred to in retinal pathology animal studies as 24 mg/day. Doses greater than 24 mg/day have not	Tablets: 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, and 1.5 mg. The maximal recommended dose is 4.5 mg/day.	Immediate release tablets: 100 mg/10 mg; 100 mg/25 mg; 250 mg/25 mg (initial dosage for patients currently treated with levodopa alone, or patients without prior levodopa therapy). Controlled release tablets: 200 mg/50 mg (initial dosage for patients currently treated with levodopa alone).	Capsules: 50 mg/12.5 mg, 100 mg/25 mg, 200 mg/50 mg. The initial recommended dose is one capsule of PROLOPA 100–25 once or twice a day.

	Rotigotine	Ropinirole	Pramipexole	Levodopa/Carbidopa	Levodopa/Benserazide
		been included in clinical trials. In clinical trials, initial benefits were observed with 3 mg/day and higher doses. The recommended maximum dose is 18 mg/day in patients receiving regular dialysis.		100 mg/25 mg (patients without prior levodopa therapy).	
Serious Side Effects/Safety Issues	**Contraindications**: • Hypersensitivity to rotigotine or excipients **Serious W&P:** • Sudden onset of sleep **W&P:** • Elevation of BP and HR • Orthostatic hypotension • Fluid retention and weight gain • Fibrotic complications — includes cardiac valvulopathy; unknown if both non-ergolinic and ergot DAs cause this • Sulfite sensitivity • RLS augmentation or rebound • Neuroleptic malignant syndrome (sudden discontinuation) • Dyskinesia • Hallucinations or abnormal thinking and	*Similar to rotigotine* **Additional W&P**: • Rhabdomyolysis — a single case • Excreted through kidneys — caution if renal insufficiency • 25% to 30% lower total clearance in > age 65; no difference in AE reported	*Similar to rotigotine*	**Contraindications:** • Hypersensitivity • When use of a sympathomimetic drug is contraindicated • Use of nonselective monoamine oxidase inhibitors • Narrow angle glaucoma • Uncompensated cardiovascular, endocrine, renal, hepatic, hematologic, or pulmonary disease • Levodopa may activate malignant melanoma; should not be used if suspicious undiagnosed skin lesions or history of melanoma **Serious W&P:** • Sudden onset of sleep **W&P:** • Cardiovascular — atrial,	*Similar to levodopa/carbidopa*

	Rotigotine	Ropinirole	Pramipexole	Levodopa/Carbidopa	Levodopa/Benserazide
	behaviour • Impulse control disorders • Retinal degeneration (preclinical) • Application site reactions • Melanoma • Geriatrics: similar plasma concentrations in age 65 to 80 vs. age 50 to 64; absorption in age > 80 years not studied, but may be higher due to skin changes with aging			nodal or ventricular arrhythmias or history of myocardial infarction • Upper gastrointestinal hemorrhage with history of peptic ulcer disease • Neurologic — involuntary movements and "on and off" phenomena may appear earlier in combination with carbidopa; involuntary movements and mental disturbances; dyskinesia may occur at lower dosages and sooner in combination with carbidopa; neuroleptic malignant syndrome; psychomotor performance (somnolence, sudden onset of sleep) • Psychiatric — monitor for development of depression with suicidal tendencies; treat with caution if past or current psychoses; impulse control disorders; hallucinations • Melanoma	

AE = adverse event; APD = advanced Parkinson's disease; BP = blood pressure; C = contraindication; DA = dopamine agonist; EPD = early Parkinson's disease; HR = heart rate; PD = Parkinson's disease; W&P = warnings and precautions; RLS = restless legs syndrome.

[a] Health Canada indication.

[b] Rotigotine transdermal patches are also available in nominal doses of 1 mg and 3 mg for idiopathic RLS.

Note: The potential for retinal degeneration is based on a similar mechanism between humans and the preclinical model.

Source: Health Canada product monographs.[1,31,42-44]

2. SUBMISSION HISTORY

The initial submission was considered by CDEC in February 2014 and reconsidered in May 2014, with a recommendation of "do not list" for the treatment of idiopathic PD.[2]

The reason for the recommendation was the uncertain comparative clinical benefit of rotigotine versus other less costly non-ergolinic DAs, i.e., immediate release (IR) oral formulations of ropinirole and pramipexole. This was based on the failure in two phase 3, randomized controlled trials (RCTs) (SP513 and SP515) to demonstrate consistently that rotigotine was non-inferior to ropinirole or pramipexole.

- SP513 (N = 561) compared rotigotine monotherapy with ropinirole and placebo in patients with EPD.[3,45] Although superior to placebo, rotigotine failed to demonstrate non-inferiority to ropinirole for change from baseline in the Unified Parkinson's Disease Scale (UPDRS) Parts II + III subtotal score, based on a preset non-inferiority margin of 2.9 points. Rotigotine also failed to show non-inferiority against ropinirole for the proportion of responders to therapy achieving a ≥ 20% reduction in UPDRS Parts II + III subtotal score, based on a non-inferiority margin of –15%.
- SP515 (N = 506) compared rotigotine with pramipexole in patients with APD, in combination with levodopa. [4,46] Rotigotine was non-inferior to pramipexole for change from baseline in absolute *off* time, based on a preset non-inferiority margin of 1.2 hours, but not for the proportion of responders achieving ≥ 30% reduction in absolute *off* time, based on a non-inferiority margin of –15%.
- Issues raised for both trials included uncertainty regarding the appropriateness of the non-inferiority margins for both the continuous and dichotomous outcomes used in the trials, and for SP513, potential dose non-equivalence, with higher ropinirole doses. The dose non-equivalence may have favoured rotigotine in terms of AEs and favoured ropinirole in terms of efficacy.

The committee noted there were insufficient data to confirm the benefit of transdermal administration, compared with oral administration, with respect to patient adherence and clinical end points, and that application site reactions were the most commonly reported AEs leading to discontinuation by rotigotine-treated patients in both SP512 (5%) and SP513 (8%).

It was also noted that there was insufficient evidence regarding the long-term efficacy of rotigotine.

2.1 Basis of Resubmission

The basis of the resubmission, as indicated by the manufacturer, is new clinical information, specifically two RCTs in the subgroup of patients with APD, and a change in price for the incremental doses of rotigotine ([redacted]) as reflected in a cost minimization analysis.[5]

There is also a change in the manufacturer's requested listing. The listing is restricted to use of rotigotine as adjunctive therapy to levodopa for the treatment of patients with APD.

Because the Health Canada–approved indication is for monotherapy in EPD and adjunctive therapy in APD, both subgroups of patients are considered in the clinical evidence.

3. OBJECTIVES AND METHODS

3.1 Objectives

To perform an updated systematic review of the beneficial and harmful effects of rotigotine (up to 16 mg/24 h) for the treatment of the signs and symptoms of idiopathic PD.

3.2 Methods

Studies selected for inclusion in this systematic review include the pivotal or critical studies provided in the manufacturer's submission as well as those meeting the selection criteria presented in Table 5.

The only substantive change to the review protocol compared with the protocol for the CADTH Common Drug Review (CDR) of the previous submission is the removal of the restriction of RCTs to durations of ≥ 16 weeks; CDR review protocols no longer restrict inclusion criteria based on study duration. A minor change was the removal of the word "severe" from the subgroup of interest (patients with gastrointestinal problems).

Studies included in the previous CDR review are excluded from the current review. However, because of the removal of the duration restriction, trials that had been excluded from the original review on the basis of duration were reassessed to determine if they meet current inclusion criteria.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years of age) with idiopathic EPD and APD **Subgroups of interest:** Patients with GI problems (e.g., dysphagia, absorption problems, gastroparesis) Patients who are uncontrolled or intolerant on pramipexole or ropinirole
Intervention	EPD: rotigotine transdermal system (patch) alone at recommended doses APD: rotigotine transdermal system (patch) at recommended doses, in combination with levodopa[a]
Comparators	**EPD:** DAs (pramipexole, ropinirole) Levodopa[a] **APD (all in combination with levodopa):**[a] DAs (pramipexole, ropinirole) Entacapone Monoamine oxidase B inhibitors (rasagiline, selegiline)
Outcomes	**Key efficacy outcomes:** **EPD:** UPDRS subscale score (parts II + III)* Response to therapy[b] HRQoL measured with a validated scale* Functional capacity* Adherence* Patient's satisfaction with therapy* Nocturnal sleep* **APD:** Time spent *off* (loss of optimum effects of treatment)* Response to therapy[c]

	HRQoL measured with a validated scale* Functional capacity* Adherence* Patient's satisfaction with therapy* Nocturnal sleep* **Other efficacy outcomes:** Motor symptoms (UPDRS Part III score only)* Activities of daily living (UPDRS Part II score only)* Neuropsychiatric symptoms* **Harms outcomes:** Mortality AEs*, SAEs, WDAEs AEs of interest: arrhythmias, impulsive/asocial behavior*, sudden onset of sleep, syncope, and valvulopathy
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; APD = advanced Parkinson's disease; DA = dopamine agonist; EPD = early Parkinson's disease; GI = gastrointestinal; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] In combination with a dopamine decarboxylase inhibitor (carbidopa, benserazide).
[b] Defined as a ≥ 20% decrease in the sum of scores from the activities of daily living and motor examination sections in the UPDRS Parts II + III from the baseline visit to the end of the double-blind maintenance phase.
[c] Defined as a ≥ 30% decrease in absolute time spent *off* from baseline to the end of the double-blind maintenance period.
* Asterisked outcomes were mentioned in patient input. If a specific outcome fell into a category of outcomes identified by patient input, it was asterisked even if the specific scale or score had not been identified.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were rotigotine and Neupro.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. This report makes use of a literature search conducted in August 2013 for the original Neupro CDR review. For the current report, database searches were rerun on June 17, 2015 to capture any articles published since the initial search date.

Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on October 21, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials.

Google and other Internet search engines were used to search for additional Web-based materials.

These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the drug manufacturer was contacted for information regarding unpublished studies. The grey literature search was also updated to include documents made available since July 2012.

Two CDR clinical reviewers independently screened the titles and abstracts of studies identified in the literature search, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant or of uncertain relevance by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and any differences were resolved through discussion. Trials that were excluded from the prior review were also assessed using the modified eligibility criterion for duration (i.e., removal of the ≥ 16-week duration restriction).

4. RESULTS

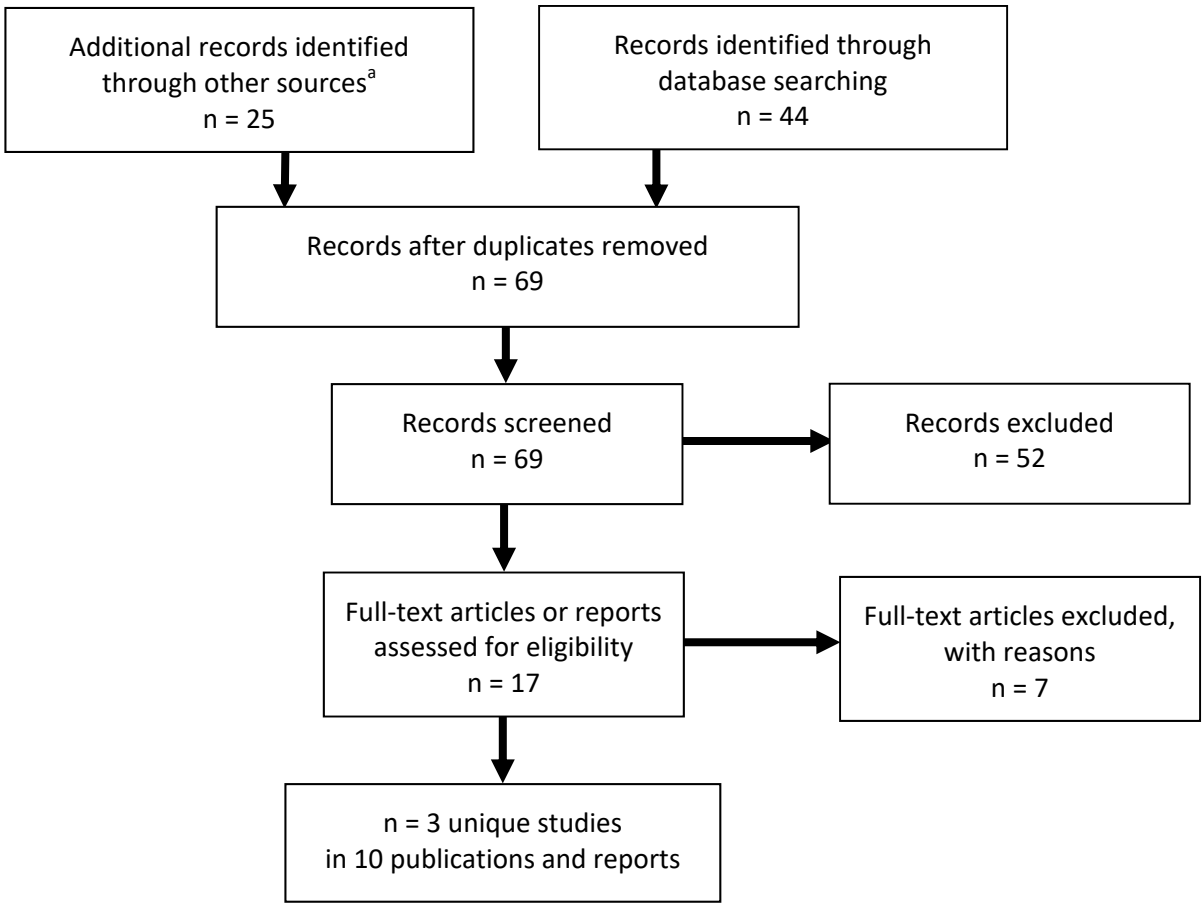
4.1 Findings From the Literature

Three RCTs were identified for inclusion in the systematic review. One active comparator RCT was identified from the literature search, and two placebo RCTs were identified — one from the prior submission (originally excluded on the basis of duration) and another from the resubmission.

A list of studies identified in the literature search and excluded following full-text assessment is presented in Appendix 3: Excluded Studies. The reassessment of excluded studies from the original submission is also presented in Appendix 3.

A PRISMA flowchart is presented in Figure 1, and Table 6 presents details about the included studies.

FIGURE 1: PRISMA FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



[a] Other sources for the identification of records included: the manufacturer's resubmission, the prior CADTH Common Drug Review excluded study list, and the Health Canada report.

TABLE 6: DETAILS OF INCLUDED STUDIES

		APD Population		Mixed (EPD + APD)
		Mizuno 2014	Nomoto 2014	SP889
DESIGNS & POPULATIONS	**Study Design**	DB, DD, 3-group, parallel-group active comparator and placebo-controlled phase 3 RCT MC (62 sites) 2:2:1 randomization (rotigotine: ropinirole: placebo)	DB, 2-group, parallel-group, placebo-controlled dose-finding phase 2 RCT MC (sites NR) 1:1 randomization	DB, 2-group, parallel-group, placebo-controlled phase 3b RCT MN, MC (49 sites) 2:1 randomization (rotigotine: placebo)
	Locations	Japan	Japan	Europe, New Zealand, South Africa, US
	Randomized (N)	420	174	336

		APD Population		Mixed (EPD + APD)
		Mizuno 2014	Nomoto 2014	SP889
	Inclusion Criteria	• Diagnosis of PD by UK Bank Brain Criteria • Hoehn & Yahr stage 2 to 4 • UPDRS Part III sum score (*on* state) ≥ 10 points • Age > 30 and < 80 years • Patients exhibiting: [redacted] ○ [redacted] ○ inability to have levodopa increased to an optimal level because of AEs or other reasons • Stable levodopa doses ≥ 28 days before starting treatment • Selegiline, entacapone permitted if stable dose ≥ 28 days before starting treatment • Anticholinergic drugs permitted if stable ≥ 14 days prior to starting treatment	• Diagnosis of PD by Research Committee of MHLW-specified Intractable Neurodegenerative Diseases 1995 • Age > 30 and < 80 years • Hoehn & Yahr stage 2 to 4 (on) • UPDRS Part III (on) ≥ 10 points • Patients exhibiting: ○ wearing-off phenomenon ○ on-off phenomenon ○ delayed-on and/or no-on phenomenon ○ inadequate control due to AE ○ weakening of levodopa efficacy • Stable dose of levodopa > 28 days • Selegiline, amantadine, and anticholinergic drugs permitted if stable dose for > 28 days before baseline	• Diagnosis of PD by bradykinesia and > 1 of resting tremor, rigidity, impairment of postural reflexes • Age ≥ 18 years • Hoehn & Yahr stage 1 to 4 • Unsatisfactory control of early morning symptoms (investigator-defined) • On or off levodopa • If on levodopa (+ benserazide or carbidopa), stable dose for ≥ 28 days before baseline • Anticholinergics, MAO inhibitors, NMDA antagonists, entacapone, sedatives, hypnotics, SSRI, anxiolytics, and other CNS medications permitted if stable dose for ≥ 28 days before baseline
	Exclusion Criteria	Psychiatric symptoms; orthostatic hypotension; history of epilepsy or convulsion; history of serious cardiac disease, arrhythmia, or QT prolongation; abnormal liver function; history of allergy to topical drugs; concomitant use of drugs that may affect symptoms of PD, cause QT prolongation or interact with ropinirole.	Psychiatric symptoms including delusion, hallucination; orthostatic hypotension; history of epilepsy; history of cardiac disorders or QT prolongation; history of hepatic or renal disorders; history of skin sensitivity to adhesives or other transdermal medications; prior history of other DAs or neuroleptics.	Controlled release levodopa, other centrally acting dopaminergic drugs, monoamine oxidase-A inhibitors, tolcapone, budipine, or neuroleptics (except olanzapine, ziprasidone, aripiprazole, clozapine, or quetiapine) within 28 days prior to baseline.

		APD Population		Mixed (EPD + APD)
		Mizuno 2014	Nomoto 2014	SP889
DRUGS	**Intervention**	Rotigotine 2 mg/24 h to 16 mg/24 h transdermal system (patch) (+ oral placebo) Patches rotated on a daily basis	Rotigotine 2 mg/24 h to 16 mg/24 h transdermal system (patch) Patches rotated on a daily basis (abdomen, thigh, hip flank, shoulder, upper arm)	Rotigotine 2 mg/24 h to 16 mg/24 h transdermal system (patch) Patches rotated on a daily basis
	Comparator(s)	• Ropinirole PO 0.75 mg/day to 15 mg/day (+ transdermal placebo) • Placebo: oral capsule • + transdermal patch	Placebo transdermal patch	Placebo transdermal patch
DURATION	**Phase**			
	Run-in screening Period	2 weeks	4 weeks	4 weeks Baseline day –2 to day 1 (hospital stay)
	Double-blind	Titration period up to 12 weeks (8 weeks for rotigotine; 12 weeks for ropinirole) Maintenance period 4 weeks Dose taper 4 weeks	Titration period 8 to 10 weeks Maintenance period 4 weeks Dose taper up to 2 weeks	Titration period up to 8 weeks (1 week to 8 weeks) Maintenance period ≥ 4 weeks Dose taper up to 2 weeks
	Follow-up	1 week or enrolment in Study 243-08-002, OL extension	1 week or enrolment in Study 243-06-001, OL extension	30 days or enrolment in Study SP915, OL extension
OUTCOMES	**Primary End Point(s)**	Change in UPDRS Part III (*on* state) sum score from baseline to week 16	Change in UPDRS Part III sum score from baseline to week 12	Change from baseline to week 12 in: • UPDRS Part III in early morning (*off* state) • PDSS-2
	Other End Points	Major secondary end point: change in UPDRS Part III (*on*) from baseline to week 8 or week 10 Change from baseline to week 16 in: • Time spent on and off • *On* time with dyskinesia disturbing daily activities • UPDRS Part IIa • UPDRS Parts II + III • Individual items of UPDRS Parts I, IIb, III, and IV • PDSS-2 sum score and • individual items	Change from baseline to week 12 in: • *Off* time • UPDRS Part II Scores[a] • UPDRS Part I • UPDRS Part IV • UPDRS Parts II[b] + III • Total UPDRS Score: Parts I + II[b] + III + IV • Modified Hoehn & Yahr stage Responder rates: • ≥ 20% or ≥ 30% reduction in UPDRS Part III (on) • ≥ 20% or ≥ 30%	Change from baseline to week 12 in: • UPDRS Part II • UPDRS Parts II + III • UPDRS Part IV • NDACS Sum Score and individual items • PDNMS • BDI-II • 11-point Likert pain scale • PDQ-8 • PDSS-2 Responder Rates: • UPDRS Part I • UPDRS Parts II + III

		APD Population		Mixed (EPD + APD)
		Mizuno 2014	Nomoto 2014	SP889
		Responder rates: • ≥ 20% or ≥ 30% reduction UPDRS Part III (*on*) • ≥ 20% or ≥ 30% reduction UPDRS Part IIb • ≥ 30% reduction in *off* time CGI Dystonia at an early hour and in the daytime Revised Hoehn & Yahr scale **Safety** AE; laboratory values; BP/HR; ECG; echocardiography; skin irritation assessment score; physical and neurologic exam; mMIDI for ICD interview; cardiac valve regurgitation; drug dependency	reduction in *off* time **Safety** AE; application site evaluation; VS; ECG; laboratory parameters; plasma concentration (unconjugated and metabolites) **Pharmacokinetics:** Relationship between dose and plasma concentration Relationship between plasma concentration and primary outcome UPDRS Part III, UPDRS Part II, and *off* time, prolactin, AE, and QT_c interval	Nocturia Post hoc: • Individual items of PDSS-2; • PDSS-2 subtotal scores **Safety** AE Laboratory values; VS; ECG; physical and neurological findings; mMIDI for ICD
NOTES	**Publications**	Mizuno 2014[6]	Nomoto 2014[8]	Trenkwalder 2011[10] Secondary publications: Chaudhuri 2013;[47] Kassubek 2014;[12] Swick 2014;[11] Ghys 2011[14]
	Study numbers and identifiers	243-08-001 NCT0162896	243-05-001 NCT01628848	SP889 NCT00474058
	Related Studies	OL extension 243-08-002[17] NCT01631825	OL extension 243-06-001[48] NCT01631825	OL extension SP915[19] NCT00519532

AE = adverse event; BDI-II = Beck Depression Inventory; BP = blood pressure; CNS = central nervous system; DB = double-blind; DD = double-dummy; ECG = electrocardiography; EOM = end of maintenance; h = hours; HR = heart rate; ICD = impulse control disorder; MC = multi-centre; MHLW = Ministry of Health, Labour and Welfare (Japan); mMIDI = modified Minnesota Impulsive Disorder Interview; MN = multinational; NADCS = Nocturnal Akinesia, Dystonia and Cramps Score; OL = open-label; PD = Parkinson's disease; PDNMS = Parkinson's Disease Non-Motor Symptom Scale; PDSS = Parkinson's Disease Sleep Scale; PO = orally; QT_c = corrected QT interval; SSRI = selective serotonin uptake inhibitor; UPDRS = Unified Parkinson's Disease Rating Scale; VS = vital signs.

[a] Reported for the *on* state, the *off* state, and the mean of the *on* and *off* states.

[b] Mean of *on* and *off* state.

Source: Trenkwalder 2011;[10] Clinical Study Report, SP889;[15] Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014;[8] clinicaltrials.gov for Nomoto 2104.[49]

4.2 Included Studies

4.2.1 Description of studies

Three parallel-group, double-blind (DB) RCTs met the inclusion criteria for this review. Two were trials that enrolled patients with APD,[6-9] and the third included patients with PD at all stages (mixed population)[10-14] (Table 6). Only one trial was an active comparator RCT.

a) Advanced Parkinson's disease

Mizuno 2014 (N = 420) was a 16-week, three-group active comparator and placebo-controlled trial that evaluated rotigotine as adjunct therapy to levodopa in patients with APD. The study was designed to demonstrate superiority to placebo and non-inferiority to ropinirole in a hierarchical manner (see statistical analysis). Patients were randomized 2:2:1 to receive rotigotine (transdermal), ropinirole IR, or placebo. [redacted].[50] In both trials, patients were assessed every week until the maintenance dose was determined, then every two weeks during the maintenance phase.

b) Mixed population (advanced Parkinson's disease and early Parkinson's disease)

The third trial, SP889 (N = 336), was a 12-week, two-group placebo-controlled trial that assessed control of early morning motor function (before application of a new transdermal patch), nocturnal sleep, and non-motor symptoms in patients with EPD and APD. About 80% of all participants were on levodopa. Randomization was 2:1 and stratified by site. Assessment visits post-randomization were every two weeks during titration, at the start and end of the maintenance period, and a follow-up visit at 30 days. Patients were hospitalized for two nights at baseline and at the end of the maintenance period. Efficacy assessments took place on the first or second night of hospitalization, depending on the outcome measure.

All three trials were similarly designed (Table 6). A run-in phase of two[6] to four weeks[8,10] prior to randomization was conducted. During this period, screening tests were conducted and eligibility confirmed. There was no specific process identified for drug discontinuation, nor data provided for any drug discontinuation in the run-in periods of the trials. However, patients needed to be on stable doses of allowed medications for 28 days or 14 days (for anticholinergic drugs in Mizuno 2014) in all three trials prior to randomization, and were screened out if medications included any that were not permitted. Some participants in Mizuno 2014 had previously been on DAs (see baseline characteristics section), including pramipexole or ropinirole, and the presence/absence of deterioration on discontinuation were noted. However, it could not be ascertained from the Clinical Study Report how or when discontinuation occurred. In addition to the run-in period, SP889 conducted an additional baseline phase (day –2 to day +1) consisting of in-patient hospitalization for two days. [redacted].[15] Post-randomization phases included a dose-titration phase followed by a maintenance phase during which the dose could not be modified. During the titration phase, one[6,10] or two[8] levels of back-titration were allowed if an AE developed. Patients entered the maintenance phase once the maximum allowable

dose had been reached, or when an optimal dose had been attained, as assessed on the basis of preset criteria for the control of symptoms and anticipated improvement at higher doses and tolerability. The maintenance period was four weeks for Mizuno 2014[6] and Nomoto 2014,[8] and at least four weeks for SP889.[10] Each trial also had a dose-tapering phase of two to four weeks due to the potential for parkinsonism-hyperpyrexia syndrome (neuroleptic malignant syndrome) and other withdrawal symptoms; this phase was not included in the efficacy outcome assessment, but was included for safety.

4.2.2 Populations

a) Inclusion and exclusion criteria

Two of the trials, Mizuno 2014[6] and Nomoto 2014,[8] enrolled patients with APD (i.e., Hoehn & Yahr stages 2 to 4), all of whom were on levodopa and experiencing at least one issue associated with levodopa treatment, such as motor fluctuations (wearing-off phenomena), dyskinesia, or dystonia, or were unable to tolerate an increase in levodopa because of AEs. The third trial, SP889,[10] enrolled patients who had investigator-defined, unsatisfactory control of early morning symptoms and were at any stage of disease. In the latter trial, although treatment with levodopa was not a requirement for enrolment, the majority of participants were on levodopa. [redacted].[15] Use of long-acting levodopa was not specifically mentioned as an exclusion criterion in the other two trials. Differences in the specific criteria used to diagnose PD and the lower age limit across trials are not considered to be of importance given the hallmark features of PD and its higher prevalence in adults over the age of 50. Exclusion criteria were similar across trials; patients who were more likely to experience AEs — e.g., patients with cardiac disease, including QT prolongation, psychiatric symptoms, orthostatic hypotension, or a history of skin sensitivity — were screened out.

b) Baseline characteristics

APD studies

Both the Mizuno 2014 and Nomoto 2014 trials were conducted in Japan.[6,8] Mean age was similar in the two trials (65 to 67 years). Overall, more females than males were enrolled in both trials (e.g., 59% of participants were female in the largest trial, Mizuno 2014), and slightly more females received active drug than placebo in both trials. The average duration of PD was similar in Mizuno 2014 (6.9 years) and Nomoto 2014 (6.5 years), although the average PD duration was unequal in the two intervention groups of Nomoto 2014 (rotigotine 7.5 years; placebo 5.4 years). *Off* time was measurable at baseline in 65% to 69% of participants in both trials. Duration of *off* time was approximately five hours across treatment groups in Mizuno 2014 and approximately six to seven hours in Nomoto 2014, based on patient diaries. Baseline measurements including UPDRS Part III (motor examination) (*on*) and UPDRS Part II (ADL) were similar across intervention groups in both trials.

In Mizuno 2014,[6] the majority of patients were experiencing a wearing-off phenomenon (65% to 68%); the dose of levodopa was deemed insufficient in 83% to 85% of patients. Few patients had dyskinesia during *on* time, with slightly more patients experiencing this complication at baseline in the rotigotine group (14%) compared with patients in the ropinirole (10%) or placebo (6%) group. However, this was a small subset of patients overall, and the small difference between groups is unlikely to have affected efficacy outcomes to a meaningful extent. Approximately half (54%) of patients had prior experience with DAs, including pramipexole (21% to 31% of patients) and ropinirole (11% to 14% of patients). Of the total population, about a third (30% to 37%) in each group had experienced worsening of PD symptoms with discontinuation of prior DAs. It is unclear whether all patients with prior DAs had the DA discontinued specifically for pre-trial screening and enrolment. In Nomoto 2014,[8] a similar proportion of patients were experiencing wearing-off phenomenon (65%) and insufficient levodopa effect (83%).

Dyskinesia was not measured at baseline in this trial. The proportion of patients with gastrointestinal disorders (e.g., gastroparesis, dysphagia, absorption problems) was not reported for the APD studies.

Mixed population studies

SP889[10] was a multinational trial in which the majority of participants were Caucasian. In contrast to the Japanese APD studies, SP889 enrolled more males than females (36% female, 64% male). SP889 had a shorter average duration of disease as anticipated based on enrolment criteria (see Table 6) and did not report daily *off* time for those patients who experienced it. Approximately 80% of participants were taking levodopa, so the population was predominantly APD. All participants had investigator-defined early morning problems with motor function that were likely related to wearing-off of medication. UPDRS Part III (motor) scores and Parkinson's Disease Sleep Scale (PDSS)-2 scores were similar at baseline in the intervention groups. Approximately 27% to 28% of the participants had gastrointestinal disorders at baseline, which were not further defined.

None of the studies identified participants who were intolerant of or uncontrolled on pramipexole or ropinirole IR.

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS FOR ADVANCED PARKINSON'S DISEASE STUDIES, FULL ANALYSIS SET

Characteristics	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 84	Rotigotine N = 86	Placebo N = 86
Sex	M 61 (37%) F 103 (63%)	M 68 (41%) F 98 (59%)	M 42 (50%) F 42 (50%)	M 34 (40%) F 52 (61%)	M 44 (51%) F 42 (49%)
Age mean (SD)	64.8 (8.8)	67.0 (7.9)	65.3 (7.9)	67.0 (6.8)	66.8 (8.3)
Duration of PD mean (SD)	7.0 (4.9)	6.8 (4.2)	7.0 (4.2)	7.5 (6.0)	5.4 (3.0)
Hoehn & Yahr stage average	2.7 (0.6)	2.8 (0.6)	2.8 (0.6)	NR	NR
Hoehn & Yahr stage, n (%)	NR	NR	NR	Stage 2: 11 (12.8%) Stage 2.5: 22 (25.6%) Stage 3: 45 (52.3%) Stage 4: 8 (9.3%)	Stage 2: 22 (25.6%) Stage 2.5: 20 (23.3%) Stage 3: 38 (44.2%) Stage 4: 6 (7.0%)
Proportion with *off* time, n (%)	111 (67.7%)	113 (68.1%)	57 (67.9%)	56 (65.1%)	59 (68.6%)
Off time (hours), mean (SD)	4.5 (3.4)	5.0 (3.6)	4.9 (3.0)	6.6 (3.5)	6.0 (3.4)
On time (hours), mean (SD)	13.1 (3.6)	12.5 (3.8)	12.6 (3.7)	NR	NR
Proportion experiencing *on* time with troublesome dyskinesia n (%)	23 (14.0%)	16 (9.6%)	5 (6.0%)	NR	NR
On time with troublesome dyskinesia (hours), mean (SD)	2.4 (2.6)	1.6 (1.5)	0.7 (1.2)	NR	

Characteristics	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 84	Rotigotine N = 86	Placebo N = 86
Early morning dystonia, n (%)	24 (14.6%)	25 (15.1%)	13 (15.5%)	NR	NR
Gastrointestinal disorders, n (%)	NR	NR	NR	NR	NR
Levodopa Dose and Issues with Levodopa					
Pre-treatment levodopa, n (%)	164 (100%)	166 (100%)	84 (100%)	86 (100%)	86 100%
Levodopa (mg) mean (SD)	367.7 (151.9)	350.6 (125.3)	370.5 (146.6)	348.8 (170.3)	329.1 (132.5)
Wearing-off, n (%)	107 (65.2%)	110 (66.3%)	57 (67.9%)	[redacted]	
On-off phenomenon, n (%)	26 (15.9%)	35 (21.1%)	17 (20.2%)	[redacted]	
Delayed-*on*, no-*on* phenomenon, n (%)	25 (15.2%)	33 (19.9%)	17 (20.2%)	[redacted]	
Dyskinesia, n (%)	42 (25.6%)	43 (25.9%)	15 (17.9%)	[redacted]	
Levodopa effect insufficient n (%)	139 (84.8%)	138 (83.1%)	73 (86.9%)	[redacted]	
Concomitant Anti-Parkinson Medication					
Dopamine receptor agonists, n (%)	[redacted]	[redacted]	[redacted]	NA (exclusion criterion)	NA
Prior DA discontinuation worsened PD	[redacted]	[redacted]	[redacted]	NA	NA
Breakdown of: Ropinirole	[redacted]	[redacted]	[redacted]	NA	NA
Breakdown of: Pramipexole	[redacted]	[redacted]	[redacted]	NA	NA
Breakdown of: Cabergoline	[redacted]	[redacted]	[redacted]	NA	NA
Breakdown of: Pergolide	[redacted]	[redacted]	[redacted]	NA	NA
Breakdown of: Talipexole	[redacted]	[redacted]	[redacted]	NA	NA
Breakdown of: Bromocriptine	[redacted]	[redacted]	[redacted]	NA	NA
Entacapone, n (%)	40 (24.4%)	57 (34.3%)	33 (39.3%)	0	0
Anticholinergic drugs, n (%)	33 (20.1%)	32 (19.3%)	16 (19.0%)	19 (22.1)	11 (12.8)
Amantadine, n (%)	38 (23.8%)	40 (24.1%)	27 (32.1%)	36 (41.9)	31 (36.0)
Selegiline, n (%)	60 (36.6%)	69 (41.6%)	35 (41.7%)	42 (48.8)	41 (47.7)
Droxidopa, n (%)	12 (7.3%)	11 (6.6%)	8 (9.5%)	NR	NR
Zonisamide, n (%)	16 (9.8%)	13 (7.8%)	12 (14.3%)	NR	NR
Baseline UPDRS Part II (ADL) Score					
UPDRS Part II (average *on* and *off* state)	11.0 (6.2)	10.6 (5.6)	11.0 (7.0)	11.8 (6.1)	10.3 (4.6)
Baseline UPDRS Part III (Motor Function) Score					
UPDRS Part III (*on* state) mean (SD)	25.8 (10.6)	25.8 (11.0)	25.6 (10.4)	28.1 (12.2)	26.2 (10.4)

Characteristics	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 84	Rotigotine N = 86	Placebo N = 86
Nocturnal Sleep — PDSS-2 Score					
PDSS-2	12.3 (8.9)	14.3 (9.2)	15.0 (9.2)	NR	NR

ADL = activities of daily living; DA = dopamine agonist; F = female; M = male; NA = not applicable; NR = not reported; PD = Parkinson's disease; PDSS = Parkinson's Disease Sleep Scale; UPDRS = Unified Parkinson's Disease Rating Scale; SD = standard deviation.
Note: The following drugs are not available in Canada: cabergoline, droxidopa, talipexole, and zonisamide.
Source: Mizuno 2014;[6] Nomoto 2014;[8] clinical trials.gov for Nomoto 2014;[49] manufacturer's response to request for additional information, Aug. 6, 2015.[51]

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS FOR SP889 (MIXED POPULATION)

Characteristics	SP889	
	Rotigotine N = 191	Placebo N = 96
Sex	M 123 (64%) F 68 (36%)	M 61 (64%) F 35 (36%)
Age mean (SD)	64.8 (9.3)	64.4 (10.6)
< 65 years	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]
Race/ethnicity	Caucasian 177 (93%) Black 1 (1%) Asian 1 (1%) Other 11 (6%)	Caucasian 85 (89%) Black 1 (1%) Asian 1 (1%) Other 9 (9%)
Duration of PD mean (SD)	4.6 (0.2)	4.9 (4.6)
Concomitant gastrointestinal disorders, NOS	[redacted]	[redacted]
Pre-treatment Parkinson's Medication		
Levodopa use, n (%)	155 (81%)	79 (82%)
Other concomitant Parkinson's medication		
Dopaminergic drugs	[redacted]	[redacted]
Dopa and dopa derivatives	[redacted]	[redacted]
Dopamine agonists	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Adamantane derivatives	[redacted]	[redacted]
Baseline UPDRS Part III (motor) Score		
UPDRS Part III mean (SD)	29.6 (12.3)	32.0 (13.3)
Nocturnal Sleep – PDSS-2 Score		
PDSS-2 Score Mean (SD)	19.3 (9.3); range: 1 to 49	20.5 (10.4); range: 3 to 49

F = female; M = male; NOS = not otherwise specified; PD = Parkinson's disease; PDSS = Parkinson's Disease Sleep Scale; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Trenkwalder 2011;[10] Clinical Study Report, SP889.[15]

4.2.3 Interventions

Treatments and dosing regimens are summarized in Table 9. All three studies[6,8,10] used a titration regimen up to an individualized optimal dose or the maximal allowable dose of 16 mg/24 h of rotigotine. The maximum dose corresponds to the maximum approved dose for APD in Canada.

Mizuno 2014[6] compared rotigotine with placebo and with ropinirole up to 15 mg/day for 16 weeks' duration (dose escalation/maintenance phase). The maximum allowable dose for ropinirole is less than the maximum recommended dose in Canada, which is 24 mg/day. Rotigotine was initiated at 2 mg/24 h and increased every week by 2 mg/24 h up to 16 mg/24 h. Ropinirole was initiated at 0.75 mg (0.25 mg three times daily), increased weekly by 0.75 mg to 3.0 mg/day, then increased to 15 mg/day in weekly increments of 3.0 mg to match the titration scheme of rotigotine. [redacted][7,52]. [redacted].[52] Incremental increases could be stopped if AEs occurred, if the optimal dose in terms of symptom control was attained, or if an AE resolved during back-titration. Nomoto 2014[8] and SP889[10] had a similar titration scheme for rotigotine. The optimal dose for SP889 was defined by adequate control of early morning symptoms. One or two levels of back-titration were allowed during the titration phase, depending on the trial (Table 9). Patch sites were rotated on a daily basis for all three trials. Matching placebos were used for blinding, as well as a double-dummy technique in Mizuno 2014.[6]

TABLE 9: DOSING REGIMENS — ADVANCED PARKINSON'S DISEASE AND MIXED POPULATION STUDIES

Study	Drug	Maximum Dose	Starting Dose	Increments	Back-titration Allowed	Duration of Dose-titration/ Maintenance Phase
Mizuno 2014	Rotigotine[a]	16 mg/24 h transdermal patch	2 mg/24 h transdermal patch	2 mg every week	1 level	16 weeks • 12 weeks' titration • 4 weeks' maintenance
	Ropinirole	15 mg/day PO	0.75 mg/day PO (0.25 mg t.i.d)	0.75 mg/day every week up to 3.0 mg/day, then 1.5 mg every week up to 15 mg/day		
	Placebo	Transdermal patch; tablet PO	--	--		
Nomoto 2014	Rotigotine	16 mg/24 h transdermal patch	2 mg/24 h[a] transdermal patch	2 mg every week	2 levels	12 weeks to 14 weeks[b] • 8 weeks' titration • 4 weeks' maintenance
	Placebo	Transdermal patch	--	--		

Study	Drug	Maximum Dose	Starting Dose	Increments	Back-titration Allowed	Duration of Dose-titration/ Maintenance Phase
SP889	Rotigotine	16 mg/24 h transdermal patch	2 mg/24 h transdermal patch	2 mg every week	1 level	12 weeks • 8 weeks' titration (maximum) • ≥ 4 weeks' maintenance
	Placebo	Transdermal patch	--	--		

PO = orally; t.i.d. = three times daily.
[a] Rotigotine doses for Mizuno 2014 and Nomoto 2014, depending on the source of data, have been transformed from total dose to nominal dose (2 mg = 10 cm^2, 4.5 mg total drug).
[b] Maximum 14 weeks if 1 to 2 levels of back-titration from higher doses.
Source: Mizuno 2014;[6] Nomoto 2014;[8] SP889.[10]

a) Concomitant Medications

For Mizuno 2014,[6] all patients had to be on stable doses of levodopa (in combination with benserazide or carbidopa) from 28 days prior to the start of test dose to the end of the dose escalation and maintenance period. A mean levodopa dose of 351 mg/day to 371 mg/day during the clinical trial period was reported (Table 10). The clinical trial period includes the dose-tapering period (not included for efficacy) during which dosage adjustment could be made to compensate for the tapering of the active test drug. Levodopa dosage for the maintenance period alone was not identified from the available documentation. The average levodopa doses are relatively modest compared with usual practice in Canada. Additional concomitant medications that were allowed in doses that were stable prior to baseline included other anti-Parkinson medications: MAO inhibitors (selegiline), the COMT inhibitor entacapone, anticholinergic drugs, amantadine, droxidopa, and zonisamide. The least frequently used drugs, droxidopa (used to treat orthostatic hypotension) and zonisamide, are not approved in Canada for PD. The only drug that differed across treatment groups was entacapone, which was least frequently used in the rotigotine group (Table 10). Domperidone was permitted to treat nausea and vomiting. In Nomoto 2014,[8] similar average levodopa doses were used as in Mizuno 2014. Concomitant anti-Parkinson drugs in fixed stable doses prior to test treatment were allowed, but no patients were on entacapone because this drug was not approved in Japan at the time the trial took place (Table 10).

TABLE 10: CONCOMITANT ANTI-PARKINSON MEDICATION DURING THE CLINICAL TRIAL PERIOD — STUDIES ON ADVANCED PARKINSON'S DISEASE (FULL ANALYSIS SET)

Drug	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
Levodopa					
Levodopa, n (%)	164 (100%)	166 (100%)	84 (100%)	86 (100%)	86 (100%)
Levodopa (mg), mean (SD)	367.7 (151.9)	351.2 (125.5)	370.5 (146.6)	348.8 (170.3)	329.1 (132.5)
Other Concomitant Anti-Parkinson Medication, n (%)					
Entacapone	40 (24.4%)	58 (34.9%)	33 (39.3%)	0	0
Anticholinergic drugs	33 (20.1%)	32 (19.3%)	16 (19.0%)	19 (22.1%)	11 (12.8%)
Amantadine	39 23.8%)	39 (23.5%)	27 (32.1%)	36 (41.9%)	31 (36.0%)
Selegiline	60 (36.6%)	69 (41.6%)	35 (41.7%)	42 (48.8%)	41 (47.7%)
Droxidopa	12 (7.3%)	11 (6.6%)	6 (7.1%)	NR	NR
Zonisamide	16 (9.8%)	13 (7.8%)	12 (14.3%)	NR	NR

NR = not reported; SD = standard deviation.
Note: Data are shown for Mizuno 2014 for entire clinical trial period, i.e., from initiation to last follow-up. Data for the maintenance period were not provided separately.
Note: The following drugs are not available in Canada: cabergoline, droxidopa, and zonisamide.
Source: Clinical Study Report, Mizuno 2014;[7] Nomoto 2014.[6]

For SP889, 18% to 19% of the population was not on levodopa at trial initiation.[10] [redacted].[15] The mean dose for the subset on levodopa in each treatment group was higher than in the other trials, perhaps reflecting fewer restrictions on adjustment in the titration phase or titration to different symptoms of interest, i.e., early morning symptoms (Table 11). SP889 did not allow controlled release levodopa. For this trial, sleep-modifying medication was also permitted in stable doses, as were antiemetics to treat nausea/vomiting.

TABLE 11: CONCOMITANT PARKINSON'S MEDICATIONS DURING THE MAINTENANCE PERIOD — MIXED POPULATIONS (SAFETY SET)

Intervention Group	SP889	
	Rotigotine N = 191	Placebo N = 96
Concomitant anti-Parkinson medications during maintenance period, n (%)		
Any anti-Parkinson drug	[redacted]	[redacted]
Dopaminergic drugs	[redacted]	[redacted]
Dopa and dopa derivatives	[redacted]	[redacted]
Monoamine oxidase B inhibitors	[redacted]	[redacted]
Adamantane derivatives	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other dopaminergic drugs	[redacted]	[redacted]
Dopamine agonists	[redacted]	[redacted]
Anticholinergic drugs	[redacted]	[redacted]
Levodopa dose (mg), mean (SD)		
Baseline	[redacted]	[redacted]
Start of maintenance	[redacted]	[redacted]
End of maintenance	[redacted]	[redacted]
Dose at withdrawal	[redacted]	[redacted]

SD = standard deviation.
Source: Clinical Study Report, SP889.[15]

4.2.4 Outcomes

a) Unified Parkinson's Disease Rating Scale

The UPDRS assesses the signs and symptoms of PD, providing a measure of disability and impairment. It comprises four parts: Part I (mentation, behaviour and mood, four items); Part II (activities of daily living [ADL], 13 items); Part III (motor examination, 14 items), and Part IV (complications of therapy, 11 items).[53] Parts I, II, and IV are based on information from the preceding week and are interview-based, whereas Part III is a clinical examination of motor assessment conducted by a health professional. Parts I to III are scored on a 5-point scale (0 to 4) for each item, with higher scores indicating greater disability or worsening symptoms; then the item scores are summed for each part. Part IV contains some items that are scored from 0 or 1 based on the presence (1) or absence (0) of the symptom in addition to items using a 5-point scale. See Appendix 5: Validity of Outcome Measures.

The primary end point in all three trials was the change from baseline in the motor component of the UPDRS (Part III). UPDRS Part III includes an assessment of speech, tremors, rigidity, repeated movements (e.g., rapidly alternating movements of the hands), as well as gait, postural stability, and other kinetic parameters, with total score ranging from 0 (no disability) to 56 (worst). A reduction in score represents an improvement. UPDRS assessments took place on multiple clinic visits for each trial, with the primary end point assessed at the end of the maintenance period of each trial.

In APD, fluctuations in motor function occur in most patients, so it is important that patients be examined in similar conditions, i.e., in defined *on* and *off* states. For example, the latter may be achieved by examining the patient 12 hours after the last dose of medication. Mizuno 2014[6] and Nomoto 2014[8] measured UPDRS Part III in the *on* state. In contrast, SP889 assessed motor function in the early morning, prior to re-application of a new patch, when therapeutic benefit is wearing off; this time period is practically defined as an *off* state (SP889).[10]

Other parts of the UPDRS, Parts I,[6,8] II,[6,8,10] and IV,[6,8] were assessed in the studies. For Mizuno 2014, Part II (ADL) was assessed in *on* and *off* states as well as averaged across both states.[6] Each study also reported UPDRS Part II + Part III for a subtotal score. Several estimates of a minimal clinically important difference (MCID) have been reported for the various UPDRS sum and subtotal scores. For the minimal clinically important improvement in UPDRS Part III, four studies reported values ranging from 2.4 points to 6.6 points. The studies varied in methodology, including patient population (EPD, a mix of all stages of PD, or APD), interventions, and study type.[54-57] For further information, see Appendix 5: Validation of Outcome Measures.

b) Nocturnal Sleep Disturbance

PDSS-2 was the co-primary end point for SP889,[10] and was also assessed in Mizuno 2014.[8] PDSS-2 consists of 15 questions about sleep and nocturnal disturbances over the preceding week. The validated scale is subclassified into three domains: 1) nocturnal motor symptoms, such as akinesia, early morning dystonia, tremor during waking periods at night, and rapid eye movement behaviour disorder; 2) nocturnal non-motor symptoms, such as hallucinations, confused states, pain, muscle cramps, difficulties in breathing with snoring, and immobility; and 3) sleep-specific disturbances, such as insomnia, sleep maintenance, unrestored sleep, having to get up at night because of nocturia, and overall quality of sleep. Patients (or caregiver proxies) rate each question on a scale from 0 (never) to 4 (very frequent), with total scores from 0 (no disturbance) to 60 (maximum disturbance).[58] Estimates of MCID have not been published. See Appendix 5: Validity of Outcome Measures for further information.

c) Time Spent *Off*

The reduction in absolute time spent *off* from baseline to the end of the DB maintenance phase was a primary outcome in two trials.[6,8] Reduction in absolute time spent *off* was measured by self-completed Parkinson's Disease Home Diaries (PDHD). The PDHD is a validated tool that assesses the amount of *on* and *off* time patients experience in a 24-hour period.[54] Further details on diary use were not provided for either trial. Published MCIDs for *off* time range from 1.3 to 1.9 hours.[54,55] See Appendix 5: Validity of Outcome Measures.

d) Response to Therapy

Responder rates were reported for UPDRS Part III sum scores in Mizuno 2014, defined as ≥ 20% or ≥ 30% reduction in score from the baseline. Taking into account the baseline values reported in this trial, a 20% reduction would be approximately 5 points, and less than the MCID of 6.5 points.[55] This defined cut point therefore does not meet a clinically meaningful threshold, whereas a 30% reduction from baseline values exceeds the available MCID. Responder rates using the same thresholds for UPDRS Part III were also reported for Nomoto 2014, which had similar baseline values as Mizuno 2014. For *off* time, response was defined as a 30% reduction from baseline in both Mizuno 2014 and Nomoto 2014. For Mizuno 2014, this amount of change from baseline would meet the lower limit of a range of MCIDs (1.3 to 1.9 hours) but would not exceed the higher MCID value.[54,55] Participants in Nomoto 2014 had a greater amount of *off* time at baseline and a 30% reduction would be in the range of 1.8 hours to 2.0 hours, approximating the higher threshold for MCID. Responses to therapy as defined by 20%, 25%, or

30% reduction from baseline in UPDRS Part II, UPDRS Part III, and UPDRS Part II + III were also reported for SP889, but were not preplanned analyses.

e) Health-related Quality of Life

Health-related quality of life (HRQoL) was measured in one trial using a short form of the Parkinson's Disease Questionnaire (PDQ)-8, which was completed at baseline and at the end of the maintenance phase or withdrawal assessment. The PDQ-8, derived from the PDQ-39, is a validated tool designed for self-completion by patients. It consists of one item each on the following dimensions of quality of life (QoL): mobility, ADL, emotions, stigma, social support, cognition, communication, and bodily discomfort. Each item is graded on a 5-point scale (where 0 = never and 4 = always), with higher scores indicating worse QoL. Scores are summed and transformed into a score from 0 to 100. The PDQ-8 index score of patients who reported that their health status worsened only "a little bit" ranged from 5.8 points to 7.4 points in a population of patients with Hoehn and Yahr stages 1 to 3.[59] It is not known whether the reported MCID also directly applies to improvement rather than worsening.

f) Adherence

Adherence was measured in each trial, but the precise method of measurement could not be ascertained for Mizuno 2014 and Nomoto 2014. [redacted].[15]

Method of Assessment for Harms

Patients were assessed at least every two weeks during the maintenance phase of each trial, and more frequently during the preceding titration phase. A subset of AEs was actively ascertained through the use of UPDRS Part IV (complications of therapy), the modified Minnesota Impulse Control Disorder Interview (mMIDI), echocardiography,[7,15] and electrocardiogram (ECG) monitoring, including assessment of QT prolongation and bloodwork.

4.2.5 Statistical analysis

a) Advanced Parkinson's disease

- The main analysis for the primary end points, UPDRS Part III, in both studies, was conducted on the full analysis set (FAS) population.
- Missing data for the primary outcomes were imputed using last observation carried forward (LOCF).

Mizuno 2014

- [redacted].[7] If superiority over placebo was verified, then the 95% CI for the mean difference in change from baseline between rotigotine and ropinirole was calculated and non-inferiority determined using the preset non-inferiority margin.
- Sample size for superiority of rotigotine over placebo was calculated based on a two-tailed significance level of 5%, 90% power, and effect sizes from two prior placebo-controlled trials that reported a between-group mean difference in change from baseline of 5.4 points (SD: 9.0) (rotigotine versus placebo)[8] and 5.0 points (SD: 8.7) (ropinirole versus placebo).[60]

- The non-inferiority margin for comparison with ropinirole was chosen on the basis of effect sizes in placebo-controlled RCTs of rotigotine, pramipexole, and ropinirole conducted in Japan and elsewhere. The range of treatment effect sizes obtained from these trials, i.e., the between-group (active comparator versus placebo) mean difference in the change from baseline, was 3.8 to 5.4 points for rotigotine,[4,8,61] 5.0 to 6.5 points for ropinirole,[60,62] and 5.9 to 6.9 points for pramipexole.[63,64] The sample size requirement was calculated to be 88 patients for the rotigotine group and 44 patients for the placebo group.[7] Based on the prior treatment effect data and, discussions with the Japanese regulatory authority, a non-inferiority margin was preset at 2.5 points,[7,65] which is less than the available MCID of 6.5 points.
- Sample size calculation for the assessment of non-inferiority of rotigotine to ropinirole was based on the number of patients required to ensure an 80% probability that the upper limit of the 95% CI for the between-group mean difference in change from baseline was no more than the non-inferiority margin (N = 152 in each group). Thus, the study's recruitment target was set at 160 patients for each active drug group and 80 patients for the placebo group (2:2:1 randomization).
- Adjusted means (least squares means) are provided in the publication for reported outcomes, conducted by analysis of covariance (ANCOVA) with treatment as factor and baseline value as a (continuous) covariate. This analysis was identified as the primary analysis of the primary outcome in the publication,[6] although this is not clear from the translated Clinical Study Report.[7] The Clinical Study Report identifies [redacted].[7]
- Many secondary outcomes were measured and reported. Secondary continuous outcomes are reported to have been analyzed [redacted].[7] For dichotomous outcomes, the proportion of patients who achieved a ≥ 20% or ≥ 30% reduction was calculated along with 95% CIs.

Nomoto 2014

- An English-language clinical study report is not available for this trial. The following is based on a clinical synopsis[9] and the publication.[8] Sample sizes were calculated based on a between-group mean difference in the change from baseline in UPDRS Part III score of 5 points, SD 11, and a power of > 80% to detect a significant difference between the two groups. No rationale is provided for choosing these parameters in the available English-language documentation.
- The primary end point, UPDRS Part III, was analyzed by between-group comparison using a t-test with a two-sided level of significance of 5%. Secondary analyses of the primary outcome using responder rates (the proportion of patients with a decrease of ≥ 20% or ≥ 30% from baseline sum score) were compared using two-sided chi square tests.
- Secondary outcomes (e.g., UPDRS Part II, *off* time) [redacted].[9] However, according to the publication methods,[8] the continuous measures were to be compared using the Kruskal–Wallis test, even though t-tests are reported. No rationale is given for the use of the non-parametric Kruskal–Wallis test. FAS with LOCF was also used for secondary outcomes.
- [redacted]

[redacted].[24] No rationale for these could be ascertained from the available English-language documentation.

b) Mixed population studies

SP889

- The co-primary outcomes were change from baseline to the end of the maintenance period in early morning UPDRS Part III score and PDSS-2 sum scores conducted on the FAS population.[10]
- Missing data for the primary outcomes [redacted].[15]
- If one item from a questionnaire was missing, the total scores were set to missing, and LOCF was used for imputation of the total scores. No sensitivity analysis was undertaken replacing only the missing item with LOCF.
- [redacted].[15]
- Both primary outcomes were analyzed by ANCOVA, with treatment and pooled sites (regions) as factors and the baseline value as a continuous covariate, and calculated as least squares mean.
- Sample size calculation was based on [redacted].[15] Justification for the chosen parameters was not provided.
- The same sample size, with a power of [redacted], was also sufficient to detect a difference in the change from baseline between rotigotine and placebo for the co-primary outcome, PDSS-2, based on a treatment difference of [redacted].[15] No justification was provided for the parameters chosen.
- The manufacturing process was changed during this trial due to a problem with crystallization in the original rotigotine patches.[66] [redacted].[15] .
- [redacted].[15]
- There were many secondary outcomes. [redacted].[15]

Analysis populations

Full Analysis Set: FAS was defined slightly differently in each trial. In Mizuno 2014, FAS included those participants who [redacted].[7] This dataset excluded patients [redacted].[7] For Nomoto 2014, all randomized patients who received at least one dose of trial medication were included in FAS.[8] However, this excluded [redacted]

[redacted]. [9] FAS in SP889 included patients who [redacted]. [15] The definitions of the FAS did not represent a true intention-to-treat analysis in any study.

Per-protocol set: For Mizuno 2014, in addition to excluding patients [redacted], the per-protocol set (PPS) excluded patients who [redacted]. [7] Similar exclusions for the PPS were identified in Nomoto 2014. [24] For SP889, the PPS comprised patients [redacted]. [15]

Safety data set: Mizuno 2014 included [redacted], in its safety set. [7] The safety set for Nomoto 2014 [8] included all randomized patients, and for SP889, [15] [redacted].

Additional data sets were defined in Mizuno 2014 [7] for pharmacokinetic and pharmacodynamics data, and in SP889, [15] a completer set.

To evaluate the non-inferiority of rotigotine to ropinirole, Mizuno 2014 provided three datasets for UPDRS Part III: a per-protocol analysis (with LOCF), FAS with LOCF, and an analysis on FAS without compensating for missing data (FAS-observed case). For Nomoto 2014 and SP889, FAS with LOCF was used for the primary outcome. In SP889, additional analyses of the co-primary outcomes were conducted on the PPS (with LOCF), a completer set (with LOCF), and FAS (observed cases) to test robustness of the findings.

4.3 Patient Disposition

Patient disposition is summarized in Table 12. For the APD studies, a total of 420 patients in Mizuno 2014 [6] and 214 in Nomoto 2014 [8] were randomized. The percentage of discontinuations was moderate: 14% to 20% in Mizuno 2014, and 14% to 16% in Nomoto 2014 across treatment groups, with 84% and 88% of participants completing the trials, respectively. AEs were the most frequent reason for discontinuation in both studies, with similar frequency across treatment groups (Table 12). In Mizuno 2014, there were more withdrawals due to adverse events (WDAEs) in the placebo group (11%) than in the two active drug treatment groups (7% to 8%), but overall numbers were low. More dropouts occurred because of lack of efficacy in the placebo group in both studies (Table 12). However, the number of dropouts in this category was small in both studies. In SP889, [10] 86% of patients completed the trial, with 13% of the rotigotine group and 17% of the placebo group discontinuing. The frequency of WDAEs was similar in both treatment groups (6% each).

TABLE 12: PATIENT DISPOSITION FOR STUDIES ON ADVANCED PARKINSON'S DISEASE POPULATION (ENROLLED SET)

Study	Mizuno 2014			Nomoto 2014	
Intervention	Rotigotine	Ropinirole	Placebo	Rotigotine	Placebo
Screened, n	NR			214	
Randomized, n (%)	168	167	85	87 (100%)	87 (100%)
Discontinued, n (%)	26 (15.5%)	23 (13.8%)	17 (20.2%)	12 (13.8%)	14 (16.1%)
FAS, n (%)	164 (97.6%)	166 (99.4%)	84 (98.8%)	86 (98.9%)	86 (98.9%)
PP, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, n (%)	168 (100%)	167 (100%)	85 (100%)	87 (100%)	87 (100%)
Reasons for Discontinuation n (%)					
Protocol violation	0	1 (0.6%)	0	--	--
AEs	13 (7.7%)	11 (6.6%)	9 (10.6%)	9 (10.3%)	7 (8.1%)
Lack of efficacy	[redacted]	[redacted]	[redacted]	0	4 (4.6%)
Withdrawal of consent	[redacted]	[redacted]	[redacted]	0	2 (2.3%)
Criteria for trial discontinuation as set out in protocol	[redacted]	[redacted]	[redacted]	3 (3.4%)	0
Physician decision other than for reasons above	[redacted]	[redacted]	[redacted]	--	--
Other	--	--	--	0	1 (1.2%)

AE = adverse event; FAS = full analysis set; NR = not reported; PP = per-protocol.
Source: Clinical Study Reports: Mizuno;[7] Mizuno 2014;[6] Nomoto 2014;[8] Nomoto.[2.4]

TABLE 13: PATIENT DISPOSITION FOR STUDIES ON MIXED POPULATIONS (ENROLLED SET)

SP889		
Participants	**Rotigotine**	**Placebo**
Screened, n	333	
Randomized, n (%)	[redacted]	[redacted]
Discontinued, n (%)[a]	[redacted]	[redacted]
FAS, n (%)	[redacted]	[redacted]
PP, n (%)[b]	[redacted]	[redacted]
Safety, n (%)	[redacted][c]	[redacted][c]
Reasons for Discontinuation n (%)		
Protocol violation	[redacted]	[redacted]
AEs	[redacted][d]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Other	[redacted]	[redacted]

AE = adverse event; FAS = full analysis set; PP = per-protocol set.
[a] Discontinuations include [redacted]
[b] [redacted]
[c] [redacted][15] [redacted][10] [redacted].
[d] [redacted].
Source: Clinical Study Report, SP889.[15]

4.4 Exposure to Study Treatments

All three trials[6,8,10] used a dose of rotigotine up to 16 mg/24 h. In Mizuno 2014, the dose of ropinirole was up to a maximum of 15 mg/day.[6]

a) Studies on advanced Parkinson's disease

In Mizuno 2014, the mean maintenance dose was 12.9 mg/24 h for rotigotine and 9.2 mg/day for ropinirole.[6] Duration of exposure during the dose escalation and maintenance periods was an average of 103 days (SD 25) for rotigotine, 103 days (SD 26) for ropinirole and 100 days (SD 30) for placebo (Table 14). Overall, 81 out of 168 patients (48%) achieved the maximum dose of rotigotine; five patients who received the maximum rotigotine dose did not enter the maintenance phase. Of the patients who entered the maintenance phase, 50% (76 out of 153) in the rotigotine group and 29% in the ropinirole group received the maximum allowable dose of active drug. In the rotigotine group, of the 76 patients who received the maximum dose of rotigotine, 38 received the maximum sham dose of ropinirole and 38 received less than the maximum placebo dose of ropinirole, because of the differences in the durations of the titration schemes. Note that there is a discrepancy between the clinical study report[7,52] and the Mizuno 2014 publication;[6] [redacted] (see Appendix 4: Detailed Outcome Data).[52] Exposure by dose is presented in Table 15. Reasons for moving into the maintenance phase without reaching the maximum dose are presented in Appendix 4: Detailed Outcome Data.

In Nomoto 2014, a similar proportion of participants in the maintenance phase were taking the maximal allowable dose of rotigotine (51%); mean and median maintenance doses are not available.[8,50] Table 15 provides the distribution of exposure during the titration and maintenance phases. Duration of exposure was, on average, [redacted] for rotigotine and [redacted] for placebo.[50]

b) Studies on mixed populations

The average duration of exposure was shorter in SP889 than in Mizuno 2014: 71 days for rotigotine and 73 days for placebo (Table 16).[10] The mean dose of rotigotine, calculated based on the safety set, was 9.6 mg/24 h, and based on FAS, 11.2 mg/24 h.

TABLE 14: TOTAL DAYS EXPOSURE OF STUDY MEDICATION — SAFETY ANALYSIS SET

Drug	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87
Duration of Exposure in Titration and Maintenance Period					
Days, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Days, median/range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose in Maintenance Phase					
N (%) moving into maintenance phase	153 (91.1%)	153 (91.6%)	75 (88.2%)	[redacted]	[redacted]
Mean maintenance dose of test interventions	12.9 mg/24 h	9.2 mg/day	NA	[redacted]	[redacted]
Maximum dose at start of maintenance period, n (%)	76/153 (49.7%)	44/153 (28.8%)	31/75 (41.3%)	[redacted]	[redacted]

AE = adverse events; NA = not applicable; NR = not reported.
Source: Mizuno 2014,[6] Clinical Study Report, Mizuno;[7] manufacturer's response to request for additional information, Aug. 4, 2014;[50] manufacturer's response to request for additional information, Aug. 11, 2014.[52]

TABLE 15: ROTIGOTINE EXPOSURE BY DOSE REACHED IN ADVANCED PARKINSON'S DISEASE STUDIES, DOSE ESCALATION AND MAINTENANCE PERIOD, SAFETY SET

Mizuno 2014 — Active Drug Exposure in Escalation and Maintenance Period					
Rotigotine Exposure N = 168		**Extent of Rotigotine Exposure (Days)/n**			
Dose Reached	**N**	**Mean (SD)**	**Median**	**Range**	
2 mg/24 h					
4 mg/24 h					
6 mg/24 h					
8 mg/24 h					
10 mg/24 h					
12 mg/24 h					
14 mg/24 h					
16 mg/24 h					
Rotigotine total	168				
Ropinirole Exposure N = 166		**Extent of Ropinirole Exposure (Days)/n**			
Dose reached	**N**	**Mean (SD)**	**Median**	**Range**	
0.75 mg to 3.0 mg					
4.5 mg to 6.0 mg					
7.5 mg to 9.0 mg					
10.5 mg to 12.0 mg					
13.4 mg to 15.0 mg					

Nomoto 2014: Rotigotine Exposure in Titration/Maintenance Period													
Dose reached	**N**	**Mean (SD)**	**Median**	**Range**									
2 mg/24 h													
4 mg/24 h													
6 mg/24 h													
8 mg/24 h													
10 mg/24 h													
12 mg/24 h													
14 mg/24 h													
16 mg/24 h													
Rotigotine Total	83												

SD = standard deviation.

Source: Clinical Study Report, Mizuno;[7] Nomoto 2014, manufacturer's response to request for additional information, Aug. 4, 2015.[50]

TABLE 16: STUDY MEDICATION EXPOSURE IN ROTIGOTINE GROUP BY DOSE DURING MAINTENANCE PERIOD IN STUDY SP889

SP889: Rotigotine Exposure in Maintenance Period (Safety Set) N = 257				
Maintenance Dose/n	**N**	**Extent of Exposure (Days)**		
		Mean (SD)	**Median**	**Range**
Placebo (0 mg)	[redacted]	[redacted]	[redacted]	[redacted]
2 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
4 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
6 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
8 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
10 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
12 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
14 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
16 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
Rotigotine total	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: Clinical Study Report, SP889.[15]

4.5 Critical Appraisal

4.5.1 Internal validity

The risk of bias for each trial was assessed using domains identified in the Cochrane Collaboration risk of bias tool.[67] Empirical evidence indicates that bias in these domains can lead to an overestimate or underestimate of treatment effect, particularly for more subjective outcomes.

a) Randomization methods and allocation concealment (selection bias)

A dynamic allocation procedure was used for randomization in two trials: Mizuno 2014[6] and Nomoto 2014.[8] Although many investigators consider this method acceptable,[68] it can compromise allocation concealment[69] and lacks the theoretical basis for eliminating bias on all known and unknown factors.[68] In Mizuno 2014, the process was designed to balance a number of factors across treatment groups: [redacted].[7] The exact methods are not described, including whether a random probability was added to the algorithm to reduce predictability.[69,70] [redacted].[50] [redacted].[15] The generation of randomization sequence was not adequately described, but was conducted by a computerized randomization schedule and a central interactive voice system that seem sufficient to conceal allocation.

b) Blinding (selection bias and performance bias)

All three trials were blinded. Mizuno 2014 used a double-dummy blinding technique, with placebo identical in appearance to the rotigotine transdermal patches and tablets identical in appearance to ropinirole. Blinding may have been compromised by the high incidence of application site reactions associated with rotigotine in Mizuno 2014[6] as well as Nomoto 2014,[8] and to a lesser extent in SP889,

which had a lower incidence of application site reactions. In Mizuno 2014, [redacted].[52] No trial assessed whether blinding was maintained throughout the treatment period.

c) Patient disposition and dropout rates (attrition bias)

Overall, withdrawal rates were moderate in all three trials, with the highest rate (20%) in the placebo group in Mizuno 2014.[6] Dropouts in the rotigotine and ropinirole groups in Mizuno 2014 were similar (14% to 16%). Although empirical data have not identified a single dropout threshold at which the validity of data is consistently compromised,[71] the dropout rates in the studies were at or below the historical threshold used: 20%. Reasons for dropouts were provided for each treatment group in all trials. There were some differences in reasons for withdrawal, with more discontinuations due to lack of efficacy in the placebo group, but numbers were relatively small (e.g., in Mizuno 2014, five patients [6%] in the placebo group dropped out for lack of efficacy, compared with two patients (1%) in the rotigotine group and one (< 1%) patient in the ropinirole group). The frequency of WDAEs was similar across treatment groups within each trial.

Selective outcome reporting was not identified as an issue for efficacy outcomes in Mizuno 2014 or SP889, based on the totality of available documentation. Not all efficacy outcomes were provided in the Nomoto 2014 publication[8] and clinical synopsis,[9] but were reported on the clinicaltrials.gov Web site.[49] Treatment-emergent harms data were reported for more common events, with a threshold incidence of 5% or 3% in a single treatment group, depending on the trial, and for harms identified by investigators as notable, but not for all harms.

Statistical Analysis

In Mizuno 2014,[7] derivation of the non-inferiority margin for the primary outcome (UPDRS Part III) was based on prior placebo-controlled trials of non-ergolinic DAs, including trials on rotigotine,[4,8,61] ropinirole,[60,62] and pramipexole,[63,64] with treatment effect sizes in the range of 3.8 to 5.4 points, 5.0 to 6.5 points, and 5.9 to 6.9 points. The margin was preset at 2.5 points in discussion with the Japanese regulatory authorities, and appears to be reasonable, taking into account the available MCID of 6.5 points, according to the clinical expert involved in this review. Appropriate hierarchies were carried out for the primary outcomes to control for type I error in Mizuno 2014 and SP889. There was no control for type I error in the secondary outcomes; therefore, these can be considered exploratory only.

For all studies, [redacted].[7,15] For non-inferiority trials, such as Mizuno 2014, FAS with LOCF may not be the most conservative approach.[72,73] A per-protocol analysis was provided for Mizuno 2014 [redacted].[7] FAS with LOCF [redacted].[7]

[redacted].[15] [redacted].[15]

For all three trials, the ability to capture uncommon events could be limited by the sample size. The grading of application site reactions by each investigator — from "–" to" "++++" in terms of severity — was not assessed for rater variability, and is unlikely to be very precise.

4.5.2 External validity

a) Population

The trials included in this review involved patients with APD or a mixed population that was predominantly APD. No new trials were identified for EPD. The findings are not generalizable to rotigotine monotherapy in EPD because of differences in concomitant medication use and the maximum recommended dose of rotigotine, as well as differences in disease features.

Two of the three trials, including the only active comparator trial, were conducted in Japan. Some minor differences in the pharmacokinetics of rotigotine in Japanese and Caucasian healthy adults have been noted.[74,75] In a steady-state pharmacokinetics study on healthy Japanese (N = 24) and Caucasian adults (N = 24), higher peak plasma concentration and overall exposure (area under the curve $[AUC]_{0\text{-}24\ (ss)}$) were observed in the Japanese participants, which was attributable to differences in body weight.[74] The mean apparent (nominal) dose was higher for Caucasians, and also ranged from 50% to 70% of the total dose in the patch, higher than indicated for the formulation in monograph information. It was suggested that the higher apparent doses among Caucasian study participants were due to differences in adhesiveness. Total rotigotine (unconjugated and conjugated) peak plasma concentration and $AUC_{0\text{-}24\ (ss)}$ were about 15% lower in Japanese than Caucasian adults, but conjugated forms are regarded as inactive, so this was deemed unlikely to be clinically relevant. Rotigotine is metabolized by multiple routes, including CYP450 enzymes, and the incidence of poor metabolizers for CYP2C19 is higher in Japanese populations than in Caucasian populations.[76,77] However, there are multiple routes of metabolism, and a study inhibiting CYP2C19 in Caucasians had little effect; therefore, the clinical relevance of this is uncertain. Inter-individual variability is high, and may be more important than ethnicity differences.

There were more females than males in the Japanese trials. Females have higher rotigotine plasma concentrations due to their smaller body mass indices.[74] This could affect the trials' generalizability to North American populations, since PD is more common in males, as reflected in multinational trials.[78] The results' applicability to usual clinical practice may also be limited, based on the relatively narrow inclusion criteria and extensive screening out of individuals who are more susceptible to AEs, as well as the restriction of some medications during the trial. Controlled release levodopa was explicitly prohibited in SP889 and not commented on in the other two trials. In addition, it seems likely that many elderly patients with APD may not have been able to meet the rigorous documentation required (e.g., diary keeping) and may have been screened out on this basis. Generalizability may also be limited by the levodopa doses used in the Japanese APD trials,[6,8] which, on average, were lower than those used in SP889[10] and in other APD trials (SP515[4] and SP650,[16] assessed in the prior CDR review).

Dose choice/comparators: The choice of ropinirole IR as the active comparator was appropriate in Mizuno 2014 because the long-acting formulations of ropinirole and pramipexole are not available in Canada. The maximum dose of ropinirole in this study was lower than the maximum allowable dose in Canada (24 mg/day),[43] but a dose up to 15 mg/day is consistent with usual clinical practice, according to this review's clinical expert. It is unclear whether the doses attained in Mizuno 2014 are equivalent (see Section 5: Discussion), and whether the difference in time to achieve the maximum dose in the titration phase (four weeks longer for ropinirole) may have affected efficacy outcomes. A discrepancy was noted in the Mizuno 2014 publication,[6] which reported that [redacted]

[redacted]; as verified in the Clinical Study Report[7] and by the manufacturer,[52] [redacted].

In SP889, the dose of rotigotine for participants with EPD was higher than the maximum recommended dose for EPD (8 mg/24 h), since all patients were titrated up to a maximum of 16 mg/24 h. The study's average dose during the maintenance period was 12.9 mg/24 h. This study's findings are, therefore, not generalizable to patients with EPD. In addition, the study focused on early morning symptoms, which may not be as relevant to patients with newly diagnosed, mild PD who are not experiencing wearing-off phenomena.

b) Outcome measures

Outcome measures were those commonly used to assess Parkinson's disease (UPDRS sum scores), as well as a relatively recent modification of the PDSS scale (PDSS-2). These outcome measures, including PDSS-2, have been validated (Appendix 5: Validity of Outcome Measures). MCIDs are available for UPDRS scores in APD populations, but an MCID is not published for PDSS-2, limiting interpretation of this outcome. SP889 assessed sleep disturbances using PDSS-2 but did not assess sleep architecture. Secondary outcomes included measurement tools that have not undergone validation (e.g., the Nocturnal Akinesia, Dystonia, and Cramps Score [NADCS]), and were exploratory only. The potential interdependence of the two co-primary end points — early morning motor function (UPDRS Part III) and nocturnal sleep disturbances (PDSS-2) — in SP889 was not discussed.

c) Length of follow-up

RCTs were 16 weeks or less in duration, each having a four-week maintenance period during which the maximal or individually optimized dose of drug was administered. The findings provide no information on long-term efficacy and safety for a drug administered on a chronic basis for a progressive disease during which response to at least some medications (e.g., levodopa) is modified. Although open-label extension studies of one year were conducted following completion of these trials, such data are limited by their selective enrolment of RCT completers and the lack of a control group (Appendix 6: Summary of Other Studies).

4.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 3: Inclusion Criteria for the Systematic Review). See Appendix 4: Detailed Outcome Data for additional data.

For continuous outcomes, i.e., UPDRS or PDDS-2 sum scores and *off* times, a between-group difference reported as a negative value means that rotigotine reduced the score or time, representing an improvement, more than the comparator did. For the dichotomous outcome "responders," a positive value reported for individual studies means there were more responders in the rotigotine group compared with the control group.

4.6.1 Advanced Parkinson's disease

a) UPDRS Part III (Motor Examination) Sum Score

The UPDRS Part III (*on* state) sum score was the primary efficacy outcome for the non-inferiority trial, Mizuno 2014, and for Nomoto 2014. In Mizuno 2014, baseline values were 26 to 28 points out of a possible 56 points. The adjusted mean difference (MD) in change from baseline between rotigotine and placebo was statistically significant: MD —6.4 points [95% CI, –8.6 to –4.2], demonstrating statistically significant superiority of rotigotine over placebo by an amount that approximates a published MCID of 6.5 points.[55] Because superiority over placebo was verified, non-inferiority was tested for the

comparison of rotigotine versus ropinirole. In a per-protocol analysis, the adjusted between-group mean difference in change from baseline for rotigotine versus ropinirole was [redacted] [95% CI [redacted]]. Because the upper limit of the 95% CI did not cross the preset non-inferiority margin of 2.5, rotigotine was shown to be non-inferior to ropinirole. Analyses using FAS with LOCF and FAS without data imputation were consistent with the per-protocol analysis.

In Nomoto 2014, a statistically significant between-group mean difference in the change from baseline was demonstrated for rotigotine versus placebo: mean difference –5.7 points [95% CI, –8.2 to –3.2], which did not meet the available minimal clinically important threshold of 6.5 points.[55] Adjusted mean differences (adjusted for a variety of covariates) were in the range of [redacted].[51]

Responder rates for UPDRS Part III sum scores were also reported in both trials, with response defined as a 20% or greater improvement in motor score. For the comparison of rotigotine versus ropinirole, in Mizuno 2014 there were 11% more responders compared with placebo — a difference that was statistically significant (Table 17).

TABLE 17: UPDRS PART III SUM SCORES (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON'S DISEASE

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
UPDRS Part III (*On* State) Sum Score					
Mean Change from Baseline to End of Maintenance Period, Per-protocol Analysis					
LS mean change (SE) from baseline to end point	[redacted]			NA	NA
Rotigotine — placebo difference in adjusted mean (95% CI)	[redacted]			NA	
Rotigotine — ropinirole difference in adjusted mean[a] (95% CI)	[redacted][b]			NA	
Mean Change from Baseline to End of Maintenance Period, FAS with LOCF					
Baseline mean (SD)	25.8 (10.6)	25.8 (11.0)	25.6 (10.4)	28.1 (12.2)	26.2 (10.4)
End of maintenance mean (SD)	[redacted]			NR	NR
Mean change from baseline	–10.9 (8.1)	–9.5 (8.7)	–4.5 (9.7)	–10.1 (9.0)	–4.4 (7.4)
Rotigotine — placebo difference	–6.4 (95% CI, –8.7 to –4.1) *P* < 0.001			–5.7 (95% CI, –8.2 to –3.2) *P* < 0.001	
Rotigotine — ropinirole difference	–1.4 (95% CI, –3.2 to 0.5) *P* = 0.156			NA	
LS mean change from baseline (SE)	–10.9 (0.6)	–9.5 (0.6)	–4.5 (0.9)	NR	NR
Rotigotine — placebo Difference in adjusted mean	–6.4 (95% CI, –8.6 to –4.2) *P* < 0.001			NR	
Rotigotine — ropinirole Difference in adjusted mean	–1.4 (95% CI, –3.2 to 0.4) *P* = 0.137			NA	

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
Responders (≥ 20% Reduction from Baseline), FAS with LOCF					
Responder rate, n (%)	132 (80.5%)	114 (69.1%)	47 (56.6%)	63 (73.3%)	37 (43.0%)
Rotigotine —placebo difference	23.9 (95% CI, 11.6 to 36.1) *P* < 0.001			30.2% (95% CI, 16.2 to 44.3) *P* < 0.001	
Rotigotine —ropinirole difference	11.4 (95% CI, 2.1 to 20.7) *P* = 0.017			NA	

CI = confidence interval; LS = least squares; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error.
[a] Test of non-inferiority with a pre-defined non-inferiority margin of 2.5 points.
[b] Data from p. 605, Table 14.2-2 of Clinical Study Report, Mizuno.[7]
Note: Missing end-of-maintenance-phase visit data were imputed using last observation carried forward (LOCF) method for outcomes unless otherwise specified. For Mizuno 2014, a per-protocol analysis is reported for UPDRS Part III, as this was used to test non-inferiority. Least squares mean from ANCOVA with treatment as a factor and baseline value as a continuous covariate are reported in the publication. Unadjusted means reported for Mizuno 2014 are from the Clinical Study Report.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014.[8]

b) *Off* time

For this outcome, only patients who were evaluable and had documented *off* time at baseline were included, so that change could be quantified. In Mizuno 2014,[6] baseline *off* time ranged from 4.5 to 5.0 hours, and in Nomoto 2014,[8] 6.0 to 6.6 hours. For the comparison of rotigotine versus ropinirole, ropinirole was associated with a mean 0.5-hour greater reduction in *off* time (adjusted), which was not statistically significant: MD 0.5 hours [95% CI, –0.2 to 1.2]. (The unadjusted mean difference was 0.7 hours and not statistically significant.) MCID estimates ranged from 1.3 hours, based on patient-reported global improvement,[55] to 1.9 hours, based on clinician global impression[54] (Appendix 7: Validity of Outcome Measures). The between-group difference in change from baseline for the comparison of rotigotine with ropinirole was less than the lowest MCID value. Rotigotine was statistically significantly superior to placebo: adjusted mean difference –1.1 hours [95% CI, –1.9 to –0.3]. The difference did not quite meet the lower estimate for MCID. The unadjusted mean difference for rotigotine versus placebo [redacted].[7]

In Nomoto 2014, rotigotine was better than placebo in reducing *off* time: unadjusted MD –1.4 hours (95% CI, –2.5 to –0.3), meeting the lower range for an MCID.[8] Adjusted mean differences [redacted] when a variety of covariates were used including baseline value.[51]

c) Response to therapy (*off* time)

Responders were defined as patients who experienced a 30% or greater decrease in *off* time. In both studies, more patients responded to rotigotine than placebo. In Mizuno 2014, the difference was reported to be not statistically significant (Table 18); a statistical analysis was not provided for Nomoto 2014. In Mizuno 2014, for the comparison of rotigotine versus ropinirole, there were 7% fewer responders in the rotigotine group, a difference that was not statistically significant (Table 18).

TABLE 18: *OFF* TIME (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON'S DISEASE — FULL ANALYSIS SET (LAST OBSERVATION CARRIED FORWARD)

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
Absolute *Off* Time (Hours/Day)[a]					
Baseline mean (SD)	4.5 (3.4) N = 111	5.0 (3.6) N = 113	4.9 (3.0) N = 57	NR N = 54	NR N = 56
End of maintenance, mean (SD)	3.2 (3.3) N = 110	3.0 (2.7) N = 113	4.5 (3.7) N = 57	NR	NR
Mean change from baseline (SD)	–1.3 (2.9)	–2.0 (3.0)	–0.4 (2.7)	–2.1 (3.1)	–0.7 (2.8)
Rotigotine — placebo difference	–0.9 (95% CI, –1.8 to 0.1) *P* = 0.065			–1.4 (95% CI, –2.5 to –0.3) *P* = 0.014	
Rotigotine — ropinirole difference	0.7 (95% CI, 0.0 to 1.5) *P* = 0.060			NA	
LS mean change from baseline (SE)	–1.4 (0.2) N = 110	–1.9 (0.2) N = 113	–0.4 (0.3) N = 57	NR	NR
Rotigotine — placebo difference in adjusted mean	–1.1 (95% CI, –1.9 to –0.3) *P* = 0.009			NR	
Ropinirole — placebo difference in adjusted mean	Reported as *P* < 0.001 without numbers			NA	
Rotigotine — ropinirole difference in adjusted mean	0.5 (95% CI, –0.2 to 1.2) *P* = 0.148			NA	
Response to Therapy[b]					
Responders, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	N = 110	N = 113	N = 57	N = 54	N = 56
Rotigotine — placebo difference	[redacted]			[redacted]	
Rotigotine — ropinirole difference	[redacted][c]			NA	

CI = confidence interval; LS = least squares; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error.
[a] For Mizuno 2014, least squares mean from ANCOVA with treatment as factor and baseline value as covariate are reported in the publication. Unadjusted means reported for Mizuno 2014 are from the Clinical Study Report. Unadjusted means are reported for Nomoto 2014.
[b] Patients with a 30% reduction or greater in absolute *off* time from baseline to end of maintenance are "responders."
Note: Missing end-of-maintenance-phase visit data were imputed using last observation carried forward (LOCF) method.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno 2014;[7] Nomoto 2014;[8] clinicaltrials.gov for Nomoto 2014;[49] Clinical Study Report, Nomoto.[4]

e) UPDRS Part II Sum Score (Activities of Daily Living)

Findings are reported in this section for the average of the *on* and *off* states. For results reported separately in each state, see Appendix 4: Detailed Outcome Data. In Mizuno 2014, the adjusted mean difference in change from baseline between rotigotine and ropinirole was not statistically significant: MD –0.6 points [95% CI, –1.4 to 0.1]. This difference was less than the published MCID values of 2.3 to 3.0 points.[55,56] The adjusted mean difference in change from baseline between rotigotine and placebo was –2.4 points [95% CI, –3.3 to –1.5], which approximates the lower value (2.3 points) of the published MCID estimates, but does not meet or exceed the higher threshold value.

In Nomoto 2014, the between-group unadjusted mean difference in change from baseline indicated [redacted]

[redacted]. The treatment difference, adjusted for a variety of covariates, ranged [redacted].[51]

TABLE 19: UNIFIED PARKINSON'S DISEASE RATING SCALE PART II SUM SCORES (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON'S DISEASE — FULL ANALYSIS SET (LAST OBSERVATION CARRIED FORWARD)

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
UPDRS Part II (Mean of *On* and *Off* State)					
Baseline mean (SD)	11.0 (6.2)	10.6 (5.6)	11.1 (7.0)	11.8 (6.1)	10.3 (4.6)
End-of-maintenance mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Mean change from baseline (SD)	–3.6 (4.1)	–2.9 (3.5)	–1.3 (3.4)	–3.8 (3.6)	–1.6 (2.6)
Rotigotine — placebo difference	–2.4 (95% CI, –3.4 to –1.4) *P* < 0.001			[redacted]	
Rotigotine — ropinirole difference	–0.7 (95% CI, –1.5 to 0.1) *P* = 0.086			NA	
ls mean change from baseline (SE)	–3.6 (0.3)	–3.0 (0.3)	–1.2 (0.4)	NR	NR
Rotigotine — placebo difference in adjusted mean (SE)	–2.4 (95% CI, –3.3 to –1.5) *P* < 0.001			NR	
Rotigotine — ropinirole difference in adjusted mean (SE)	–0.6 (95% CI, –1.4 to 0.1) *P* = 0.106			NA	

CI = confidence interval; LS = least squares; NA = not applicable; NR = not reported; SE = standard error.
Note: Missing end-of-maintenance-phase visit data were imputed using last observation carried forward (LOCF) method.
For Mizuno 2014 reports the least squares mean from ANCOVA with treatment as a factor and baseline value as covariate.
Unadjusted means reported for Mizuno 2014 are from the Clinical Study Report. Unadjusted means were reported in the Nomoto 2014 publication.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014.[8]

f) Health-related quality of life

Neither study reported on this outcome.

g) Adherence

For Mizuno 2014, adherence was not reported by intervention group. The precise method of measuring adherence could not be ascertained in the available documentation. Adherence for either the transdermal rotigotine or placebo patch was < 100% in 71 out of 420 patients (17%); one patient had an adherence rate of < 85% (unknown whether active drug or placebo). For oral tablets, [redacted].[7] no conclusions can be drawn about the relative adherence to oral ropinirole or transdermal rotigotine. For Nomoto 2014, [redacted]

[redacted].[24,79] The method of assessing adherence could not be ascertained from the partial translation of the Clinical Study Report.[24]

h) Patient's satisfaction with therapy

None of the trials assessed this outcome.

i) Nocturnal sleep

One APD trial, Mizuno 2014, reported on this outcome as assessed by PDSS-2.[6] Average scores at baseline (ranging from 12 to 15 points out of a maximum of 60, with higher scores indicating more sleep disturbance) were below or at a cut-off value (15 points) suggested to differentiate poor sleepers from good sleepers, as assessed in the Japanese version of the scale.[80] Patients above this cut-off point have sleep disturbances. There was no statistically significant difference between rotigotine and ropinirole, with a between-group mean difference in change from baseline of –0.7 points [95% CI, –1.9 to 0.6]. The adjusted mean difference between rotigotine and placebo was statistically significant: –2.6 points [95% CI, –4.1 to –1.1]. An MCID is not available for PDSS-2 to help interpret the between-group differences.

TABLE 20: PARKINSON'S DISEASE SLEEP SCALE-2 SUM SCORE IN ADVANCED PARKINSON'S DISEASE (BASELINE TO END OF MAINTENANCE PHASE) — FULL ANALYSIS SET (LAST OBSERVATION CARRIED FORWARD)

Outcome	Mizuno 2014		
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85
Baseline mean (SD)	12.3 (8.9) N = 162	14.3 (9.2) N = 165	15.0 (9.3) N = 81
End-of-maintenance mean (SD)	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]
Rotigotine — placebo difference	[redacted]		
Rotigotine — ropinirole difference	[redacted]		
LS mean change from baseline (SE)	–3.7 (NR)	–3.0 (NR)	–1.1 (NR)
Rotigotine — placebo difference in adjusted mean	–2.6 (95% CI, –4.1 to –1.1) *P* < 0.001		
Rotigotine — ropinirole difference in adjusted mean	–0.7 (95% CI, –1.9 to 0.6) *P* = 0.277		

CI = confidence interval; NR = not reported; SD = standard deviation; SE = standard error.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno.[7]

4.6.2 Mixed populations (early and advanced Parkinson's disease)

The key outcomes reported for SP889[10] are those identified for APD, because the mixed population included predominantly APD patients. The trial's primary outcomes are reported here; other outcomes, including those identified as key for EPD, are reported in Appendix 4: Detailed Outcome Data.

a) Early morning Unified Parkinson's Disease Rating Scale III Sum Score (motor function)

SP889 reported UPDRS in the early morning period, before the application of a new transdermal patch (i.e., distinct from the *on* state) as a co-primary outcome. The adjusted mean difference in change from

baseline between rotigotine and placebo was statistically significant: MD –3.6 points [95% CI, –5.4 to –1.7].[10] An MCID specific for this time period (an *off* period) has not been published.

b) Nocturnal sleep

For SP889, average PDSS-2 scores at baseline (19 to 20 points out of a possible 60) were above the cut-off value (15 points) that was suggested to differentiate poor sleepers from good sleepers (as assessed in the Japanese version).[80] The adjusted mean difference in change from baseline between rotigotine and placebo was statistically significant: MD –4.3 points (95% CI, –6.1 to –2.5).[10] An MCID is not available to gauge the clinical meaningfulness of the between-group difference.

c) *Off* time

SP889 did not report on this outcome.

d) Response to therapy (*off* time)

SP889 did not report on this outcome.

e) Early morning Unified Parkinson's Disease Rating Scale II Sum Score (activities of daily living)

For SP889, this outcome was reported for FAS, observed cases only.[10,15] The adjusted mean difference in change from baseline between rotigotine and placebo was statistically significant: MD –1.5 points [95% CI, –2.3 to –0.7].

TABLE 21: KEY EFFICACY OUTCOMES FOR MIXED POPULATION STUDY SP889 — FULL ANALYSIS SET (WITH OR WITHOUT LAST OBSERVATION CARRIED FORWARD)

SP889		
Outcome	**Placebo N = 89**	**Rotigotine N = 178**
UPDRS Part III Sum Score Early Morning Period (FAS with LOCF)		
Baseline, mean (SD)	31.8 (13.6)	29.7 (12.4)
End-of-maintenance mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM)	–3.55 (95% CI, –5.37 to –1.73) *P* = 0.0002	
PDSS-2 Total Score (FAS with LOCF)		
Baseline mean (SD)	20.3 (10.2)	19.3 (9.2)
End-of-maintenance mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM)	–4.26 (95% CI, –6.08 to –2.45) *P* ≤ 0.0001	
UPDRS Part II Sum Score Early Morning Period (FAS, Observed Cases)		
Baseline mean (SD)	13.5 (6.3) N = 89	12.7 (5.6) N = 178
End-of-maintenance mean (SD)	[redacted]	[redacted]
Mean change from baseline (SD)	–1.5 (3.5)	–2.8 (3.6)
Difference between rotigotine and placebo in adjusted mean (LSM)	–1.49 (95% CI, –2.32 to –0.65)[a] *P* = 0.0005	

SP889		
Outcome	**Placebo N = 89**	**Rotigotine N = 178**
PDQ-8 (FAS, Observed Cases)		
Baseline mean (SD)	31.1 (17.0) N = 89	30.8 (18.2) N = 177
End-of-maintenance mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM)	–5.74 (95% CI, –8.74 to –2.75)[a] *P* = 0.0002	

CI = confidence interval; FAS = full analysis set; LSM = least squares mean; LOCF = last observation carried forward; SD = standard deviation; SE = standard error.
[a] Difference is considered exploratory.
Note: Full analysis set (FAS) with data imputed using last observation carried forward (LOCF) method was conducted for UPDRS Part III and PDSS-2. Other outcomes were analyzed using the dataset FAS-Observed Cases only. Adjusted least squares means are presented from ANCOVA, with treatment and regions as factors and baseline value as covariate.
Source: Trenkwalder 2011;[10] Clinical Study Report, SP889.[15]

f) Health-related quality of life

PDQ-8,[81] a short, validated form of PDQ-36, was used to assess HRQoL (see Appendix 5: Validity of Outcome Measures). This outcome was reported for FAS, observed cases only, and was considered exploratory. An adjusted mean difference from baseline between rotigotine and placebo was [redacted] [95% CI, [redacted]].[15] Estimates of the MCID for health status that worsened "only a little bit" are in the range 5.8 to 7.4 points; it is not clear whether these values are directly applicable to improvement rather than worsening in health status.[59]

g) Adherence

Treatment adherence (defined by use of [redacted]) was [redacted].[15]

TABLE 22: COMPLIANCE IN STUDY SP889, SAFETY SET

SP889		
Outcome	**Placebo N = 89**	**Rotigotine N = 178**
Compliant, n (%)	[redacted]	[redacted]
Non-compliant, [redacted], n (%)	[redacted]	[redacted]
Non-compliant, [redacted], n (%)	[redacted]	[redacted]

Source: Clinical Study Report, SP889.[15]

h) Other efficacy outcomes

A number of other efficacy end points were reported for the APD studies, and are summarized in Appendix 4: Detailed Outcome Data. For Mizuno 2014, the largest and only study with an active drug comparator, these included change from baseline in: UPDRS Part I (intellectual impairment, behaviour, and mood, including depression) and Part IV (complications of therapy, including dyskinesia, *off* time, and early morning dystonia), as well as UPDRS Part II + III subtotal score, and UPDRS total score. Of these outcomes, for the comparison of rotigotine versus ropinirole, the UPDRS Part IV sum score was reduced slightly more by ropinirole and the UPDRS total score was reduced slightly more by rotigotine (Appendix 4: Detailed Outcome Data). However, for each of these scores, the magnitude of difference is unlikely to be clinically meaningful.

For the comparison of rotigotine versus placebo, in Mizuno 2014, most of the reported outcomes showed more improvement with rotigotine than with placebo except for UPDRS Part IV. For some outcomes (e.g., UPDRS Part I), the between-group mean differences in change from baseline were small and unlikely to be clinically meaningful. For Nomoto 2014, UPDRS Part II + III, Part I, Part IV, and the Total UPDRS Score were reported without statistical analyses on clinicaltrials.gov, and indicated modestly greater improvement with rotigotine (Appendix 4: Detailed Outcome Data). For SP889 (mixed population), many outcomes were measured and assessed using FAS without imputation of data, and were considered exploratory; therefore, conclusions are not drawn on these. Outcomes included: UPDRS Part II + III subtotal score; individual items of Part IV; NADCS; Parkinson's Disease Non-Motor Symptom Scale; Beck Depression Inventory; and an 11-point Likert pain scale, with very modest improvement in scores versus placebo, some of which are unlikely to be clinically meaningful.

Subpopulations of Interest

No RCTs were identified that reported efficacy outcomes specifically for the subpopulation of patients with PD who have gastrointestinal problems such as dysphagia, gastroparesis, or malabsorption. There were also no trials that specifically enrolled patients who were uncontrolled on, or intolerant of, pramipexole or ropinirole, or trials that reported on this subgroup separately.

4.7 Harms

Only those harms identified in the review protocol are reported below (Table 3, Protocol). See Appendix 4: Detailed Outcome Data for detailed harms data.

4.7.1 Adverse events

a) Total adverse events

The overall frequency of treatment-emergent adverse events (TEAEs) was generally high across treatment groups in all three studies (Table 23). In the APD studies, the proportion of patients experiencing one or more AEs was 89%, 78%, and 69% in the rotigotine, ropinirole, and placebo groups, respectively, in Mizuno 2014, and 94% and 89% in the rotigotine and placebo groups, respectively, in Nomoto 2014. In SP889, 72% and 62% of patients in the rotigotine and placebo groups, respectively, experienced one or more AEs.

b) Common adverse events

The most common AEs across the two APD studies, with a greater incidence associated with active drug, were application site reactions, dyskinesia, nausea, perception disturbances or hallucination, vomiting, and somnolence (Table 23). Other AEs that showed a difference between rotigotine and placebo in Nomoto 2014 were constipation, postural dizziness, and anorexia. Common AEs were similar in SP889 (Table 23).

Application site reactions were the most frequent AE in the two APD studies. In Mizuno 2014, 58%, 19%, and 15% of the participants in the rotigotine, ropinirole, and placebo groups, respectively, experienced application site reactions. In Nomoto 2014, 66% of patients in the rotigotine group had application site reactions compared with 25% in the placebo group. In Study SP889, 15% and 4% of participants in the rotigotine and placebo groups had application site reactions, respectively. The lower incidence of rotigotine-associated application site reactions in SP889 may have reflected a lower average dose of rotigotine and/or a shorter duration of exposure overall.

TABLE 23: TOTAL AND COMMON TREATMENT-EMERGENT ADVERSE EVENTS FOR ADVANCED PARKINSON'S STUDIES AND MIXED POPULATION STUDIES, SAFETY SET

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
AEs, n (%)							
Patients with ≥ 1 AEs	149 (88.7%)	130 (77.8%)	59 (69.4%)	82 (94.3%)	77 (88.5%)	137 (71.7%)	54 (56.3%)
Most Common Adverse Events, n (%)							
Subset reported[a]	Incidence ≥ 3%[b] in any treatment group			Incidence ≥ 5%[b] in any treatment group		Incidence ≥ 5% in any treatment group	
Application site reactions[c]	97 (57.7%)	31 (18.6%)	13 (15.3%)	57 (65.5%)	22 (25.3%)	29 (15.2%)	4 (4.2%)
Dyskinesia	27 (16.1%)	23 (13.8%)	1 (1.2%)	12 (13.8%)	7 (8.0%)	15 (7.9%)	4 (4.2%)
Nausea	25 (14.9%)	23 (13.8%)	7 (8.2%)	17 (19.5%)	5 (5.7%)	41 (21.5%)	9 (9.4%)
Vomiting	11 (6.5%)	11 (6.6%)	2 (2.4%)	9 (10.3%)	1 (1.1%)	NR	NR
Constipation	[redacted]	[redacted]	[redacted]	9 (10.3%)	1 (1.1%)	NR	NR
Somnolence	11 (6.5%)	9 (5.4%)	2 (2.4%)	12 (13.8%)	1 (1.1%)	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	7 (8.1%)	2 (2.3%)	20 (10.5%)	6 (6.3%)
Postural dizziness	[redacted]	[redacted]	[redacted]	7 (8.1%)[d]	1 (1.2%)	NR	NR
Orthostatic hypotension (based on BP)	5 (3.0%)	7 (4.2%)	4 (4.7%)	2 (2.3%)	2 (2.3%)	[redacted]	[redacted]
Perception disturbances[e]	17 (10.1%)	16 (9.6%)	3 (3.5%)	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	3 (1.8%)	5 (3.0%)	2 (2.4%)	NR	NR	[redacted]	[redacted]
Cystitis	3 (1.8%)	3 (1.8%)	4 (4.7%)	NR	NR	NR	NR

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
Peripheral edema	0	2 (1.2%)	3 (3.5%)	NR	NR	[redacted]	[redacted]
Sleep disturbances[f]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	NR	NR	13 (6.8%)	5 (5.2%)
Anorexia	[redacted]	[redacted]	[redacted]	6 (6.9%)	0	[redacted]	[redacted]

AE = adverse event; BP = blood pressure; NR = not reported.
[a] The subset of reported common AEs had an incidence of at least 3% or at least 5% in one or more treatment groups, depending on the study. If an AE reached the threshold incidence in only one study, these data were obtained for the other studies, if available, to facilitate comparison.
[b] Additional common AEs — nasopharyngitis, upper respiratory inflammation, fall, and contusion — that met the threshold incidence but were not consistently greater in the active drug groups across trials are reported in Appendix 4: Detailed Outcome Data.
[c] The MedDRA high-level term for application and instillation site reactions includes application site reaction, pruritus, erythema, irritation, oedema, discolouration, and exfoliation. For Nomoto 2014, data for this category were obtained from the CDR clinical review team's own translation of Clinical Study Report.[24]
[d] For Nomoto 2014, the degree of overlap between dizziness and postural dizziness is unknown; therefore, these two categories could not be combined.
[e] MedDRA high-level terms: hallucination; hallucination visual and hallucination auditory, delusion, illusion. For SP889, [redacted].[15]
[f] Includes insomnia and middle insomnia.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno.[7] Mizuno 2014, the Clinical Study Report data were preferred. Nomoto 2014;[8] Clinical Synopsis Nomoto;[9] clinical trials.gov results;[49] SP889: Trenkwalder 2011;[10] Clinical Study Report, SP889.[15]

4.7.2 Serious adverse events

In all three studies, there were few serious adverse events (SAEs) (Table 24). In Mizuno 2014, 3%, 4%, and 7% of participants in the ropinirole, rotigotine, and placebo groups had at least one SAE. In Nomoto 2014, 3.5% of patients reported SAEs in the rotigotine and placebo groups. In the mixed population study, SP889, about 5% of patients in each of the rotigotine and placebo groups had at least one SAE. For SP889, the SAE in the placebo group included two deaths.

In rotigotine-treated patients, SAE included abnormal posture and torticollis,[6] delusion,[6,8] neuroleptic malignant syndrome,[8] visual or auditory hallucination,[8,10] and sleep attacks or sudden onset of sleep[10] (Table 24). Delusion was also reported as an event leading to discontinuation in the ropinirole group. The case of neuroleptic malignant syndrome in Nomoto 2014 is described as having occurred in the dose de-escalation phase, and is consistent with the known Parkinson hyperpyrexia syndrome (Clinical Study Report, Mizuno,[7] p. 47). Further details on the SAEs in Mizuno 2014 and SP889 are provided in Appendix 4: Detailed Outcome Data. In these two studies, SAEs were observed at doses of rotigotine from 2 mg/24 h to 16 mg/24 h, and for ropinirole, from 4.5 mg/day to 7.5 mg/day.

4.7.3 Withdrawal due to adverse events

WDAEs were relatively infrequent (6% to 10%), and similar across treatment groups. There was no difference in WDAEs for the comparison of rotigotine versus ropinirole (8% in each group).[6]

The most common reasons for withdrawal associated with use of the active drug were application site reactions, hallucination, dyskinesia, and vomiting (Table 23). There were too few events in each category to draw conclusions about the comparative risks of individual events. One patient in the ropinirole group withdrew due to pulmonary hypertension; no details are available regarding potential underlying etiopathology.

4.7.4 Mortality

No deaths occurred in Mizuno 2014 or Nomoto 2014. In SP889, there were no deaths in the rotigotine group and two deaths (2.1%) in the placebo group (one completed suicide and the other due to aspiration pneumonia).

TABLE 24: SERIOUS ADVERSE EVENTS (FATAL AND NON-FATAL) FOR ADVANCED PARKINSON'S STUDIES AND MIXED POPULATION STUDIES, SAFETY SET

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
SAEs							
Patients with ≥ 1 SAE, n (%)	7 (4.2%)	5 (3.0%)	6 (7.1%)	3 (3.5%)	3 (3.5%)	10 (5.2%)	[redacted]
Description of SAE	• Abnormal posture and torticollis [redacted] • Gastric ulcer [redacted] • [redacted] • Spinal compression fracture [redacted]	[redacted] • [redacted] • Worsening of PD	[redacted] • [redacted] • Angina [redacted]	• Anemia • Malaise and CPK increase • Neuroleptic malignant syndrome delusion and auditory hallucination	• Inguinal hernia • Gastroenteritis and bacterial arthritis • Loss of consciousness	[redacted] • Hallucination, visual [redacted] • [redacted]	[redacted]
Deaths	0	0	0	0	0	0	[redacted]

[redacted]; CPK = creatinine phosphokinase; [redacted]; PD = Parkinson's disease; SAE = serious adverse event.

Note: Each bullet point in the table describes one or more SAE for a single patient.

Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014;[8] clinicaltrials.gov for Nomoto 2014;[49] manufacturer's response to request for additional information, Aug. 4, 2015.[50]

TABLE 25: WITHDRAWALS DUE TO ADVERSE EVENTS FOR ADVANCED PARKINSON'S STUDIES AND MIXED POPULATION STUDIES, SAFETY SET

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
WDAEs							
WDAEs, n (%)	13 (7.7%)	13 (7.8%)	8 (9.4%)	9 (10.3%)	7 (8.1%)	12 (6.3%)	6 (6.3%)
Most Common Reasons for WDAEs							
Application site reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][a]	[redacted]
Hallucination, delusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted][b]	[redacted]
Dyskinesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea or vomiting	[redacted]	[redacted]	[redacted]	[redacted][c]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported; WDAE = withdrawal due to adverse event.

[a] In the SP889 rotigotine group, application site reactions included erythema (3), application site reaction (1), application site rash (1), and skin reaction not otherwise specified (2).

[b] Includes [redacted]

[c] [redacted].

Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014;[8] clinicaltrials.gov for Nomoto 2014;[49] SPP89: Trenkwalder 2011;[10] Clinical Study Report, SP889.[15]

4.7.5 Notable harms

Several AEs of particular interest were identified a priori: sudden onset of sleep when sleep is not expected to occur (sleep attacks); arrhythmias (e.g., ventricular arrhythmias and sudden death, electrocardiographic [ECG] changes of QT prolongation); valvulopathy; syncope; and impulsive/asocial behaviour. In all three studies, the incidence of notable harms was low (Table 26). Events were too infrequent to draw conclusions about the comparative risk of events associated with rotigotine versus ropinirole or placebo.

a) Sudden onset of sleep

Sudden onset of sleep occurred in [redacted] in Mizuno 2014, at [redacted].[7] There were [redacted] in Nomoto 2014.[50] SP889 reported [redacted].[15]

b) Valvulopathy

In Mizuno 2014, [redacted].[7] At the end of the maintenance period, 51%, 55%, and 49% of patients tested had reflux at any valve in the rotigotine, ropinirole, and placebo groups, respectively. A similar proportion of patients had evidence of valvular regurgitation at individual valves across treatment groups. Nomoto 2014 reported [redacted].[50] SP889 did not report on this outcome.

c) Arrhythmias

In Mizuno 2014, [redacted].[7] No arrhythmias were identified as SAEs or reasons for discontinuation. There were no cases of sudden death, which can result from ventricular arrhythmias arising from QT prolongation. Nomoto 2014 reported [redacted].[50] In SP889, three cases (1.6%) of arrhythmias were reported in the rotigotine group (left bundle branch block; bradycardia; first degree atrioventricular heart block) and one case (1.0%) was reported in the placebo group (supraventricular extrasystoles). In terms of the arrhythmias observed in patients treated with rotigotine or ropinirole, all have multiple potential causes. There were infrequent events of ECG evidence of QT prolongation across treatment groups in Mizuno 2014, no cases of QT prolongation in the rotigotine-treated group in Nomoto 2014, and infrequent cases in SP889 (Appendix 4: Detailed Outcome Data).

d) Syncope

In Mizuno 2014, [redacted].[7] [redacted] in Nomoto 2014.[50] In SP889, [redacted].[15] [redacted].

e) Impulsive/asocial behaviour

In Mizuno 2014, there were no clinical reports of AEs for obsessive-compulsive or impulse control disorders for any treatment group.[7] Patients underwent screening at baseline and at the end of the maintenance period using the mMIDI modules (buying disorders, compulsive sex disorders, compulsive eating disorders, and repetitive stereotyped behaviour disorders). [redacted]. [50] In SP889, there were also no clinical reports of AEs. [redacted]. [15] [redacted] in Nomoto 2014.[50]

TABLE 26: NOTABLE HARMS FOR ADVANCED PARKINSON'S AND MIXED POPULATION STUDIES, SAFETY SET

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
Notable Harms							
Sudden onset of sleep	1 (0.6%)	1 (0.6%)	0	0	0	2 (1.1%)	0
Syncope	[redacted]	[redacted]	[redacted]	0	0	[redacted]	[redacted]
Syncope vasovagal	--	--	--	--	--	[redacted][a]	[redacted]
ICD — clinical AE	[redacted]	[redacted]	[redacted]	0	0	0	0
ICD identified on mMIDI[b]	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]	2 (2.1%)
Valvulopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Arrhythmias	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; ICD = impulse control disorders; mMIDI = modified Minnesota Impulse Disorder Interview; NR = not reported.

[a] It is unclear whether the one event of vasovagal syncope in SP889 overlaps with the category syncope; thus, the categories are reported separately.

[b] Mizuno 2014: [redacted]. [50] SP889: [15] [redacted].

Source: Clinical Study Report, Mizuno;[7] manufacturer's response to request for additional information, Aug. 4, 2015;[50] SP889.[10,15]

5. DISCUSSION

5.1 Summary of Available Evidence

The prior CDR review included four published manufacturer-sponsored RCTs: two in EPD (SP512 and SP513) and two in APD (SP515 and SP650). Only two, SP513 and SP515, were active comparator trials. These did not consistently demonstrate non-inferiority of rotigotine compared with other non-ergolinic DAs.

One issue identified in the original review was potential dose non-equivalence for rotigotine and ropinirole in SP513. SP513 was a trial of approximately nine months' duration and compared rotigotine up to 8 mg/24 h, the maximum recommended dose for EPD, with ropinirole up to 24 mg/day, also the maximum recommended dose in Canada.[3,45] In the trial, [redacted] reached the maximum dose of rotigotine, whereas [redacted] in the ropinirole group were at maximum dose. The range of ropinirole doses was [redacted]. The mean doses in the maintenance phase (safety set) were rotigotine [redacted] and ropinirole [redacted].[45] Median doses were [redacted] for rotigotine and [redacted] for ropinirole, and average time of exposure was [redacted] for rotigotine and for ropinirole, [redacted].[45] [redacted]. This could favour ropinirole for efficacy (if a linear dose response exists up to 24 mg/day) and rotigotine for dose-dependent AEs common to both drugs.

The second active comparator trial in the prior review, SP515, was conducted in patients with APD, and compared pramipexole (up to 4.5 mg/day) with rotigotine up to its maximum recommended dose for APD, 16 mg/24 h. The mean doses in the maintenance phase were rotigotine 13.0 mg/24 h and pramipexole 3.1 mg/day.[4] Rotigotine was statistically non-inferior to pramipexole for absolute time spent *off*, but not for the proportion of patients responding to therapy, as defined by a 30% or more reduction in absolute *off* time.

This review updates the active comparator RCT data with one additional published, manufacturer-sponsored trial, Mizuno 2014, a phase 3 trial in APD.[6] The new trial compares rotigotine up to 16 mg/24 h with ropinirole up to 15 mg/day, the maximum allowable dose in Japan, where the trial was conducted. Mizuno 2014 partially addresses, but does not fully resolve, one of the issues in the original CDEC recommendation:[2] that of potential dose non-equivalence of ropinirole and rotigotine in the SP513 trial. The new trial, however, was conducted in a different population (APD), and its findings are not generalizable to the EPD population.

There were no new active comparator trials identified in the literature that compare rotigotine monotherapy with ropinirole, pramipexole, or levodopa in EPD. There were also no new trials that compare rotigotine with pramipexole, entacapone, or MAO-B inhibitors as adjunct therapy in APD.

The other two trials included in this review are placebo-controlled only. They include a phase 2 trial conducted in an APD population[8] and a trial conducted in a mixed population (APD and EPD) that focused on early morning symptoms and nocturnal sleep.[10] These provide no information about a potential comparative advantage of rotigotine compared with other drugs.

All three trials were DB and treatment groups were generally similar at baseline across treatment groups within each trial. Two of the trials used a dynamic allocation process for randomization that could

compromise the allocation concealment, particularly for Mizuno 2014, which sought to balance groups on a number of factors.[6,8] The high incidence of application site reactions may have compromised blinding, particularly for Mizuno 2014 and Nomoto 2014. One placebo-controlled trial, SP889, terminated recruitment early, which reduced the trial's power but still provided an acceptable probability of a type II error.[10] The two trials conducted in Japan[6,8] enrolled more females than males, and used lower average doses of levodopa than might be encountered in North American populations, features that could affect generalizability to usual clinical practice in Canada. Only one trial, the placebo-controlled trial in a mixed population, SP889, assessed QoL, and none of the trials assessed patient or caregiver satisfaction. QoL was identified as particularly relevant to patients in the patient input (see Appendix 1: Patient Input Summary).

No data were identified (either in subgroup analyses or in trials specifically recruiting the subpopulations of interest) for patients with gastrointestinal disorders such as dysphagia, gastroparesis, or absorption issues, or for patients who are uncontrolled on, or intolerant of, pramipexole or ropinirole IR. One RCT with patients with gastroparesis (NCT01536015) was identified through clinical trial registries; this trial, however, was terminated due to insufficient recruitment.

Another gap noted in the original CDR review was the lack of long-term efficacy data. Although the included trials had one-year, open-label extension studies that provided uncontrolled data, this review did not identify any longer-term active comparator RCTs. The three included trials were of ≤ 16 weeks' duration.

5.2 Interpretation of Results

5.2.1 Efficacy

a) Advanced Parkinson's disease studies

The primary efficacy outcome in the APD trials was the mean change from baseline in the UPDRS Part III (motor) sum score measured in the *on* state. In contrast, the primary outcomes in the APD trials (SP515 and SP650) included in the prior CDR review were absolute *off* time and response in terms of a 30% or more reduction in *off* time.[5] For the comparison of rotigotine versus ropinirole, Mizuno 2014 demonstrated in a per-protocol analysis that rotigotine was non-inferior to ropinirole using a preset non-inferiority margin of 2.5 points. An analysis using FAS with LOCF was also conducted, and was consistent with the per-protocol analysis.[72] The a priori non-inferiority margin was based on previous placebo-controlled RCTs on rotigotine, ropinirole, and pramipexole, with effect size ranges of 3.8 to 5.4 points,[4,8,61] 5.0 to 6.5 points,[60,62] and 5.9 to 6.9 points,[63,64] respectively — not all of which were superiority studies with UPDRS Part III as the primary variable.[72] The non-inferiority margin was also set in discussion with Japanese regulatory authorities, and was smaller than the one published MCID of 6.5 points. The available MCID was based on placebo-controlled RCT data from an APD population treated with pramipexole, and has not yet been replicated. In Mizuno 2014, rotigotine was statistically significantly superior to placebo, with greater improvement in the UPDRS Part III motor sum score by an amount similar to the available MCID,[55] suggesting this was a clinically meaningful between-group difference. Similar results were obtained in Nomoto 2014.

Responders were also reported, defined as those achieving a 20% or more reduction from baseline in the UPDRS Part III sum score. However, given the baseline values for both trials, this amount of change would not meet or exceed the published MCID for APD; therefore, it may not be clinically meaningful. In Mizuno 2014, for the comparison of rotigotine with ropinirole, there was a statistically significant difference in responders, which favoured rotigotine by 11% at the 20% threshold of response, but there

was no statistically significant difference when the more clinically meaningful 30% reduction from baseline scores was used.

Absolute time spent *off* was measured in the subset of patients who were experiencing *off* time at baseline. For the comparison of rotigotine versus ropinirole, in Mizuno 2014 the comparator ropinirole reduced absolute time spent *off* to a greater extent than rotigotine by an average of 0.5 hours, a difference that was not statistically significant. Time spent *off* was reduced more by rotigotine than by placebo in both APD trials. For Mizuno 2014, [redacted].[7] Estimates of an MCID for *off* time in APD have ranged from 1.3 hours to 1.9 hours using different methods and treatments.[54,55] Responders, defined by a 30% reduction in *off* time, were reported in both trials. This is a reasonable cut point, as the baseline mean for Mizuno 2014 was in the range of 4.5 hours to 5.0 hours, and a 30% reduction (1.3 hours to 1.5 hours) would correspond to the lower MCID in the range of published values. Nomoto 2014 participants had greater amounts of *off* time at baseline, and a 30% reduction would be in the amount of 1.8 hours to 2.0 hours. In Mizuno 2014, for the comparison of rotigotine versus ropinirole, there were 6% fewer responders in the rotigotine group, a difference that was not statistically significant. In both trials, the proportion of responders was statistically significantly greater in the rotigotine group compared with the placebo group.

The treatment effect sizes reported in Mizuno 2014 are similar in magnitude to those reported for SP515 in the prior CDR review, a trial that compared rotigotine with a different DA, pramipexole, in patients with APD.[4] The titration and maintenance phase of SP515 (N = 405 receiving active drug) was 23 weeks overall, with a shorter titration phase (7 weeks, in contrast to 12 weeks in Mizuno 2014) and a maintenance phase of 16 weeks rather than four weeks. It demonstrated non-inferiority of rotigotine to pramipexole on the basis of absolute time spent *off* as the primary outcome, with a mean difference of 0.35 hours in favour of pramipexole. The non-inferiority margin had been preset at 1.2 hours.[4] The trial reported responder rate as a co-primary outcome because of the different regulatory requirements of the European Medicines Agency (EMA) and US FDA, and failed to demonstrate non-inferiority for this outcome. Response was defined as a 30% reduction or more in absolute *off* time, and the preset non-inferiority margin for responder rate was 15%.[4] The drug doses used in the trial (rotigotine 13.0 mg/24 h [SD 3.5] and pramipexole 3.1 mg/day [SD 1.2]) approximate the 4:1 dosage conversion ratio suggested by some investigators.[82] [redacted].[5]

The two non-inferiority trials, Mizuno 2014 and SP515, are the only available active comparator RCTs in APD patients. The only other trial that has compared rotigotine with ropinirole was SP513, included in the prior CDR review. This was a 36-week trial in patients with EPD that assessed, as primary outcome, the combined UPDRS subtotal score for motor function (Part III) plus ADL (Part II). Although superior to placebo, rotigotine failed to demonstrate non-inferiority against ropinirole for change from baseline in the UPDRS Part II + Part III score and for the number of responders achieving a 20% or more reduction in the same outcome. The manufacturer suggested that failure to demonstrate non-inferiority was attributable to the non-equivalent higher dose of ropinirole.[3,45] A higher dose of ropinirole could favour ropinirole for efficacy (if a linear dose response exists up to 24 mg/day) and rotigotine for dose-dependent AEs common to both drugs. The trial compared rotigotine up to 8 mg/24 h, the maximum recommended dose for EPD, with ropinirole up to 24 mg/day, the maximum recommended dose in Canada.[3,45] In the trial, [redacted]

[redacted][45]. [45]

In Mizuno 2014, the mean maintenance dose of rotigotine was 12.9 mg/24 h (SD not reported) and ropinirole, 9.2 mg/day (SD not reported) — i.e., a higher average dose was attained for rotigotine than ropinirole, in contrast to SP513. Median doses were not provided. Limited information is available about the distribution of doses for ropinirole (e.g., distribution of days of exposure are not reported). Ropinirole doses ranged from [redacted][7,52] About 70% of patients on rotigotine in the maintenance phase received 12 mg/24 h to 16 mg/24 h, whereas ropinirole doses appeared to be more widely distributed. Whether the average doses are equivalent remains unknown. The dose of ropinirole could be titrated to a maximum of 15 mg/day, which is the maximum allowed dose in Japan and lower than the 24 mg/day dose allowed in Canada. A dose up to a maximum of 15 mg/day is consistent with usual clinical practice. According to the clinical expert involved in this review, the usual ropinirole dose range in clinical practice was 10 mg/day to 15 mg/day at the time of the prior CDR review, but may be 9 mg/day to 12 mg/day in current practice. However, it has been suggested that patients who do not respond to lower doses of ropinirole may respond to > 15 mg/day.[83] Mizuno et al. suggested that the magnitude of improvement for lower average doses of ropinirole in their trial[6] and in another trial conducted by the same investigators in Japan[60] is similar to that achieved with higher doses in trials conducted in other countries because of differences in body weight in the trial populations. The average rotigotine dose in Mizuno 2014 is similar to the average dose in another trial with patients of higher average body weight, so rotigotine doses did not show a similar shift. Therefore, it remains unclear whether the different doses attained in different trials are related to population characteristics or reflect different approaches to practice in different regions. This potentially limits the generalizability of the findings in Mizuno 2014 to the Canadian context. The doses attained in Mizuno 2014 are also not consistent with the manufacturer's proposed dosage conversion ratio (rotigotine: ropinirole dosage of [redacted][5]) or the 1:1 dosage ratio proposed by others.[84]

b) Mixed population studies (advanced Parkinson's disease and early Parkinson's disease)

The third trial included in this review, SP889, was a mixed population trial (predominantly APD) that focused on early morning motor symptoms before re-application of the transdermal patch, as well as nocturnal sleep disturbance as assessed by UPDRS Part III and PDSS-2 sum scores.[10] The population comprised patients with a range of sleep disturbances, as this was not one of the eligibility criteria. Average PDSS-2 scores at baseline were above the cut-off value of 15 points — the suggested threshold for identifying poor sleepers. Compared with placebo, rotigotine improved both co-primary outcomes. No MCID for UPDRS Part III specific to the early morning period is available. There are no published MCID estimates for PDSS-2 to help interpret whether the between-group difference (4 points) was clinically relevant. Additionally, the potential interdependence of the two co-primary outcomes was not addressed.

5.2.2 Harms

The overall frequency of TEAEs was generally high across treatment groups in all three studies. The AE profile for the comparison of rotigotine versus placebo was similar to that previously reported for rotigotine, with more application site reactions, dyskinesia, nausea, perception disturbances or hallucination, vomiting, and somnolence associated with rotigotine. WDAEs and SAEs were similar in frequency across treatment groups.

In the one active comparator trial, 11% more patients experienced one or more AEs in the rotigotine group compared with ropinirole.[6] The AE profiles of rotigotine and ropinirole were similar except for the higher frequency of application site reactions associated with rotigotine. Dyskinesia was experienced by 16% of patients in the rotigotine group and by 14% of patients in the ropinirole group. Somnolence was reported in 7% and 5% of patients in the rotigotine and ropinirole treatment groups, respectively. There were similar frequencies of vomiting (7% in each group) and perception disturbances (10% in each group, mainly hallucinations of any type). There were no deaths in the active drug groups. Discontinuations due to AEs (8% in each group) and non-fatal SAEs (3% to 4%) were similar in frequency. The trial was limited in its ability to capture uncommon events because of sample size. One patient in each active drug group (0.6%) had sudden onset of sleep (sleep attacks). For obsessive-compulsive disorders (OCDs), no events were reported as clinical AEs. However, on the screening interview for impulse control disorders, 4.2% of patients in the rotigotine group and 6.6% of patients in the ropinirole treatment group had positive findings on a gateway question with or without affirmative responses on the remaining questions. There were no events of valvulopathy. [redacted] experienced syncope [redacted]. Arrhythmias [redacted].[7]

The included trials were relatively short (12 weeks to 16 weeks) and do not provide information on the longer-term efficacy or AEs of rotigotine. This may be particularly important given the changes in neuromodulation that occur with disease progression and/or with medication use.

a) Supplementary Information on Harms

A total of four extension studies assessed the long-term safety, tolerability, and efficacy of rotigotine in patients with APD and EPD. In three open-label extension studies [redacted], AEs experienced [redacted].[17-19] Interpretation of these data is limited because of the uncontrolled nature of the data and the highly selected population — e.g., the majority had previously demonstrated they could tolerate a non-ergolinic DA (because of the unbalanced randomization, with more patients randomized to active drug in the two largest RCTs). Among the most commonly reported AEs were application site reactions, dyskinesia, somnolence, hallucinations or delusion, nausea, fall, dizziness, and (in one study), feeling abnormal. The number of patients experiencing SAEs ranged from 6% to 19%, and 13% to 19% withdrew because of AEs. Gastric ulcer hemorrhage occurred as an SAE in three patients (0.9% of the total study population) in the largest study (N = 321 patients with APD), which was conducted in Japan, a region with a higher incidence of peptic ulcer disease than North America. In the three open-label extension phases, the frequency of sudden onset of sleep was 0.8% to 3.6%; syncope 0% to 1.2% (two studies); impulse control disorder 0.8% to 1.2%; and arrhythmias 0% to 0.3% (two studies); no events of valvulopathy were reported.

There was one sudden death in each open-label extension study (incidence: 0.3% to 1.2%). Sudden death can be due to ventricular arrhythmias, which can arise from QT prolongation. As noted in the product monograph, a study evaluating treatment-related QT effects, with doses up to 24 mg/24 h, did not detect QT prolongation associated with rotigotine.[1] Two of the patients were known to have underlying cardiovascular disease. One patient's death was deemed unrelated to treatment in the context of diabetes and a prior aortocoronary bypass. Another death was assessed as related to treatment, while the evaluation of the third in relation to treatment is not known due to the absence of

a translated Clinical Study Report. No autopsy information is available for any of the patients. The relation of rotigotine to the sudden deaths is unclear.

The only new supplementary information on rotigotine use in patients with EPD was a pooled post hoc analysis of the incidence of dyskinesia in two open-label extension studies of up to six years' duration. In the pooled population (N = 596), 19% of patients developed dyskinesia.[21] Of the patients who were not taking levodopa (N = 173), approximately 15% developed dyskinesia, with a median onset of approximately 2.5 years earlier than those on levodopa. It is unknown whether these patients have any distinguishing features that would confer susceptibility to dyskinesia. Dyskinesia, in the absence of levodopa, has also been reported for pramipexole and ropinirole.[22,23] This study, which is exploratory only, does not provide comparative data with which to evaluate whether any particular DA is associated with less dyskinesia.

b) Supplementary information on efficacy

In the uncontrolled, open-label, single-group studies of Mizuno 2014 and SP889, the observed improvement in efficacy slightly diminished over the one-year period, but no statistical analysis was performed. It is not possible to distinguish whether this might represent disease progression or tolerance, and conclusions cannot be drawn from these data. Controlled efficacy data are required to determine whether rotigotine or short-acting non-ergolinic DAs have any potential advantage in the long-term with respect to this phenomenon.

A manufacturer-sponsored network meta-analysis (NMA) combined direct and indirect RCT evidence to compare non-ergolinic DAs as adjunct therapies in APD and as monotherapies in EPD. This study was summarized on the basis of its study report as supplemental information in the prior review, and has since been published.[85] When pramipexole, ropinirole, and rotigotine were compared with each other, their effect estimates were similar, and did not reach statistical significance in EPD or APD. In EPD, levodopa was found to be more efficacious than rotigotine in improving both motor function and UPDRS Part II + Part III subtotal scores at the 11-week to 16-week time point, although treatment differences were small, and exceeded the MCID for motor scores only. For APD, at 11 weeks to 16 weeks, the mean improvement in UPDRS Part III scores was of similar magnitude for all three non-ergolinic DAs versus placebo, ranging from –3.8 points (rotigotine) to –5.0 points (pramipexole). Reduction in *off* time was similar, –1.4 hours to –1.5 hours, for the DAs versus placebo. No statistically significant differences were detected between DAs. Data at the 24-week to 28-week time point also showed similar efficacy for the three drugs. AEs were not incorporated into the NMA.

The manufacturer provided an independent systematic review and meta-analysis by Zhou et al.[86] Zhou et al. compared the efficacy, tolerability, and safety of long-acting non-ergolinic DAs (i.e., pramipexole extended release [ER], ropinirole prolonged release, or rotigotine transdermal patch) with standard release non-ergolinic DAs (pramipexole or ropinirole) in patients with PD. Individual drugs were pooled within each category and no information was provided on drug dosages. Eight DB RCTs were included (N = 2,402), four studies each in patients with EPD and APD. The trial durations ranged from nine weeks to 37 weeks. Concomitant levodopa was administered with the non-ergolinic DAs in all APD trials, and was permitted in one EPD trial, with about half of the participants on levodopa. One trial was designed as a superiority trial, five were non-inferiority trials, and two studies were not designed for formal non-inferiority testing. All trials were rated to be of higher methodologic quality based on blinding, randomization, and a description of dropouts only, with Jadad scores of 4 or 5. The included rotigotine trials were Giladi et al. 2007 in EPD (comparator ropinirole IR)[3] and Poewe et al. 2007 in APD

(comparator pramipexole IR).[4] However, the rotigotine trials were pooled with long-acting formulations of ropinirole and pramipexole, neither of which are available in Canada.

Based on Zhou et al.,[86] tolerability was similar between long- and short-acting DAs, with no statistically significant differences detected in overall withdrawals, WDAEs, withdrawals due to lack of efficacy, or SAEs. No statistically significant differences were found for the most common AEs — somnolence, nausea, and dyskinesia — or for dizziness, headache, constipation, hallucination, orthostatic hypotension, vomiting, or back pain. The findings were consistent for subgroups with EPD or APD. AEs were incompletely reported; therefore, some analyses were based on sparse data, and there were no long-term data. Given that rotigotine was pooled with other long-acting drugs, the utility of these data is limited, and is insufficient to assess the risks of rotigotine versus other non-ergolinic DAs.

A Cochrane systematic review[87] and an updated journal version[88] compared DAs, COMT inhibitors, and MAO-B inhibitors in APD (N = 45 trials, with nearly 9,000 patients in total). The DAs included in the review were: rotigotine (one trial, SP515,[4] included in Stowe 2011[88]), ropinirole, pramipexole, bromocriptine, pergolide, and cabergoline. There were no head-to-head comparisons of drug classes in this review, other than a comparison between rasagiline (a MAO-B inhibitor) and entacapone (a COMT inhibitor). To assess differences between the three drug classes, indirect comparisons using tests for heterogeneity were made. Based on these, DAs were more efficacious for reducing *off* time (–1.6 hours) than COMT (–0.8 hours) or MAO-B inhibitors (–0.9 hours), as well as for reducing levodopa dose and improving UPDRS scores. DAs and COMT inhibitors had a similar overall incidence of AEs that was higher than that associated with MAO-B inhibitors. Indirect comparisons suggested a possible difference in the frequency of dyskinesia, with more dyskinesia in the DA and COMT inhibitor drug classes compared with MAO-B inhibitors. Comparisons of drugs within the DA class suggested the risk of dyskinesia may be greater for ropinirole than for pramipexole, rotigotine, bromocriptine, and cabergoline, and that pramipexole produced larger improvements on the UPDRS motor score compared with ropinirole, rotigotine, and cabergoline. However, the authors noted there were generally insufficient data to draw conclusions reliably for within-class comparisons. All indirect comparisons need to be interpreted cautiously, as conclusions are based on inference and heterogeneity in populations, dosing regimens, and use of concomitant medications, and outcome measures could contribute to spurious results. The authors noted the majority of trials were six months or less in duration, and only three included patient-rated QoL. They identified a need for large, long-term, randomized, head-to-head trials that included QoL measures.

Common themes seen as important in patient-group input were the need for ease of administration, improved medication adherence, prolonged drug effectiveness, and reducing or eliminating wearing-off periods (Appendix 1: Patient Input Summary). Although adherence is high in RCTs for the transdermal patch (based on the information across groups in Mizuno 2014 and the reported adherence in SP889), patients are highly screened in trials and have more frequent follow-up than in clinical practice. This degree of adherence may not be representative of the general population of patients.

Another issue raised in the patient-group input was control of non-motor symptoms, such as sleep disturbances. There are limited comparative RCT data on non-motor symptoms. Mizuno 2014 showed similar improvement of sleep disturbances with rotigotine and ropinirole, based on the PDSS-2 score. SP515, included in the prior CDR review, reported on the unmodified PDSS scale, with similar improvement in scores for rotigotine and pramipexole. Interpretation of both scales is limited because an MCID has not been formally derived for either version. These data have not demonstrated that a long-acting formulation has an advantage over IR ropinirole or pramipexole for non-motor symptoms. In

the placebo-controlled trial SP889, many outcomes were measured that assess various aspects of non-motor symptoms, but these were exploratory. An additional placebo-controlled RCT, not identified in this submission, has assessed the Non-Motor Scale (NMS) as a primary outcome, and has reported that rotigotine was no better than placebo.[89]

Comparative RCT data are sparse. There are no comparative RCTs that have assessed the role of rotigotine in patients who might be intolerant of other non-ergolinic DAs, or in those who have gastrointestinal problems (e.g., dysphagia, gastroparesis). A transdermal application system may be perceived as a useful alternative to oral drugs in patients who have severe gastrointestinal problems (e.g., dysphagia, gastroparesis) — issues that occur more commonly in APD. However, it is not known whether rotigotine is as efficacious as the short-acting oral formulations of ropinirole and pramipexole, because the only available trials were designed as non-inferiority trials. For APD, there are no comparative data on long-term efficacy, as the trial in this review was 16 weeks long, and in the prior review, 23 weeks long. Therefore, it is not known whether a long-acting formulation with continuous exposure to drug provides any advantage, in the long term, for control of motor symptoms when used on a chronic basis. There is also insufficient evidence to conclude that rotigotine has an advantage over short-acting, oral, non-ergolinic DAs for the control of non-motor symptoms, such as sleep disturbances, or for improving HRQoL. No comparative long-term safety data are available that assess the comparative risk of serious but relatively uncommon events, including arrhythmias and sudden death.

The findings in this review cannot be generalized to the use of rotigotine monotherapy in EPD, based on differences in recommended dose, concomitant medications, and disease features. This review thus provides no additional comparative evidence to support the use of rotigotine in EPD. Uncontrolled data suggest, as is the case for other non-ergolinic DAs, that a minority of patients may develop dyskinesia while taking rotigotine in the absence of levodopa.

5.2.3 Potential place in therapy[2]

Among the many problems faced by patients (and their caregivers) with advancing PD is dysphagia. In addition to having an impact on feeding and increasing the risk of aspiration pneumonia, dysphagia can become an important barrier to the reliable administration of oral antiparkinsonian medications. Currently in Canada, all approved antiparkinsonian medications are administered only by mouth. A drug that could be given by a non-oral route would be potentially useful in APD.

The evidence from the clinical trial considered in this review suggests that transdermal rotigotine has efficacy that is non-inferior to ropinirole in APD. In the original review, one trial in patients with EPD failed to demonstrate non-inferior efficacy of rotigotine to ropinirole, and one trial in APD showed inconsistent non-inferiority to pramipexole. Rotigotine might be an alternative to ropinirole or pramipexole for the treatment of APD. Transdermal rotigotine may find a niche in APD patients whose oropharyngeal dysfunction interferes significantly with the oral administration of pills, and that a once-daily rotigotine skin patch could replace three-times-daily oral ropinirole or pramipexole in this specific population. Such patients would be readily identified at follow-up clinic visits by asking the patient or caregiver whether there are any difficulties taking medicines by mouth. No special testing, imaging, or other investigations would be needed.

[2] Based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5.3 Other Considerations

a) Comparator Dose Equivalence: Ropinirole Doses

The manufacturer had conducted post hoc analyses [redacted][45] [redacted]. A publication by Korczyn et al. was referenced.[90] Korczyn et al., in their summary of ropinirole monotherapy trials, indicate that even though 75% of those who experienced a therapeutic response did so at doses ≤ 7.5 mg/day, mean doses in long-term trials of EPD were higher.[22,90] Additionally, dose analyses of ropinirole in US FDA documentation suggest onset of efficacy response can occur at higher doses.[83] Korzyn et al. suggested there is benefit of continued dose-titration of ropinirole in most patients with EPD, and that the maximum dose of ropinirole, 24 mg/day, may be necessary.[90] In a five-year RCT, the average daily dose of ropinirole, based on the observed set, was 10.1 mg at six months (median dose 9.0 mg), 14.4 mg at three years (median dose 15.0 mg) and 16.6 mg at five years (median dose 18.0 mg), regardless of levodopa supplementation.[43]

The following table provides information on: dose conversion schemes that have been used for overnight switching or add-on of drugs in published studies; the rotigotine and comparator doses achieved in active comparator RCTs that used titration to optimize dose; and an additional RCT that sought to identify the minimal effective dose of rotigotine for reducing *off* time more than placebo in APD patients.

TABLE 27: DOSE CONVERSION RATIOS IN THE LITERATURE AND OTHER INFORMATION RELATED TO DOSE EQUIVALENCE

Publication	Drug	"Equivalent" Dose	Ratio Rotigotine: Other Drug	Reference(s) Cited/Comments	
Manufacturer submission[5]	Pramipexole	3 mg/day	[redacted]	Human Drug Advisory Panel/ Patented Medicines Price Review Board	
	Ropinirole	12 mg/day	[redacted]		
	Rotigotine	8 mg/day	--		
Kim 2015[91]	Pramipexole[a]	2 mg/day	4:1	Reichman 2003[92]	Dose conversion used in study on add-on rotigotine to low doses of other DAs
	Ropinirole	8 mg/day	1:1	Reichman 2003;[92] Giladi 2007[3]	
	Rotigotine	8 mg/day	--	Poewe 2007;[4] Giladi 2007[3]	
Reichman 2003[92]	Pramipexole	2 mg/day	4:1	Based on neurology group's personal experience plus literature	
	Ropinirole	8 mg/day			
Lewitt 2007[84] (SP824)	Pramipexole	2 mg/day	4:1	Substitution scheme for switch from oral DAs to transdermal rotigotine based on clinical experience and the results of prior rotigotine trials — quotes Reichman 2003; authors indicate conversion scheme cannot be assumed to provide precise equivalence ratios.	
	Ropinirole	8 mg/day	1:1		
	Cabergoline	3 mg/day	4:1.5		
	Rotigotine	8 mg/day	--		
Chitnis 2012[93]	Pramipexole	2 mg/day	4:1	Uncontrolled study — switch to other drugs based on discontinuation of the original rotigotine patch. n = 5 switched to pramipexole; n = 8 switched to ropinirole. The main efficacy measurement was a	
	Ropinirole	8 mg/day	1:1		
	Rotigotine	8 mg/day			

Publication	Drug	"Equivalent" Dose	Ratio Rotigotine: Other Drug	Reference(s) Cited/Comments	
				patient rating of effectiveness on a scale of 0 (ineffective) to 5 (extremely effective). Change was –1.2 for ropinirole IR and –0.80 for pramipexole, suggesting these doses might not have been equivalent.	
Mean Doses Used in Active Comparator (Titration to Optimal or Maximum Dose) RCTs					
Publication	**Drug**	**Mean (SD) mg/day Maintenance Phase**	**Median mg/day (Range)**	**Ratio Rotigotine: Other Drug**	**Comment**
Mizuno 2014 [7] (APD) [Mean BW: 56 kg]	Rotigotine	12.9 (NR)	NR (2 mg to 16 mg)	1.4:1	Included in this review
	Ropinirole	9.2 (NR)	NR (0.75 mg to 15 mg)		
SP513[45] (EPD) [Mean BW: 76 kg]	Rotigotine	7.7 (1.1)[b]	8.0	1:2	Included in prior review; failed to demonstrate non-inferiority
	Ropinirole	14.1 (8.0)	15.0		
SP515[94] (APD) [Mean BW: 73 kg]	Rotigotine	13.0 (3.5)	NR	4.2:1	Included in prior review; failed to demonstrate consistent non-inferiority
	Pramipexole	3.1 (1.2)	NR		
Additional Information on Rotigotine Doses					
Publication	**Drug**	**Minimal Effective Dose**		**Description of study**	
Nicholas 2014[95]	Rotigotine vs. placebo	8 mg = minimal effective dose for *off* time		SP921 was a 5-group RCT that investigated rotigotine doses of 2 mg/24 h, 4 mg/24 h, 6 mg/24 h, or 8 mg/24 h vs. placebo to identify the minimal effective dose that reduced absolute *off* time significantly more than placebo. Doses higher than 8 mg/24 h were not included; therefore, it is not possible to comment on the dose response for higher doses.	

APD = advanced Parkinson's disease; BW = body weight; DA = dopamine agonist; EPD = early Parkinson's disease; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; vs. = versus.

[a] Pramipexole doses are expressed in terms of pramipexole dihydrochloride monohydrate (pramipexole salt); 1.0 mg pramipexole salt corresponds to 0.7 mg of pramipexole monohydrate (pramipexole base).

[b] Converted to nominal dose from a total dose of 17.4 mg/day.

6. CONCLUSIONS

Based on two DB RCTs in patients with APD, rotigotine adjunct therapy resulted in statistically significant and clinically meaningful improvements in UPDRS Part III motor function and time spent *off* compared with placebo. An additional DB RCT in a mixed population that was predominantly APD showed statistically significant improvement in early morning UPDRS Part III motor function and in PDSS-2 nocturnal sleep disturbance compared with placebo. The AE profile compared with placebo was similar to that previously identified.

Based on one RCT (N = 335 treated with active drug), rotigotine was non-inferior to ropinirole adjunct therapy for improvement in UPDRS Part III motor function in patients with APD. Rotigotine use was also associated with a higher proportion of patients experiencing one or more AEs. This was likely driven by a high frequency of application site reactions, which are not experienced with oral DAs. WDAEs and SAEs were similar among active drug groups. The incidence of AEs such as arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy was low, and generally appeared to be similar between rotigotine and ropinirole; however, the trial was not designed to detect differences in these events.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Patient input was received from Parkinson Society Canada (PSC). PSC serves as the national organization representing Canadians living with Parkinson's disease (PD). With 240 chapters, regional groups, and support groups, PSC is involved in research funding, education, support, and advocacy.

In 2014-2015, PSC received unrestricted education grants from AbbVie Corporation, Astra Zeneca Canada Inc., Baxter Corporation, Medtronic CryoCath, Medtronic Inc., Medtronic of Canada Ltd., Rx&D Canada's Research-Based Pharmaceutical Companies, Teva Canada Innovation GP, and UCB Canada Inc. PSC further mentioned that these contributions accounted for less than 1% of its gross revenue, and that PSC adheres to the ethical fundraising practices of the Association of Fundraising Professionals and Imagine Canada. PSC declared no conflict of interest related to the compilation of its submission.

2. Condition-Related Information

The condition-related information and current therapy-related information here and in the following section comes from the Canadian Guidelines on PD and from a national survey conducted with more than 600 individuals (70% of whom were people living with PD and 30% of whom were caregivers).

PD can be difficult to diagnose, especially in the early stages. It is characterized by motor manifestations such as slowness of movement, loss of dexterity, rigidity, tremor, restless legs, gait problems, and postural instability; and by neuropsychiatric symptoms that include depression, dementia, psychosis, cognitive impairment, speech impairment, sleep disorders, fatigue, autonomic dysfunction, urinary dysfunction, orthostatic hypotension, constipation, nausea, and erectile dysfunction. Neuropsychiatric symptoms are often observed before motor symptoms, and become more prominent and increasingly challenging to treat with disease progression. These complex, chronic symptoms contribute to increased disability and decreased quality of life (QoL). Patients reported that the most important PD symptoms to control were tremors, cognitive issues, dyskinesia, impaired balance and mobility, muscle rigidity, and sleep problems. PD is a neurodegenerative disease for which there is currently no cure.

PD has an enormous impact on a person's daily life; more than 77% of survey respondents indicated noticeable decreases in QoL. The most common issues are inability to maintain employment, reduced ability to perform household tasks and chores, reduced ability to participate in social activities and recreational events, and reduced ability to participate in family activities. Persons with PD have to plan their days carefully in order to save energy and reduce stress. Some patients reported that PD affects every aspect of their lives. Diminished capacity to work, reduced autonomy, and "off periods" (referring to the waning effect of PD medication) were raised as major issues by patients. Over time, the physical and psychological degradation takes away their lives.

3. Current Therapy-Related Information

Treatments for PD-related symptoms include medications, surgical procedures, physiotherapy, occupational therapy, and other support services. While PSC believes all of these can have a significant impact on QoL, medication is the primary treatment. The drug chosen for initiation of pharmacotherapy may depend on a range of factors, including: symptom severity; whether the symptoms affect the

dominant hand; embarrassment; ability to continue working and participating in activities such as hobbies; cost; and patient preference. As the disease progresses, an individual with PD becomes more reliant on medication, but the response wears off with time. With increases and adjustments to dosages, a positive benefit-to-harm ratio becomes more difficult to achieve as the disease progresses. Medication schedules become more complex and timing becomes crucial because of the need to be aware of "wearing-off times"— i.e., when the medication wears off before the next dose, causing symptoms to return. Some patients may take up to 50 pills during a 24-hour period. Difficulty adhering to the medication schedule and drug costs have been raised as issues by individuals living with PD as well as their caregivers.

Survey respondents stated that the most common adverse effects of oral medications for PD included nausea, vomiting, dizziness (related to drops in blood pressure), sleepiness, and visual hallucinations. In addition, "wearing-off times" can be a major issue, since they can be unpredictable. Medications must be taken at specific intervals throughout a 24-hour period to sustain a therapeutic effect, which may cause sleep problems. A proportion of 75% of survey respondents reported experiencing off periods ranging from less than one hour to five hours.

A typical day for a caregiver involves physical, emotional, and financial stress. It is not uncommon for caregivers to wake up at night to help administer medications. One caregiver mentioned exhaustion and psychological distress. A majority of caregivers (67% of survey respondents) mentioned that PD affected their QoL significantly or very significantly. The workload associated with PD was reported to increase with the stage of the disease. For advanced Parkinson's disease (APD), the caregiver faces a 24/7 task. Caregivers reported that the most challenging symptoms were mobility impairment (dyskinesia, tremors, freezing, lack of energy, and diminished strength), speech impairment, hallucinations, anxiety, and depression. Caregivers frequently noted that certain treatments cause hallucinations, mood changes, sleep disruption, and sometimes obsessive-compulsive behaviour. These adverse effects increase the burden of the disease for caregivers.

4. Expectations About the Drug Being Reviewed

For the writing of this section, PSC relied on interviews with five neurologists specializing in movement disorders to discuss their clinical experience with rotigotine, as well as interviews with 10 Canadians using rotigotine to treat their Parkinson's symptoms.

PSC reported an expectation for rotigotine to be similar to other oral dopamine agonists (DAs) in improving motor symptoms (tremor, slowness, rigidity, and dyskinesia). Additionally, PSC expects rotigotine to help with sleep issues, reduce "off periods," improve morning periods (reduced freezing, less rigidity), and improve other non-motor symptoms, such as pain. Currently, oral DAs are not expected to help with these issues. PSC expects a long-acting medication like rotigotine to have an enormous impact on QoL for people living with PD. Moreover, its mode of administration could help with adherence, and may be helpful to those with gastrointestinal and swallowing issues. Rotigotine would be the only PD treatment that is non-invasive and that potentially provides a continuous flow of medication. PSC reported adverse effects for rotigotine, such as dizziness, nausea, impulse control issues, leg edema, daytime somnolence, and hallucinations, which are similar to oral DAs. Specifically for rotigotine, a slight skin irritation at the site of application was mentioned, but was well-tolerated by respondents. Impulse control disorders (ICDs) associated with DAs are a concern regardless of delivery method. However, PSC mentioned that individuals and their caregivers are well-informed and are monitored for symptoms. The expectation is that ICDs may be corrected by lower dosages or by removal from the DAs, as the effects are not permanent.

Patients and caregivers who had experience with rotigotine mentioned improved symptoms and QoL, better sleep, and fewer off periods, although they also observed skin irritation. One caregiver observed obsessive behaviour, but felt it was tolerable given the benefits. Some patients noted significant improvement compared with previous therapies.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 17, 2015
Alerts:	Bi-Weekly/ search updates until October 21, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used. This report makes use of a literature search conducted in August 2013 for the original Neupro CDR review. For the current report, database searches were rerun on June 17, 2015 to capture any articles published since the initial search date. Conference abstracts were excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kw	Keyword
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.dp	Date of publication
.dc	Date completed
.dd	Date delivered
.ep	Electronic date of publication
.nm	Name of substance word
.ed	Entry date
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Line #	**SearchStrategy**	**Results**
1	(rotigotin* or leganto* or Neupro* or N0437 or N0923 or N0924 or "n 0437" or "n 0923" or "n 0924").ti,ot,ab,sh,rn,hw,kw,nm.	2086
2	(92206-54-7 or 112835-48-0 or 99755-69-6 or SPM 962 or SPM962 or 87T4T8BO2E).rn,nm.	1543
3	1 or 2	2086
4	(201405* or 201406* or 201407* or 201408* or 201409* or 201410* or 201411* or 201412* or 2015*).ed,dp,dc,ep.	1827035
5	3 and 4	73
6	5 use pmez	69
7	*rotigotine/	460
8	(neupro* or rotigotine* or leganto* or N0347 or N0923 or N0924 or "n 0437" or "n 0923" or "n 0924" or "SPM 962" or SPM962 or 87T4T8BO2E).ti,ab.	1057
9	7 or 8	1101
10	(201405* or 201406* or 201407* or 201408* or 201409* or 201410* or 201411* or 201412* or 2015*).dd.	1976068
11	9 and 10	113
12	11 use oemezd	113
13	conference abstract.pt.	1881420
14	12 not 13	57
15	6 or 14	126
16	remove duplicates from 15	90

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2014 – June 2015
Keywords:	Rotigotine, Neupro, Parkinson's
Limits:	No language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search
- Clinical Trials

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Chung et al. 2015[96]	Inappropriate study design (observational)
Kim et al. 2015[97]	Inappropriate study design (observational)
Giladi et al. 2014[21]	Inappropriate study design (observational)[a]
Zhou 2014[86]	Meta-analysis; pools rotigotine RCTs with other non-ergolinic dopamine agonists[b]
Thorlund 2014[85]	Mixed treatment comparison[b]

[a] Summarized in supplementary information, as it is an open-label extension of SP889.
[b] Summarized in supplementary information.

Reassessment of Excluded Studies From Initial CDR Review[a]		
Reference	**Status for This Review**	**Reason for Exclusion**
Parkinson Study Group 2003 SP506[98]	Exclude	Inappropriate study design (placebo-controlled RCT)
SP889[15]	Included because it was identified as a critical study by the manufacturer, and had been excluded on the basis of duration	NA
Trenkwalder et al. 2011[10]	Same study as above	NA
Mizuno et al. 2013[99]	Exclude	Inappropriate study design (placebo-controlled RCT)

[a] Reassessment due to change in duration eligibility criterion.

APPENDIX 4: DETAILED OUTCOME DATA

Additional Information on Drug Exposure

TABLE 28: INFORMATION ON DRUG EXPOSURE — ROTIGOTINE TREATMENT GROUP IN MIZUNO 2014

Mizuno 2014 Rotigotine Treatment Group		
Rotigotine Patient Breakdown		**Number of Patients**
Rotigotine treatment group in the safety analysis set		[redacted]
A. Patients who withdrew during titration period		[redacted]
	a. Patients whose dose of rotigotine was less than 16 mg/24 h	[redacted]
	b. Patients whose dose of rotigotine was 16 mg/24 h	[redacted]
B. Patients who entered the maintenance period		[redacted]
	a. Patients whose dose was less than 16 mg/24 h	[redacted]
	b. **Patients whose dose was 16 mg/24 h**	[redacted]
C.	a. Patients whose ropinirole placebo dose was less than 15 mg/24 h	[redacted]
	b. Patients whose ropinirole placebo dose was 15 mg/24 h	[redacted]

Source: Manufacturer's response to request for additional information, Aug. 11, 2014.[52]

TABLE 29: REASONS FOR MOVING INTO THE MAINTENANCE PHASE — ADVANCED PARKINSON'S DISEASE STUDIES

Drug	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87
Reasons for moving into maintenance phase without maximum dose					
Dose increase deemed impossible based on dose increase criteria (total)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
increased dose problematic[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
no further improvement expected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
disappearance of symptoms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
patient did not desire dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recovery from or alleviation of AE after dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event.
[a] For Nomoto 2014, this was specified as problematic due to AE.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] manufacturer's response to request for additional information, Aug. 4, 2014;[50] manufacturer's response to request for additional information, Aug. 11, 2014.[52]

TABLE 30: ADDITIONAL INFORMATION ON DRUG EXPOSURE IN STUDY SP889 (MIXED POPULATION)

SP889: Rotigotine Exposure in Maintenance Period (Safety Set) N = 257		
Dose at back-titration	**Rotigotine**	**Placebo**
2 mg/24 h		
4 mg/24 h		
6 mg/24 h		
8 mg/24 h		
10 mg/24 h		
12 mg/24 h		
14 mg/24 h		
16 mg/24 h		
Total		

Source: Clinical Study Report, SP889.[15]

Additional Data on Efficacy Outcomes

TABLE 31: EFFICACY OUTCOMES — ADDITIONAL RESULTS FOR ADVANCED PARKINSON'S DISEASE STUDIES

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
UPDRS Part III (*On* State)					
Change from Baseline to End of Maintenance Period (Per-protocol with LOCF)					
Rotigotine — placebo mean difference (SE)					
Rotigotine —ropinirole mean difference (SE)					
Responders (≥ 30% Reduction from Baseline) (FAS with LOCF)					
Responder rate, n (%)	114 (69.5%)	100 (60.6%)	33 (39.8%)	64.0%	29.1%
Rotigotine — placebo difference	29.8% (95% CI, 17.1 to 42.4) *P* < 0.001			34.9% (95% CI, 20.9% to 48.9%) *P* <0.001	
Rotigotine — ropinirole difference	8.9% (95% CI, –1.4 to 19.2) *P* = 0.090			NA	
UPDRS Part I Sum Score, FAS with LOCF					
Baseline mean (SD)					
Change from baseline mean (SD)					
Rotigotine — placebo difference					
Rotigotine — ropinirole difference					
UPDRS Part II (Mean of *On* and *Off* State), FAS with LOCF					
Responders (≥ 20% Reduction from Baseline)					
Responder rate, n (%)	105 (65.2%)	93 (56.7%)	39 (47.0%)	NR	NR
Rotigotine — placebo difference	18.2 (95% CI, 5.2 to 31.2) *P* = 0.006			NR	
Rotigotine — ropinirole difference	8.5 (95% CI, –2.1 to 19.1) *P* = 0.116			NA	

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
Responders (≥ 30% Reduction from Baseline)					
n (%)	90 (55.9%)	71 (43.3%)	24 (28.9%)	NR	
Rotigotine — placebo difference	27.0 (95% CI, 14.6 to 39.4) *P* < 0.001			NR	
Rotigotine — ropinirole difference	12.6 (95% CI, 1.8 to 23.4) *P* = 0.023			NA	
UPDRS Part II (*On*), FAS with LOCF					
Change from Baseline to End of Maintenance Period					
Baseline mean (SD)	8.5 (5.9)	7.8 (5.7)	7.9 (6.7)	NR	NR
End-of-maintenance mean (SD)	[redacted]	[redacted]	[redacted]		
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	–3.0 (3.7)	–1.2 (2.6)
Rotigotine — placebo difference	[redacted]			–1.9 (95% CI, –2.8 to –0.9) *P* < 0.001	
Rotigotine — ropinirole difference	[redacted]			NA	
LS mean change from baseline	–2.8	–2.3	–0.6	NR	NR
Rotigotine — placebo difference in adjusted mean	–2.2 (95% CI, –3.1 to –1.3) *P* < 0.001			NR	
Rotigotine — ropinirole difference in adjusted mean	–0.5 (95% CI, –1.2 to 0.3) *P* = 0.201			NA	
UPDRS Part II *(Off*), FAS with LOCF					
n	110	110	57	55	59
Baseline mean (SD)	14.9 (8.4)	15.2 (6.9)	16.1 (9.3)	NR	NR
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	–4.6 (4.5)	–1.9 (3.6)
Rotigotine — placebo difference	[redacted]			–2.6 (95% CI, –4.2 to –1.1) *P* = 0.001	
Rotigotine — ropinirole difference	[redacted]			NA	
UPDRS Part IV Sum Score, FAS with LOCF					
N				86	85
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rotigotine — placebo difference	[redacted]			[redacted]	
Rotigotine — ropinirole difference	[redacted]			[redacted]	
UPDRS Part II (Mean of *On* + *Off* state) + III (*On*), FAS with LOCF					
Change from Baseline to End of Maintenance Therapy					
Baseline mean (SD)	36.9 (15.2)	36.4 (15.2)	36.7 (16.0)	NR	NR
N	161	164	84	86	86
End-of-maintenance mean	22.4 (15.8)	24.0 (15.5)	31.1 (20.1)		

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
(SD)					
Mean change from baseline (SD)	–14.6 (10.6)	–12.5 (11.2)	–5.7 (11.9)	[redacted]	[redacted]
Rotigotine — placebo difference mean	–8.8 (95% CI, –11.8 to –5.9) *P* < 0.001			Statistical analysis not provided	
Rotigotine — ropinirole difference mean	–2.1 (95% CI, –4.5 to 0.3) *P* = 0.088			NA	
LS mean change from baseline	–14.6	–12.5	–5.7	NR	NR
Rotigotine — placebo Difference in adjusted mean	–8.8 (95% CI, –11.7 to –6.0) *P* < 0.001			NR	
Rotigotine — ropinirole difference in adjusted mean	–2.0 (95% CI, –4.4 to 0.3) *P* = 0.091			NA	
Responders (≥ 20% Reduction from Baseline)					
n (%)	78.3%	66.5%	51.8%	NR	NR
Rotigotine — placebo difference	26.5 (95% CI, 14.0 to 38.9) *P* < 0.001			NR	
Rotigotine — ropinirole difference	11.8 (95% CI, 2.2 to 21.4) *P* = 0.017			NA	
Responders (≥ 30% Reduction from Baseline)					
n (%)	68.3%	57.9%	37.3%	NR	NR
Rotigotine — placebo difference	31.0% (95% CI, 18.3 to 43.6) *P* < 0.001			NR	
Rotigotine — ropinirole difference	10.4% (95% CI, 0.0 to 20.8) *P* = 0.052			NA	
UPDRS Total Score I + II (Mean of *On* and *Off*) + II (*On*) + IV, FAS with LOCF					
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rotigotine — placebo difference	[redacted]			[redacted]	
Rotigotine — ropinirole difference	[redacted]			[redacted]	
***On* Time (Hours), FAS with LOCF**					
Baseline mean (SD)	13.1 (3.6)	12.6 (3.7)	12.5 (3.8)	NR	
Change from baseline mean (SD)	1.3 (2.7)	1.7 (2.9)	0.2 (2.6)	NR	NR
Rotigotine — placebo difference	1.0 (95% CI, 0.3 to 1.7) *P* = 0.006			NR	
Rotigotine — ropinirole difference	–0.5 (95% CI, –1.1 to 0.1) *P* = 0.130			NA	
***On* time (Hours) Without Dyskinesia Interfering with Daily Life, FAS with LOCF**					
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Change from baseline mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Rotigotine — placebo	[redacted]			NR	

Outcome	Mizuno 2014			Nomoto 2014	
	Rotigotine N = 164	Ropinirole N = 166	Placebo N = 85	Rotigotine N = 86	Placebo N = 86
difference	[redacted]				
Rotigotine — ropinirole difference	[redacted]			NA	
***On* Time (Hours) with Dyskinesia Interfering with Daily Life, FAS with LOCF**					
Proportion of patients with dyskinesia on any one day from baseline to end of maintenance n/N (%)	[redacted]	[redacted]	[redacted]	NR	NR
On time with dyskinesia (hours) change from baseline	NR			NR	NR
Dystonia, FAS with LOCF					
n/N (%) with early morning dystonia	[redacted]	[redacted]	[redacted]	NR	NR
End-of-maintenance early morning dystonia[a]	[redacted]	[redacted]	[redacted]	NR	NR
n/N(%) with diurnal dystonia	[redacted]	[redacted]	[redacted]	NR	NR
End-of-maintenance diurnal dystonia[a]	[redacted]	[redacted]	[redacted]	NR	NR
Severity of Disorder (Clinical Global Impression)					
Decrease in CGI n/N (%)	[redacted]	[redacted]	[redacted]	NR	NR
Increase in CGI n/N (%)	[redacted]	[redacted]	[redacted]	NR	NR
Compliance					
Adherence < 85% n/N (%)	NR by intervention group			[redacted]	

CGI = clinical global impression; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; NR = not reported; NA = not applicable; SE = standard error; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Grades 1 to 4.

Note: Mizuno 2014: Least squares mean, an adjusted mean, was reported in Mizuno 2014[6] from ANCOVA with baseline value as covariate. Unadjusted means are reported from data in the Mizuno Clinical Study Report.[7]

Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014 clinicaltrials.gov;[49] Clinical Study Report, Nomoto;[24] manufacturer's response to request for additional information, Aug. 5, 2015.[79]

TABLE 32: ADDITIONAL EFFICACY END POINT RESULTS IN MIXED POPULATIONS STUDIES (STUDY SP889)

Outcome	SP889	
	Placebo N = 89	Rotigotine N = 178
PDSS-2 Individual Items — Mean Difference in Change from Baseline (FAS with LOCF)		
Overall, sleep well during last week	[redacted]	[redacted]
Difficulty falling asleep each night	[redacted]	[redacted]
Difficulty staying asleep	[redacted]	[redacted]
Restlessness of limbs disrupt your sleep	[redacted]	[redacted]
Urge to move limbs disturbed sleep	[redacted]	[redacted]
Suffer from distressing dreams	[redacted]	[redacted]
Suffer from distressing hallucinations	[redacted]	[redacted]
Nocturia	[redacted]	[redacted]
Feel uncomfortable at night	[redacted]	[redacted]
Pain in limbs which woke you up	[redacted]	[redacted]
Muscle cramps in limbs which woke you up	[redacted]	[redacted]
Woke early with painful posturing limbs	[redacted]	[redacted]
Experience tremor at awakening	[redacted]	[redacted]
Feel tired and sleepy in morning	[redacted]	[redacted]
Wake up due to breathing difficulties	[redacted]	[redacted]
Change in NADCS Total Score (FAS)		
Baseline, mean (SD)	[redacted]	[redacted]
End-of-maintenance mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM)	[redacted]	
Nocturia (FAS-Observed Cases)		
Baseline, mean (SD)	[redacted]	[redacted]
End-of-maintenance, mean (SD)	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM)	[redacted]	
UPDRS Part II + Part III Sum Score (FAS-Observed Cases)		
Baseline, mean (SD)	[redacted]	[redacted]
End-of-maintenance mean (SD)	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM) (SE)	[redacted]	
UPDRS Part IV Sum Score (FAS-Observed Cases)		
Change from Baseline to End of Maintenance in Total Sum Score		
Baseline, mean (SD)	[redacted]	[redacted]
End-of-maintenance mean (SD)	[redacted]	[redacted]

Outcome	SP889	
	Placebo N = 89	Rotigotine N = 178
Change from baseline, mean (SD)	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM) (SE)	[redacted]	
P value (95% CI)	[redacted]	
UPDRS Part IV Individual Items		
Dyskinesia duration, *on*		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Dyskinesia disability, *on*		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Dyskinesia pain, *on*		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Early morning dystonia		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Offs, predictable		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Offs, unpredictable		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Offs, period comes suddenly		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Offs, period of waking day		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Anorexia, nausea, vomiting, on		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Sleep disturbances, on		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
Symptomatic orthostasis		
Baseline, mean (SD)	[redacted]	[redacted]
Mean change from baseline to EOM (SD)	[redacted]	[redacted]
BDI-II (FAS-Observed Cases)		
Baseline, mean (SD)	[redacted]	[redacted]
EOM, mean (SD)	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]

Outcome	SP889	
	Placebo N = 89	Rotigotine N = 178
Difference between rotigotine and placebo in adjusted mean (LSM) (SE)	[redacted]	
NMSS[a] (FAS-Observed Cases)		
Baseline, mean (SD)	[redacted]	[redacted]
EOM, mean (SD)	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]
Difference between rotigotine and placebo in adjusted mean (LSM)	[redacted]	
Likert Pain Scale (FAS-Observed Cases)		
Baseline mean SD	2.6 (2.5)	2.8 (2.4)
EOM, mean SD	2.2 (2.4)	1.8 (2.3)
Change from baseline	–0.3 (2.2)	–1.0 (2.2)
Difference between rotigotine and placebo in adjusted mean (LSM)	–0.77 (95% CI, –1.28 to –0.25) *P* = 0.0037 (difference is considered exploratory)	

BDI-II = Beck Depression Inventory (second edition); CI = confidence interval; EOM = end of maintenance; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; NADCS = Nocturnal Akinesia, Dystonia, and Cramps Score; NMSS = Non-Motor Symptom Scale; PDSS = Parkinson's Disease Sleep Scale; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] The NMSS included an additional 2 items (total 32 items) that had not been included in the validated 30-item version of this scale.

Source: NEUPRO Health Canada Modules 2.7.3 and 2.7.6;[5] Clinical Study Report, SP889;[15] Kassubek 2014 (Likert Pain Scale).[12]

Additional Safety Data

TABLE 33: ADDITIONAL HARMS DATA FOR ADVANCED PARKINSON'S DISEASE AND MIXED POPULATION STUDIES

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
Other Common AEs							
Application site erythema	--	--	--	8 (9.2%)	4 (4.6%)	--	--
Application site pruritus	--	--	--	5 (5.7%)	4 (4.6%)	--	--
Excoriation	--	--	--	1 (1.2%)	4 (4.6%)	--	--
Hallucination	3 (1.8%)[g]	6 (3.6%)	0	3 (3.5%)	3 (3.5%)	[redacted]	[redacted]
Hallucination, visual	[redacted]	[redacted]	[redacted]	8 (9.2%)	2 (2.3%)	[redacted]	[redacted]
Hallucination, auditory	[redacted]	[redacted]	[redacted]	--	--	--	--
Delusion	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	--	--		

Study	Mizuno 2014			Nomoto 2014		SP889	
Intervention	Rotigotine N = 168	Ropinirole N = 167	Placebo N = 85	Rotigotine N = 87	Placebo N = 87	Rotigotine N = 191	Placebo N = 96
Application site excoriation	--	--	--	1 (1.2%)	4 (4.6%)	--	--
Insomnia	--	--	--	--	--	[redacted]	[redacted]
Nasopharyngitis	28 (16.7%)	24 (14.4%)	13 (15.3%)	18 (20.7%)	13 (14.9%)	--	--
Upper respiratory tract inflammation	3 (1.8)	1 (0.6%)	3 (3.5%)	--	--	--	--
Fall	--	--	--	6 (6.9%)	7 (8.0%)	[redacted]	[redacted]
Bruise or contusion	7 (4.2%)	2 (1.2%)	6 (7.1%)	5 (5.7%)	3 (3.4%)	[redacted]	[redacted]
Laboratory Parameters							
Increased creatinine phosphokinase, n (%)	[redacted]	[redacted]	[redacted]	7 (8.0%)	3 (3.5%)	--	--
CK increase mean (SD) IU/mL	[redacted]	[redacted]	[redacted]	--	--	--	--
Prolactin ng/mL	[redacted]	[redacted]	[redacted]	--	--	--	--
ECG Parameters — QT Prolongation							
QTc ≥ 500 ms, n (%)	0	[redacted]	0	0	NR	[redacted]	[redacted]
QTc ≥ 60 ms increase from baseline	0	[redacted]	0			[redacted]	[redacted]
QTc > 450 ms (men) or 470 ms (women) and increase ≥ 30 ms from baseline	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR

AE = adverse event; CK = creatinine kinase; ECG = electrocardiogram; SD = standard deviation.
Source: Mizuno 2014;[6] Clinical Study Report, Mizuno;[7] Nomoto 2014;[8] Nomoto 2014 clinicaltrials.gov;[49] Clinical Study Report, SP889.[15]

TABLE 34: MIZUNO 2014 (ADVANCED PARKINSON'S DISEASE): DESCRIPTION OF SERIOUS ADVERSE EVENTS AND DOSES IN ACTIVE DRUG TREATMENT GROUPS

Mizuno 2014			
Intervention	**Patient Sex/Age**	**SAE Description**	**Phase/Dose of Active Drug**
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Ropinirole	[redacted]	[redacted]	[redacted]
Ropinirole	[redacted]	[redacted]	[redacted]
Ropinirole	[redacted]	[redacted]	[redacted]
Ropinirole	[redacted]	[redacted]	[redacted]
Ropinirole	[redacted]	[redacted]	[redacted]

[redacted] SAE = serious adverse event.

Source: Clinical Study Report, Mizuno.[7]

TABLE 35: MIZUNO 2014 (ADVANCED PARKINSON'S DISEASE) DESCRIPTION OF WITHDRAWALS DUE TO ADVERSE EVENTS

Mizuno 2014	
Dose/Duration of Drug Treatment	**WDAE Description**
Rotigotine WDAE	
Rotigotine 16 mg, 56 days	[redacted]
Rotigotine 2 mg, 1 day	[redacted]
Rotigotine 2 mg, 1 day	[redacted]
Rotigotine 16 mg, 63 days	[redacted]
Rotigotine 22.5 mg, 81 days	[redacted]
Rotigotine 13.5 mg, 21 days	[redacted]
Rotigotine 22.5 mg, 34 days	[redacted]
Rotigotine 13.5 mg, 55 days	[redacted]
Rotigotine 27.0 mg, 63 days	[redacted]
Rotigotine 9.0 mg, 8 days	[redacted]
Rotigotine 22.5 mg, 29 days	[redacted]
Rotigotine 16 mg, 105 days	[redacted]
Rotigotine 16 mg, 101 days	[redacted]
Rotigotine 16 mg, 70 days	[redacted]
Ropinirole WDAE	
Ropinirole 0.75 mg, 2 days	[redacted]
Ropinirole 6.0 mg, 43 days	[redacted]
Ropinirole 4.5 mg, 70 days	[redacted]
Ropinirole 1.5 mg, 28 days	[redacted]
Ropinirole 4.5 mg, 70 days	[redacted]
Ropinirole 2.25 mg, 21 days	[redacted]
Ropinirole 0.75 mg, 4 days	[redacted]
Ropinirole 4.5 mg, 63 days	[redacted]
Ropinirole 6.0 mg, 130 days	[redacted]
Ropinirole 4.5 mg, 30 days	[redacted]
Ropinirole 4.5 mg, 70 days	[redacted]
Ropinirole 2.25 mg, 36 days	[redacted]
Ropinirole 1.5 mg, 14 days	[redacted]
Placebo WDAE	
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]

WDAE = withdrawal due to adverse event.

Note: [redacted]

Source: Clinical Study Report, Mizuno.[7]

TABLE 36: DESCRIPTION OF WITHDRAWALS DUE TO ADVERSE EVENTS IN NOMOTO 2014 (ADVANCED PARKINSON'S DISEASE)

Nomoto 2014	
Treatment	**WDAE Description**
Rotigotine WDAE	
Rotigotine	[redacted]
Rotigotine (patient 0120002)	[redacted][a]
Rotigotine	[redacted]
Rotigotine	[redacted]
Rotigotine	[redacted]
Rotigotine	[redacted]
Rotigotine	[redacted]
Rotigotine (patient 0290003)	[redacted][a]
Rotigotine	[redacted]
Placebo WDAE	
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted]
Placebo	[redacted][b]
Placebo	[redacted]
Placebo	[redacted]

WDAE = withdrawal due to adverse event.

[a] [redacted]

[b] [redacted]

Source: Manufacturer's response to request for additional information, Aug. 4, 2015;[50] Clinical Study Report, Nomoto.[24]

TABLE 37: DESCRIPTION OF SERIOUS ADVERSE EVENTS IN ROTIGOTINE TREATMENT GROUP, STUDY SP889 (MIXED POPULATION)

SP889			
Intervention	**Patient Sex/Age**	**SAE Description**	**Phase/Dose of Active Drug at Onset**
Serious Adverse Events			
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]
Rotigotine	[redacted]	[redacted]	[redacted]

[redacted]; [redacted]; [redacted]; [redacted]; SAE = serious adverse event.
Source: Clinical Study Report, SP889.[15]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To describe and assess the validity and reliability of measures used to assess functional ability, motor signs, and quality of life (QoL) in the rotigotine studies:

- Unified Parkinson's Disease Rating Scale (UPDRS)
- Hoehn and Yahr Staging
- The Parkinson's Disease Questionnaire (PDQ)-39 and its short form (PDQ-8)
- The Parkinson's Disease Home Diary (PDHD)
- The Parkinson's Disease Sleep Scale (PDSS) and its modified version (PDSS-2)

Minimal clinically important differences (MCIDs) are included where available.

Findings

TABLE 38: SUMMARY OF OUTCOMES VALIDITY

Instrument	Type	Evidence of Validation	MCID		References
			APD	EPD	
UPDRS[53,100]	Measure of disability and impairment in PD. Four parts: Part I (mentation, behaviour, and mood: four items, score 0 to 16); Part II (activities of daily living; 13 items, score 0 to 56 for each state); Part III (motor examination; 14 items, score 0 to 56); and Part IV (complications of therapy in past week; 11 items, score 0 to 23). Total score from 0 (best) to 199 (worst).	Yes	II: 3.0 points III: 6.5 points II + III: 8.8 points *Off* time: 1.3 hours to 1.9 hours	II: 0.7 points to 2.0 points III: 2.4 points to 6.1 points II + III: 8.1 points I + II + III: 3.5 points to 8.0 points	Hauser et al. 2011; Hauser et al. 2014; Schrag et al. 2006; Shulman et al. 2010.[54-57]
PDQ-8[81]	The PDQ-8 is a disease-specific QoL scale consisting of 8 items graded on a five-point scale (0 = never; 4 = always). There are eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. PDQ-8 is a short form of the	Yes	5.8 points to 7.4 points = "worsened by a little bit"		Luo et al. 2009.[59]

Instrument	Type	Evidence of Validation	MCID		References
			APD	EPD	
	PDQ-39.				
PDHD[101]	The PDHD is a PD diary where patients experiencing motor fluctuations and dyskinesia report the amount of *on* and *off* time over 24 h. Consists of five categories: (1) asleep; (2) *off*; (3) *on* without dyskinesia; (4) *on* with non-troublesome dyskinesia; and (5) *on* with troublesome dyskinesia.	Only self-validated	*Off* time: 1 hour	--	Hauser et al. 2011.[54]
PDSS-2[58]	The unmodified PDSS is a 15-item scale that assesses sleep disturbances in PD patients over the preceding week, using a VAS. It attempts to distinguish between the causes of sleep disturbances. The 15 items include: overall quality of night's sleep, sleep onset and maintenance insomnia, nocturnal restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, sleep refreshment, and daytime dozing. PDSS-2 is a modification that includes more items on nocturnal RLS, akinesia, pain, and sleep apnea, with six of the previous 15 questions modified. The VAS was modified into a frequency measure, i.e., five categories, from 0 (never) to 4 (very frequent). Items can be grouped into three domains: 1) motor problems at night; 2) PD-specific nocturnal	Yes	None, but threshold for sleep disturbance was suggested at 15 points		Suzuki et al. 2015.[102]

Instrument	Type	Evidence of Validation	MCID		References
			APD	EPD	
	non-motor symptoms; and 3) sleep-specific disturbances. Total PDSS-2 score can range from 0 (no disturbance) to 60 (maximum disturbance).				
Hoehn and Yahr Staging[103,104]	Staging system that provides an estimate of clinical function in PD. The initial scale had 5 stages, and has been modified to include stages 1.5 and 2.5, for a total of 7 stages. Not generally used for assessment of treatment.	No	None		

APD = advanced Parkinson's disease; EPD = early Parkinson's disease; MCID = minimal clinically important difference; PD = Parkinson's disease; PDHD = Parkinson's Disease Home Diary; PDQ-8 = Parkinson's Disease Questionnaire-8; PDSS = Parkinson's Disease Sleep Scale; QoL = quality of life; RLS = restless legs syndrome; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analogue scale.

Unified Parkinson's Disease Rating Scale

The UPDRS is a measure of disability and impairment in Parkinson's disease (PD). The scale comprises four parts: Part I (mentation, behaviour, and mood; four items); Part II (activities of daily living [ADL]; 13 items); Part III (motor examination; 14 items); and Part IV (complications of therapy in past week; 11 items). Individual items in Parts I to III are scored on a 5-point scale (0 to 4), with higher scores indicating worse symptoms, while Part IV also includes a number of items for which scoring is 0 (no) or 1 (yes). The total scale takes 10 to 20 minutes to administer, with a possible range of 0 (no disability) to 199 (worst disability). The range of scores for the subscales are: 1) Mentation, Behaviour and Mood (0 to 16); 2) ADL (0 to 52); 3) Motor Examination (0 to 56); and 4) Complications of Therapy (0 to 23).[100] The scale provides a relatively comprehensive assessment of the motor features of PD, but is less comprehensive in its assessment of non-motor symptoms.[53]

The UPDRS has demonstrated high internal consistency, inter-rater reliability, moderate construct validity,[105-107] and patient-investigator reproducibility;[108] however, reliability is reduced when used in mildly impaired individuals.[109] Several estimates of an MCID for the UPDRS have been made, with variation from the method of estimation (anchor- or distribution-based, patient population [early Parkinson's disease (EPD) or advanced Parkinson's disease (APD)], intervention, time of evaluation, and study type [Table 40]).[54-57] Estimates of MCID provided in the table for APD may not pertain to measurements in the *off* state.

For UPDRS Part III, the reported 5-point change for EPD corresponds to a 15% to 18% change, suggesting that a change of at least 5 points, or a mean percentage change of at least 20%, is the threshold to indicate that improvement of symptoms represents a clinically meaningful change from baseline in EPD populations (Hoehn & Yahr, stages 1 to 3).[56] This cut point is often used in EPD populations to define responders, although a higher MCID estimate of 6.1 points was recently published for EPD.[55]

Another estimate for UPDRS Part III that included patients with APD was a cross-sectional study on a mixed population in an office setting, which combined anchor-based analyses with distribution-based analyses for an MCID estimate of 2.5 points. A recently published MCID for UPDRS Part III specifically in an APD population (using placebo-controlled randomized controlled trial [RCT] data with pramipexole) estimated a higher MCID of 6.5 points.[55] It is uncertain whether the reported MCID values can be generalized to measurement of the UPDRS specifically in the *off* state; none of the available MCID studies included such data for their estimates.

Hauser 2014 assessed the MCID in two placebo-controlled trials with pramipexole (immediate release [IR] and controlled release [CR]) — one in EPD and the other in APD patients — using both patient-reported global impression of improvement data (PGI-I) and Clinical Global Impression of Improvement (CGI-I) as anchors.[55] Results with each were similar, except for the UPDRS Parts II + III scores, in which the mean change in scores for patients who rated themselves as unchanged was –8.9 points, and the mean change in scores for clinicians who rated patients as unchanged was –3.3. The estimates for this study have limitations in that the raters for CGI-I, the anchor used, were aware of the UPDRS scores, which could have influenced their ratings.[55]

The estimated MCID on the ADL component (Part II) has ranged from 0.7 points to 2.0 points for EPD, and a single estimate, 3.0 points, is available for APD. For Parts II + III, single estimates for EPD (8.1 points) and APD (8.8 points) are available. The MCID for the UPDRS motor component (Part III) has ranged from 2.4 points to 6.1 points for EPD, with a single estimate, 6.5 points, available for APD. MCID for *off* time in APD has ranged from 1.3 hours to 1.9 hours.

TABLE 39: MINIMAL CLINICALLY IMPORTANT DIFFERENCES FOR UNIFIED PARKINSON'S DISEASE RATING SCALE SCORES AND *OFF* TIME

Study	Methods/Trial Characteristics	Anchor (and Stage)	MCID				*Off* Time
			UPDRS III (Motor Score)	UPDRS II + III	UPDRS II (Activities of Daily Life)	UPDRS Subtotal Score (Subscales I + II + III)	
Schrag et al. 2006[56]	• 2 prospective randomized DB trials; 603 pts with EPD • Active comparators (RP, BC, L-dopa) • Analysis using 6 mos data, based on change from baseline	CGI-I	5 points (EPD)	NR	2 points (H&Y Stages 1/1.5 and 2) 3 points (H&Y Stages 2.5 and 3)	8 points (EPD)	ND
Shulman et al. 2010[57]	• Cross-sectional analysis assessed during routine office visits • 653 pts with PD of various stages and treatments[a] • Used anchor- and distribution-based analyses	SF-12 SE Scale H&Y Scale	2.5 points[b] (mixed)	NR	ND	4.5 points (mixed)	ND
Hauser et al. 2011[54]	• 2 randomized, PL-controlled, DB trials; comparator RS • Trial 1: 404 pts with EPD (no L-dopa), analyzed at 14 weeks (interim time point) of a 26-week trial • Trial 2: 472 pts on L-dopa, used to assess *off* time MCID; assessment at 26 weeks • Based on change from baseline,	CGI-I[c]	2.4 points (EPD)	NR	0.7 points (EPD)	3.5 points[d] (EPD)	1.9 hours (APD)

Study	Methods/Trial Characteristics	Anchor (and Stage)	MCID				*Off* Time
			UPDRS III (Motor Score)	UPDRS II + III	UPDRS II (Activities of Daily Life)	UPDRS Subtotal Score (Subscales I + II + III)	
	analyzed PL and active treatment separately						
Hauser et al. 2014[55]	• 2 multi-centre, randomized, DB, PL-controlled trials with pramipexole IR and ER • Trial 1: 539 EPD pts, assessed at 33 weeks • Trial 2: 517 APD pts, assessed at 18 weeks. Used to assess *off* time MCID • Anchor-based analysis using changes from baseline	PGI-I[e] CGI-I	PGI-I 6.1 points (EPD) 6.5 points (APD)	PGI-I 8.1 points (EPD) 8.8 points (APD)	PGI-I 2.0 points (EPD) 2.3 points (APD)	NR	PGI-I 1.3 hours (APD)

APD = advanced Parkinson's disease; BC = bromocriptine; CGI-I = Clinician-Reported Global Impression of Improvement; DB = double-blind; EPD = early Parkinson's disease; H&Y = Hoehn and Yahr Scale; L-dopa = levodopa; MCID = minimal clinically important difference; mos = months; ND = not done; NR = not reported; PD = Parkinson's disease; PGI-I = patient global improvement; PL = placebo; pts = patients; RP = ropinirole; RS = rasagiline; SE Scale = Schwab and England Activities of Daily Living Scale; SF-12 = Short Form (12) Health Survey, version 2; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] PD diagnosed in a movement disorder clinic as asymmetrical onset of at least 2 of the following 3 cardinal signs: resting tremor, rigidity, bradykinesia, and no atypical signs or exposure to dopamine blockers, with involvement of 86% of the patients attending the clinic.

[b] Mean of all analyses.

[c] For trial 1, CGI-I assessment was at 14 weeks because there was no difference in UPDRS at the 26-week study end point. For trial 2, global impression of improvement was both investigator- and patient-rated at 26 weeks, the latter likely being a better measure of clinical importance to the patient.

[d] In patients actively treated. Some differences were noted for placebo suggesting other methodology may be appropriate for calculating MCID.

[e] Results with CGI-I were similar to PGI-I with the exception of UPDRS Parts II + III where PGI-I was 5.6 points lower than CGI-I.

Source: Schrag et al.,[56] Shulman et al.,[57] Hauser et al.,[54] Hauser et al. [55]

Parkinson's Disease Questionnaire (PDQ-39 and PDQ-8)

PDQ-39 is a disease-specific QoL scale consisting originally of 39 items graded on a five-point scale (0 = never; 4 = always). There are eight domains: mobility (10 items), ADL (six items), emotional well-being (six items), stigma (four items), social support (three items), cognition (four items), communication (three items), and bodily discomfort (three items).[110] All domains and a summary index may be transformed to have a range of 0 to 100, with higher scores indicating worse QoL.

A short form of the self-administrated PDQ-39 questionnaire, the PDQ-8 has been developed using eight of the 39 original items. The items that correlated most to each dimension total in PDQ-39 were selected and summed to create an index.[81] One item was selected from each of the eight domains. PDQ-8 has been validated in English and Greek patients, and among different cultures in the US, Canada, Spain, Italy, and Japan.[81,111,112] Each item is scored from 0 (never or not at all) to 4 (always or cannot do at all). A total score is derived from the following formula: sum of scores of each question × 100/4 (maximum score per question) × 8. Individuals are asked to rate how often during the past month (never, occasionally, sometimes, often, always, or cannot do at all) they:

- had difficulty getting around in public
- had difficulty dressing
- felt depressed
- had problems with close personal relationships
- had problems with concentration
- felt unable to communicate properly
- had painful muscle cramps or spasms
- felt embarrassed in public due to PD.

The PDQ-8 was validated in a number of studies.[59,81,113,114] The internal consistency of PDQ-8 based on Cronbach's alpha coefficient was very good. Test–retest data showed good significant reliability. Criterion validity was demonstrated, as mean scores for PDQ-8 were almost identical to those for PDQ-39. Construct validity was also shown, as mean scores at different stages showed significantly higher scores obtained in cases with more advanced stages. PDQ-8 also correlated to a standardized measure of motor disability — the UPDRS Part III — and to a measure of dependence (the Schwab–England ADL score), in both *on* and *off* phases. Depression measured by the Beck Depression Inventory (BDI) also correlated with PDQ-8 scores.[111] An MCID was derived from 96 consecutive patients presenting at a tertiary neuroscience clinic for two different visits.[59] Patients were in Hoehn & Yahr stages 1 to 3, with 45% in stage 1 or 2, and 42% in stages 2.5 to 3. The PDQ-8 index score of patients who reported that their health status worsened only "a little bit" ranged from 5.8 points to 7.4 points. It is not known whether the reported MCID also directly applies to improvement rather than worsening.

The Parkinson's Disease Home Diary

The PDHD is a home diary that patients who are being treated for idiopathic PD and experiencing motor fluctuations and dyskinesia can fill out during their participation in a clinical trial. This diary aims to assess the amount of "on" and "off" time that patients experience in a 24-hour period.[101] The PDHD consists of five categories: asleep; "off"; "on" without dyskinesia (ONW); "on" with non-troublesome dyskinesia (ONN); and "on" with troublesome dyskinesia (ONT). In terms of motor function, "off" time and ONT are generally perceived by patients as "bad time," whereas ONW and ONN are considered "good time." Intervention effects can be expressed as a change in the sum of "bad time" ("off" time plus ONT) or a change in the sum of "good *on* time" (ONW plus ONN). [101]

The PDHD was only validated and found reliable within itself, and was not validated through a comparison with other validated tools.[101] The diary was shown to be both feasible and simple in its use;[101] however, increases in errors were more prevalent after three days of diary use. Non-specific variables (such as age, gender, and country) did not influence diary results, indicating its potential usefulness for international trials. The PDHD displayed good test–retest reliability and a reasonable correlation was observed between external visual analogue scale (VAS) measures and corresponding

PDHD measures when they were compared (Table 40), showing acceptable predictive validity.[101] In addition, a one-hour reduction in "off" time was considered an MCID in actively treated patients.[54]

TABLE 40: PARKINSON'S DISEASE HOME DIARY MEASURES AND CORRESPONDING VISUAL ANALOGUE SCALE QUESTIONS

PDHD Measures	VAS
Percentage of the awake day "on" with troublesome dyskinesia (ONT %)	How would you rate the severity of your dyskinesia today?
Percentage of the awake day "on" with non-troublesome dyskinesia, or with troublesome dyskinesia (ONN % + ONT %)	How much of the day today did you have dyskinesia?
Percentage of the awake day "on" with troublesome dyskinesia (ONT %)	How much of the day today did you have troublesome dyskinesia?
Percentage of the awake day "on" with troublesome dyskinesia (ONT %)	How much difficulty did dyskinesia cause you today?
Percentage of the awake day "on" without dyskinesia or with non-troublesome dyskinesia (ONG %)	How much of the day today did you experience a good response?

ONG = ONW + ONN; ONN = "on" with non-troublesome dyskinesia; ONT = "on" with troublesome dyskinesia; ONW = "on" without dyskinesia PDHD = Parkinson's Disease Home Diary; VAS = visual analogue scale.
Source: Hauser et al.[101]

The Parkinson's Disease Sleep Scale and Parkinson's Disease Sleep Scale-2

The PDSS is a 15-item scale that assesses sleep disturbances typically reported by patients with Parkinson's disease (primarily during nocturnal sleep, as opposed to daytime sleep disturbance) using a VAS.[47,115-120] It attempts to distinguish between the causes of sleep disturbances in patients with any stage of Parkinson's disease.[47] The 15 items include: "overall quality of night's sleep (item 1), sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (items 8 and 9), nocturnal motor symptoms (items 10 thought 13), sleep refreshment (item 14), and daytime dozing (item 15)."[115] Patients or caregivers (as proxies) complete the PDSS based on the patient's sleep experiences of the prior week, providing scores for each item that range from 0 (symptomatically severe, always experiencing) to 10 (symptom-free, never experience). Total scores can ranges from 0 to 150.[47,115]

The PDSS was recently modified to PDSS-2 and expanded to include more items on nocturnal restless legs syndrome (RLS), akinesia, pain, and sleep apnea, with six of the previous 15 questions modified.[58] Also, the VAS was modified into a frequency measure. The scale is subclassified into three domains: motor problems at night (PD-specific, nocturnal motor symptoms, such as akinesia, early morning dystonia, tremor during waking period at night, rapid eye movement behaviour disorder); PD-specific, nocturnal non-motor symptoms (hallucinations, confused states, pain, muscle cramps, and difficulties in breathing, with snoring and immobility); and sleep-specific disturbances (e.g., insomnia, sleep maintenance, unrestored sleep, having to get up at night because of nocturia, and overall quality of sleep). The total sum of the scale is 60. The scale consists of 15 questions about sleep and nocturnal disturbances over the preceding week, which are to be self-rated (or rated by a caregiver) using one of five categories, from 0 (never) to 4 (very frequent). Total score ranges from 0 (no disturbance) to 60 (maximum disturbance).

For the English version, internal consistency was assessed by computing Cronbach alpha for the total score (0.73) and the subscales (0.47 to 0.66). For test–retest reliability (after one to three days), the intraclass coefficient was 0.80. Convergent validity was tested with four instruments, including the Medical Outcome Sleep Scale (MOS), Clinical Global Impressions–Severity (CGI–S) of sleep disturbance, and bed partners' rating. The highest correlations (0.54) were found for the MOS. Discriminative validity testing found differences in the PDSS-2 total score, depending on CGI and Hoehn and Yahr severity levels. Item–total correlation for proving internal consistency was > 30 for most items although a few were poor.[58]

The cut-off score of 15 is reported to be useful in differentiating poor sleepers from good sleepers in clinical practice, as assessed for the Japanese version in a cross-sectional study.[102] However, no published studies were identified that reported a formal derivation of an MCID. The test–retest validity of PDSS-2 has been assessed in 92 stable PD patients over a four-week period.[121] The intraclass and linear and Lin's concordance correlation coefficients were 0.782 and 0.799, respectively.

The Japanese version of PDSS-2 has been validated.[80] Internal consistency was satisfactory and test–retest reliability was high. Item–total correlation was poor for sleep quality (item 1). In terms of convergent validity, there was correlation with sleep disturbances measured by the Pittsburgh Sleep Quality Index global and component scores, the Beck Depression Inventory-II (BDI-II), and PDQ-39.[80]

Hoehn and Yahr Staging

Introduced in 1967, the Hoehn and Yahr staging scale[103] was intended to provide an estimate of clinical function in PD.[104] This scale has largely been superseded by the UPDRS. The scale classifies patients as:

- **Stage 1:** Unilateral movement only, usually with minimal or no functional impairment
- **Stage 2:** Bilateral or midline involvement, without impairment of balance
- **Stage 3:** Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
- **Stage 4:** Severely disabling disease; still able to walk or stand unassisted
- **Stage 5:** Confinement to bed or wheelchair unless aided.

More recently, the modified Hoehn and Yahr added intermediate stages 1.5 (unilateral plus axial involvement) and 2.5 (mild bilateral disease, with recovery on pull test). In a review of the use of Hoehn and Yahr staging, the Movement Disorder Society concluded that the modified scale should not be used due to a lack of clinimetric testing, and that the broad categories of the original scale do not allow for detection of effective interventions.[104] For these reasons, the scale is used in clinical trials to define inclusion and exclusion criteria, but not typically as an outcome measure.

Conclusions

- The UPDRS has demonstrated high internal consistency and inter-rater reliability. Its reliability is reduced in mildly impaired individuals. Several estimates of MCID are published depending on the disease stage (EPD or APD) and the subcomponent (Part I, II, or III) evaluated.
- The PDQ-8 was validated for internal consistency, reliability, and construct validity. An MCID ranging from 5.8 to 7.4 points was proposed in the literature. This represents "worsening a little bit," and may not be identical for change in the opposite direction i.e., improvement.
- The PDHD was only validated and found reliable within itself, and was not validated through a comparison with other validated external tools; therefore, its external validity and reliability remain uncertain. A difference of 1.3 to 1.9 hours in *off* time was considered an MCID.

- The PDSS-2 has been demonstrated as valid and reliable in assessing nocturnal sleep disturbances in patients with Parkinson's disease. Convergent validity has been demonstrated with other sleep disturbance scales. No MCIDs were identified in the literature. However, a 15-point threshold for PDSS-2 has been suggested to distinguish patients with sleep disturbance from those without.
- The Hoehn and Yahr staging system has been superseded by the UPDRS. It should not be used as an outcome measure due to a lack of clinimetric testing, and because the broad categories of the original scale do not allow the detection of effective interventions.

APPENDIX 6: SUMMARY OF SUPPORTIVE STUDIES

1. Aim

To summarize the safety and efficacy results of:

- open-label, single-group extension studies corresponding to the included randomized controlled studies (RCTs) in this review: Study 243-08-002;[17] Study 243-06-001;[48] and SP915[19]
- Giladi 2014,[21] a new publication reporting on the pooled results of two open-label extension studies, SP702[122] and SP716,[123] that were previously summarized in the original CADTH Common Drug Review (CDR) review.

2. Long-Term Extension Studies

Extension Studies on Early Parkinson's Disease — Giladi 2014

SP702[122] and SP716[124] assessed the longer-term safety and efficacy of rotigotine in patients who were classified as having early Parkinson's disease (EPD) at the baseline of two previously completed double-blind (DB) RCTs, SP512 and SP513, respectively. These extension studies were summarized as supplementary information, but not included in the prior CDR systematic review because they were uncontrolled, single-group, open-label extension studies. One additional publication based on SP702 and SP716, which pooled results from the two studies and reported on dyskinesia, is summarized here.[21] This post hoc analysis utilizes Unified Parkinson's Disease Rating Scale (UPDRS) Part IV, items 32 (dyskinesia duration) and 33 (dyskinesia disability or severity), and reports that 19% of patients developed dyskinesia.

2.1 Study Characteristics

At the time of enrolment in the DB RCT,[45,125] [redacted][125] [redacted],[45] [redacted],[45] [redacted]

Of the 632 patients who completed the DB RCTs, 598 (95%) elected to enrol in the open-label extension studies. Eligibility included completion of the previous RCT, an absence of ongoing serious adverse events (SAEs) considered related to study medication, and an absence of features that might increase susceptibility to adverse events (AEs), such as QT prolongation, orthostatic hypotension, and hepatic, renal, or cardiac dysfunction. A Mini Mental Status Examination score of ≥ 25 was required.

In the open-label extensions, optimal rotigotine dosing for each patient was achieved by increasing the starting dose of 2 mg/24 h by weekly 2 mg/24 h increments to a maximum of 6 mg/24 h[122] or 8 mg/24 h.[123] Back-titration was permitted during titration. After titration, patients entered a maintenance phase. After the first year of the maintenance phase, rotigotine could be increased up to a maximum of 16 mg/24 h. In addition, dose adjustments of rotigotine could be made at any time during the maintenance phase at the discretion of the investigator. Investigators were encouraged to increase the dose of rotigotine to the maximum allowed prior to initiating or increasing other anti-Parkinson medications. After the first month of maintenance, other anti-Parkinson medications were allowed in combination. These included levodopa (combined with benserazide or carbidopa), monoamine oxidase B (MAO-B) inhibitors, entacapone, anticholinergic drugs, nonselective N-methyl-D-aspartate (NMDA)

antagonists, specific atypical neuroleptics, and modafinil. Visits occurred weekly during the titration phase and for the first month of the maintenance phase, then at three-month intervals thereafter. The majority of participants were Caucasian (96%), male (63%), and between the age of 50 to < 75 years of age at time of enrolment in the DB RCT (Table 41). The mean duration of PD since diagnosis was 1.3 years.

TABLE 41: BASELINE CHARACTERISTICS FOR POOLED STUDIES SP702 AND SP716, SAFETY SET

Characteristic	Pooled SP702/SP716 N = 596
Sex	M: 377 (63%); F: 219 (37%)
Age, mean (SD) (range)	62.2 (10.1) (31 to 87)
< 50 years	65 (11%)
50 to < 65 years	269 (45%)
66 to < 75	205 (34%)
≥ 75	57 (10%)
Duration of PD since diagnosis, mean (SD), years	1.3 (1.3)
Duration of PD median (range), years	0.9 (0 to 7)
UPDRS Part II sum score	8.6 (4.2)
UPDRS Part III sum score	22.4 (8.3)
UPDRS Part II + III subtotal score	31.1 (12.1)
Prior or concomitant anti-Parkinson medication, n (%)	300 (50%)

F = female; M = male; PD = Parkinson's disease; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Giladi 2014.[21]

Of the total number of participants (N = 596, safety set) in the pooled trials, 51% withdrew prior to study end. Twenty-four per cent withdrew prematurely from open-label treatment because of AEs, and 6% because of lack of efficacy (Table 42).

TABLE 42: PATIENT DISPOSITION AND DISCONTINUATIONS IN STUDIES SP702 AND SP716

Patient Disposition	SP702			SP716			
	Total	Rotigotine	Placebo	Total	Rotigotine	Ropinirole	Placebo
Randomized to DB RCT, n							
Completed DB RCT, n (%)							
Did not enrol in OL extension, n (% of RCT completers)							
Enrolled in OL extension, n (% of RCT completers)							
Safety population set, n (% of those enrolled in OL Extension)							
Premature withdrawal from study, n (%)							
Total premature withdrawals							
Major protocol violation							
Lack of efficacy							
AE							
Unsatisfactory adherence							

Patient Disposition	SP702	SP716
Withdrew consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
N at study closure[a]	[redacted]	[redacted]

AE = adverse event; CDR = CADTH Common Drug Review; DB = double-blind; NA = not applicable; OL= open-label; RCT = randomized controlled trial.

[a] [redacted]

Source: Prior CDR review; Clinical Study Report, SP513,[45] Clinical Study Report, SP512OL.[125]

2.1.1 Results

a) Rotigotine Exposure

The median patient exposure to rotigotine was 1,910 days in SP702 and 1,564 days in SP716, with wide ranges in each study (Table 43). At the end of the treatment, mean rotigotine doses were 7.2 mg/24 h in SP702 and 8.2 mg/24 h in SP716. Rotigotine treatment was supplemented with levodopa in 71% of patients overall (SP702: 74%; SP716: 69%). The median time to levodopa initiation was 374 days (approximately one year) in SP702 and 485 days (approximately one year and four months) in SP716, with similar mean levodopa doses (373.5 mg/day in SP702 and 342.9 mg/day in SP716).

TABLE 43: ROTIGOTINE EXPOSURE AND CONCOMITANT ANTI-PARKINSON MEDICATION, STUDIES SP702 AND SP716, SAFETY SET

Rotigotine Exposure		
	SP702	SP716
End of study rotigotine dose mean (SD) median	[redacted]	[redacted]
Median exposure duration Range	[redacted]	[redacted]
Concomitant Anti-Parkinson Medication		
Concomitant levodopa		
Patients initiating treatment, n (%)	[redacted]	[redacted]
Median time to initiation, days (range)	[redacted]	[redacted]
Dose over entire study, mean (SD, mg/day)	[redacted]	[redacted]
Other medications for PD, n (%)		
Anticholinergic drugs	[redacted]	[redacted]
Amantadine[a]	[redacted]	[redacted]
MAO-B inhibitors	[redacted]	[redacted]
Other DAs prior to last week of OL study[b]	[redacted]	[redacted]

CDR = CADTH Common Drug Review; DA = dopamine receptor agonists; MAO-B = monoamine oxidase B; NR = not reported; OL = open-label; PD = Parkinson's disease; SD = standard deviation.

[a] [redacted]

[b] [redacted]

Source: Prior CDR review; Clinical Study Report, SP513;[45] Clinical Study Report, SP512OL.[125]

2.2 Dyskinesia

In the pooled open-label extensions, dyskinesia was reported in 115 (19%) of participants. In the subset with dyskinesia, a similar proportion of patients had previously received DB placebo (22%) or rotigotine (21%), and a slightly smaller proportion had received DB ropinirole (14%). Slightly more women than men reported dyskinesia (25% versus 16%), which is perhaps attributable to differences in body weight and greater exposure to drug; median onset was sooner in women (816.5 days versus 1,372 days in men). Dyskinesia was more frequent in younger patients (35% of those < age 50 and 9% of those age 75 or older) (Table 44).

The majority of patients with dyskinesia were on levodopa, consistent with its postulated causes. However, 25 patients developed dyskinesia in the absence of levodopa. This corresponds to 15% of the 173 participants who were not on levodopa during the studies. Two of the 25 patients had previously received levodopa for less than six months prior to enrolment in the DB RCT, whereas the other 23 were levodopa-naive. The time of onset of dyskinesia among the subset not on levodopa was ~2.5 years earlier than in patients with levodopa exposure, which suggests that a subgroup of patients might be particularly sensitive to the development of dyskinesia in a relatively short period of time (Table 45).

This study is limited in that it is a post hoc analysis of a study that was not prospectively designed to assess dyskinesia, and is an uncontrolled, single-group study. It relied on historical information provided by participants to assess dyskinesia, with the opportunity to modify responses following investigator examination. Clinical assessors, as well as patients, were unblinded; therefore, the outcome was subjective. The study provides no information on the comparative risk of dyskinesia associated with rotigotine versus other dopamine agonists (DAs) when they are used as monotherapy or in combination with levodopa. In other studies of four or five years' duration, a small proportion of patients receiving pramipexole or ropinirole have been reported to develop dyskinesia without levodopa, based on the relevant UPDRS Part IV items.[22,126] However, without comparative data, it is not known which, if any, non-ergolinic DA might provide an advantage in terms of less dyskinesia. The data from this study suggest there may be a small subgroup of patients susceptible to developing dyskinesia at a relatively early time point in the course of the disease while being treated with rotigotine in the absence of levodopa.

TABLE 44: INCIDENCE OF DYSKINESIA IN POOLED STUDIES SP702 AND SP716, SAFETY SET

SP702/SP716							
Characteristic	Total N = 596	Male N = 377	Female N = 219	Age (years)			
				< 50 N = 65	50 to < 65 N = 269	65 to < 75 N = 205	≥ 75 N = 57
Received levodopa, n (%)	423 (71%)	271 (72%)	152 (69%)	41 (63%)	190 (71%)	154 (75%)	38 (67%)
Patients with dyskinesia, n (%)	115 (19%)	61 (16%)	54 (25%)	23 (35%)	58 (22%)	29 (14%)	5 (9%)
Dyskinesia in absence of levodopa, n (%)[a]	25 (4%)	12 (3%)	13 (6%)	6 (9%)	12 (4%)	6 (3%)	1 (2%)
Dyskinesia after starting levodopa, n (%)	90 (78%)	49 (80%)	41 (76%)	17 (74%)	46 (79%)	23 (79%)	4 (80%)

DB = double-blind; RCT = randomized controlled trial.
[a] Includes 2 patients who had previously had < 6 months levodopa prior to enrolment in the DB RCT.
Source: Giladi 2014.[21]

TABLE 45: MEDIAN TIME TO ONSET OF DYSKINESIA IN POOLED STUDIES SP702 AND SP716, SAFETY SET

SP706/SP712			
Median Onset	**Total**	**On Levodopa**	**No Levodopa**
	N = 115	**N = 90**	**N = 25**
Median time to onset of first dyskinesia after initiating levodopa, days	NA	828 days (~2 years, 3 months) Range: 70 to 1,721 days	NA
Median time to onset after initiating rotigotine[a], days	1,204 days (~3 years, 3 months) Range: 0 to 2,284 days	1,286.5 days (~3 years, 6 months) Range: 196 to 2,284 days	288 days (~ 9 months) Range: 0 to 1,927 days

NA = not applicable; RCT = randomized controlled trial.
[a] Initiation in either the RCT or extension phase.
Source: Giladi 2014.[21]

2.3 Extension Studies on Advanced Parkinson's Disease

Two unpublished, open-label extension studies were identified, one for Mizuno 2014, Study 243-08-002[17] (NCT01631825), and the other for Nomoto 2014, Study 243-06-001[18,48] (NCT01631812). Results are summarized from the Clinical Study Report for Study 243-08-002, clinicaltrials.gov website, and translated excerpts of the Clinical Study Report for Study 243-06-001, provided by the manufacturer or the CDR clinical review team as noted.

2.4 Study Characteristics

Study 243-08-002 was a one-year, open-label, single-group extension study of Mizuno 2014, with enrolment of 91% of the completers of the DB RCT. The proportion of the participants who had previously received rotigotine, ropinirole, or placebo in the trial is not reported. However, the majority must have previously received a non-ergolinic DA, based on the unbalanced randomization in Mizuno 2014 and the numbers of trial completers. Patients from the following categories were excluded: those who had an SAE during the DB RCT or at baseline; those who had persistent confusion, hallucination, delusion, or excitation during the previous RCT; those with abnormal behaviours, such as obsessive-compulsive disorder or delusion, during the RCT; and those with orthostatic hypotension, prolonged QT interval, or laboratory abnormalities.

Following the tapering phase of the RCT, upon initiation of the open-label extension study, a titration and maintenance phase of 12 weeks was initiated during which rotigotine was increased up to 16 mg/24 h in weekly 2 mg increments. One level of back-titration was allowed. Participants attended weekly visits until a maintenance dose was set, after which visits occurred every two weeks. This was followed by a 40-week maintenance phase during which the dose of rotigotine and other anti-Parkinson medications could be adjusted. Visits were every four weeks during the maintenance treatment period. A tapering period of a maximum of two weeks followed the maintenance period, for a total duration of 54 weeks. Study 243-06-001 had a similar design and duration, with 70% of completers of the corresponding DB RCT enrolling in the open-label extension phase.

Both extension phase populations included more females (57% to 58%) than males. Table 46 outlines the baseline characteristics, and Table 47 shows patient disposition and discontinuations during the extension studies.

TABLE 46: BASELINE CHARACTERISTICS IN OPEN-LABEL EXTENSIONS 243-08-002 AND 243-06-001

Characteristic	Study 243-08-002 N = [redacted]	Study 243-06-001 N = [redacted]
Age, mean (SD) (years)	[redacted]	66.9 (7.5)
< age 65	[redacted]	34
≥ age 65	[redacted]	96
Sex	[redacted]	M: 56 (43.1%); F: 74 (56.9%)
Disease duration (years)[a]	[redacted]	NR
Off time, hours (SD)	[redacted]	NR
UPDRS Part III, points (SD)	[redacted]	NR

F = female; M = male; NR = not reported; OL = open-label; RCT = randomized controlled trial; SD = standard deviation.
[a] At baseline of double-blind RCT.
Note: Unless specified, the baseline measurement or characteristic was evaluated at the baseline of the OL extension study.
Source: Clinical Study Report, 243-08-002;[17] clinicaltrials.gov.[48]

TABLE 47: PATIENT DISPOSITION IN OPEN-LABEL EXTENSIONS 243-08-002 AND 243-06-001

Disposition	Study 243-08-002 N = 321	Study 243-06-001 N = 130
Completed DB RCT, n (%)	[redacted]	188
Proportion enrolling in OL extension, n (% of RCT completers)	[redacted]	130 (69.2%)
Completed OL extension, n (%)	[redacted]	93 (71.5%)
Premature discontinuations, n (%)	[redacted]	37 (28.5%)
Adverse event, n (%)	[redacted]	25 (19.2%)
Lack of efficacy, n (%)	[redacted]	5 (3.9%)
Withdrawal by patient, n (%)	[redacted]	4 (3.1%)
Discontinuation criteria, n (%)	[redacted]	0
Physician decision, n (%)	[redacted]	3 (2.3%)

DB = double-blind; OL = open-label; RCT = randomized controlled trial.
Source: Clinical Study Report, 243-08-002[142]; clinicaltrials.gov.[48]

2.5 Results

2.5.1 Safety

a) Rotigotine exposure

For Study 243-08-002,[17] [redacted] (Table 48). Seven per cent of patients moving into the maintenance treatment period had been unable to up-titrate the dose to the maximum because of AEs, and 15% had undergone back-titration due to AEs (Table 49). Fifteen per cent of patients required adjustment of the rotigotine dose during the maintenance treatment period. Compliance was < 100% in 25% of participants and < 90% in 1% of patients. Mean duration of exposure was 334 days (range: three to 399 days). Exposure in Study 243-06-001[48] was on average 308 days (range: 14 to 392 days); the dosing regimen was similar.

[redacted] (Table 50).

[redacted] (Table 50).[17]

TABLE 48: DRUG EXPOSURE IN OPEN-LABEL EXTENSIONS 243-08-002 AND 243-06-001

243-08-002 N = 321			243-06-001 N = 130	
Rotigotine Most Common Dose	n (%)	Titration/ Maintenance and Maintenance Treatment Periods[a] Days (SD)	n (%)	Maintenance Period Days (SD)
2.0 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
4.0 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
6 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
8 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
10 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
12 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
14 mg/24 h	[redacted]	[redacted]	[redacted]	[redacted]
16 mg /24 h	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.

[a] [redacted]

Source: Clinical Study Report, 243-08-002;[17] Clinical Study Report, 243-06-001.[48]

TABLE 49: REASONS FOR MOVING INTO MAINTENANCE PERIOD FOR OPEN-LABEL EXTENSIONS 243-08-002 AND 243-06-001

Study 243-08-002 N = 321		Study 243-06-001 N = 130
Total moving into maintenance period	[redacted]	[redacted]
Reason for moving into maintenance period		
Achieved maximum dose	[redacted][a]	[redacted]
No further improvement expected from titration	[redacted]	[redacted]
Patients not wishing to titrate the dose	[redacted]	[redacted]
Unable to titrate the dose due to AEs	[redacted]	[redacted]
Parkinson's symptoms disappeared	[redacted]	[redacted]
Resolution or abatement of AEs after decreasing dose	[redacted]	[redacted]
Others (not specified)	[redacted]	[redacted]
Dose adjustment in maintenance period		
Patients requiring adjustment	[redacted]	[redacted]

AE = adverse event; NA = not available.

[a] Percentage of the total number of participants who entered into the maintenance phase.

Source: Clinical Study Report, 243-08-002;[17] Clinical Study Report, 243-06-001 (relevant table translated by CDR clinical review team).[127]

TABLE 50: CONCOMITANT ANTI-PARKINSON MEDICATION IN OPEN-LABEL EXTENSIONS 243-08-002 AND 243-06-001

Study 243-08-002 N = 321		Study 243-06-001 N = 130
Drug	**Days (SD)**	
Levodopa mean (SD), baseline to day 168	[redacted]	[redacted]
Levodopa mean (SD), day 169 onward	[redacted]	[redacted]
Anticholinergics	[redacted]	[redacted]
Amantadine	[redacted]	[redacted]
Selegiline	[redacted]	[redacted]
Droxidopa	[redacted]	[redacted]
Entacapone	[redacted]	[redacted]
Zonisamide[a]	[redacted]	[redacted]
Concomitant medications other than the above	[redacted]	[redacted]

SD = standard deviation.
[a] Zonisamide is not available in Canada.
Source: Clinical Study Report, 243-08-002;[17] manufacturer's response to request for additional information, Aug. 4, 2015.[50]

b) Adverse events

In Study 243-08-002, the most frequent AE was [redacted]. AEs that occurred in at least 5% of patients included [redacted] (Table 51). Other common AEs, [redacted]. Study 243-06-001 had a similar AE profile, with application site reactions (52%), nausea (13%), dyskinesia (16%), visual hallucination (15%), somnolence (15%), and feeling abnormal (21%) occurring in > 10% of patients.

In both studies, there was one death due to sudden death. Sudden death can be due to ventricular arrhythmias, which can arise from QT prolongation. As noted in the product monograph, a study evaluating treatment-related QT effects, with doses up to 24 mg/24 h, did not detect QT prolongation associated with rotigotine.[1] [redacted].[17] No autopsy information is available for either death. No patient was reported to have valvulopathy. In Study 243-08-002, a subset of patients (75%) underwent echocardiography at baseline, week 12, and week 52 (week 40 of the maintenance treatment period). Regurgitation at any valve in any assessment was noted in 139 patients. Clinically significant deterioration was observed in one patient, with aortic regurgitation and no obvious morphological abnormality. Another three patients developed regurgitation during the study, two at the tricuspid valve and one at the mitral valve, all judged not to be due to treatment. Other AEs of special interest were identified as sudden onset of sleep (2.2%) and impulse control or obsessive-compulsive disorder (1.2%). In Study 243-06-001, there was one case of impulse control disorder, and one patient experienced sudden onset of sleep (0.8% incidence each).

In Study 243-08-002, the most common withdrawals due to adverse events (WDAEs) were application site reactions or similar terms such as application site erythema, discolouration, edema, or pruritus (6%), hallucination/delirium (1.9%), dyskinesia (0.9%), depressed level of consciousness (0.6%), and pleurothotonus or dystonia (0.6%). Other reasons for discontinuation for which there were single cases

only (0.3% incidence) included impulse control disorder, orthostatic hypotension, decreased appetite, and abnormal posture. The most common cause of WDAEs in Study 243-06-001 was application site reactions (7% of participants).

TABLE 51: TREATMENT-EMERGENT ADVERSE EVENTS IN OPEN-LABEL EXTENSIONS 243-008-002 AND 243-06-001, SAFETY SET

Adverse Event	Study 243-08-002 N = 321	Study 243-06-001 N = 130
AEs		
n (%)	[redacted]	126
Common AEs		
Total application site reactions	[redacted][a]	[redacted]
Eczema	[redacted]	4 (3.1%)
Rash	[redacted]	4 (3.1%)
Excoriation	[redacted]	4 (3.1%)
Nausea	[redacted]	17 (13.0%)
Vomiting	[redacted]	11 (8.5%)
Dental caries	[redacted]	NR
Stomatitis	[redacted]	NR
Constipation	[redacted]	13 (10.0%)
Diarrhea	[redacted]	6 (4.6%)
Nasopharyngitis	[redacted]	27 (20.8%)
Upper respiratory tract inflammation	[redacted]	NR
Cystitis	[redacted]	4 (3.1%)
Contusion	[redacted]	15 (11.5%)
CPK increase	[redacted]	8 (6.2%)
Peripheral edema	[redacted]	8 (6.2%)
Back pain	[redacted]	13 (10.0%)
Arthralgia	[redacted]	4 (3.1%)
Dyskinesia	[redacted]	21 (16.2%)
Dystonia	[redacted]	5 (3.9%)
Abnormal posture	[redacted]	NR
Dizziness	[redacted]	10 (7.7%)
Dizziness postural	[redacted]	4 (3.1%)
Orthostatic hypotension	[redacted]	7 (5.4%)
Headache	[redacted]	7 (5.4%)
Hallucinations (any type)/delusion	[redacted]	27 (20.8%) (does not include delusion)
Hallucination, visual	[redacted]	20 (15.4%)
Hallucination	[redacted]	5 (3.9%)
Feeling abnormal	[redacted]	27 (20.8%)
Somnolence	[redacted]	19 (14.6%)
Disturbances in initiating and maintaining sleep	[redacted]	8 (6.2%)
Weight decrease reported as AE	[redacted]	NR

Adverse Event	Study 243-08-002 N = 321	Study 243-06-001 N = 130
Decreased appetite	[redacted]	4 (3.1%)
Asthenic conditions	[redacted]	NR
SBP < 100 mm Hg	[redacted]	NR
Severe laboratory abnormality, NOS	--	10 (7.7%)
Deaths		
n (%)	[redacted]	1 (0.8%)
SAEs		
Total n (%)	[redacted][b]	17 (13.1%)[b]
Hallucination/delusion	[redacted]	4 (3.1%)
Femoral neck fracture	[redacted]	2 (1.5%)
Gastric ulcer bleeding	[redacted]	0
Pneumonia	[redacted]	2 (1.5%)
Depressed level of consciousness	[redacted]	0
Subdural hematoma	[redacted]	0
WDAEs		
n (%)	[redacted]	[redacted]
Application site reactions[c] (discolouration, erythema, edema, pruritus)	[redacted]	[redacted]
Hallucination, hallucination visual, hallucination auditory	[redacted]	[redacted]
Dyskinesia	[redacted]	[redacted]
Depressed level of consciousness	[redacted]	[redacted]
Pleurothotonus (dystonia)	[redacted]	[redacted]
Notable Harms n (%)		
Sudden onset of sleep	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Impulse control/obsessive-compulsive disorders	[redacted]	[redacted]
Valvulopathy[d]	[redacted]	[redacted]
Arrhythmias	[redacted]	[redacted]

AE = adverse event; CPK = creatinine phosphokinase; NOS = not otherwise specified; NR = not reported; QTcB = QT corrected for heart rate using Bazett's formula; QTcF = QT corrected for heart rate using Fridericia's formula; SAE = serious adverse event; SBP = systolic blood pressure; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] MedDRA high-level term includes application site reaction, pruritus, erythema, discolouration, vesicles, oedema, rash, and erosion.

[b] Includes one death.

[c] Unclear if this is a high-level MedDRA term for application site reactions that includes all the terms listed under (a).

[d] Patients underwent echocardiography; of 139 patients who showed post-dose regurgitation, 3 showed deterioration but were evaluated as having no organic changes.

[e] Atrial fibrillation.

Source: Clinical Study Report, 243-08-002;[17] study 243-06-001 clinicaltrials.gov;[48] manufacturer's response to request for additional information, Aug. 4, 2015.[50]

TABLE 52: DESCRIPTION OF FATAL AND NON-FATAL SERIOUS ADVERSE EVENTS IN STUDY 243-08-002, SAFETY SET

Study 243-08-002 N = 321		
Adverse Event	**Sex, Age**	**Dose/24 h at Initiation of SAE**
Deaths		
Sudden death	[redacted]	[redacted]
SAEs		
Inguinal hernia	[redacted]	[redacted]
Spinal compression fracture	[redacted]	[redacted]
Carpal tunnel syndrome	[redacted]	[redacted]
Hemorrhoids, colonic polyps, large-intestine carcinoma	[redacted]	[redacted]
Hip fracture	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pneumonia and urinary tract infection	[redacted]	[redacted]
Subdural hematoma	[redacted]	[redacted]
Subdural hematoma (chronic)	[redacted]	[redacted]
Delirium	[redacted]	[redacted]
Hallucination visual, herpes zoster	[redacted]	[redacted]
Hyponatremia	[redacted]	[redacted]
Depressed level of consciousness (difficulty waking)	[redacted]	[redacted]
Depressed level of consciousness	[redacted]	[redacted]
PD worsening	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Heat illness	[redacted]	[redacted]
Dehydration, rhabdomyolysis following wearing-off phenomenon and inability to move	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]
Upper limb fracture	[redacted]	[redacted]
Radius fracture, ulna fracture	[redacted]	[redacted]
Jaw fracture	[redacted]	[redacted]
Intervertebral disc protrusion, osteomyelitis	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]
Gastric ulcer hemorrhage	[redacted]	[redacted]
Gastric ulcer hemorrhage	[redacted]	[redacted]
Gastric ulcer hemorrhage	[redacted]	[redacted]
Gastric cancer	[redacted]	[redacted]
B-cell lymphoma	[redacted]	[redacted]
Breast cancer	[redacted]	[redacted]

PD = Parkinson's disease; SAE = serious adverse event.
Source: Clinical Study Report, 243-08-002.[17]

TABLE 53: DESCRIPTION OF WITHDRAWALS DUE TO ADVERSE EVENTS — STUDY 243-08-002

Study 243-08-002 N = 321	
WDAE total	[redacted][a]
Application site reactions[b] (discolouration, erythema, edema, pruritus)	[redacted]
Hallucination, hallucination visual, hallucination auditory	[redacted]
Dyskinesia	[redacted]
Depressed level of consciousness	[redacted]
Pleurothotonus (dystonia)	[redacted]
Peripheral edema	[redacted]
Sepsis	[redacted]
Subdural hematoma	[redacted]
Decreased appetite	[redacted]
Back pain	[redacted]
Cervical spinal stenosis	[redacted]
Spinal compression fracture	[redacted]
Osteoarthritis	[redacted]
Intervertebral disc protrusion	[redacted]
Breast cancer	[redacted]
Gastric cancer	[redacted]
B-cell lymphoma	[redacted]
Posture abnormal	[redacted]
Impulse control disorder	[redacted]
Orthostatic hypotension	[redacted]
Atrial fibrillation	[redacted]

[a] [redacted]

[b] Application site reactions include discolouration, erythema, edema, and pruritus.

Source: Clinical Study Report, 243-08-002.[17]

TABLE 54: DESCRIPTION OF WITHDRAWALS DUE TO ADVERSE EVENTS — STUDY 243-06-001

Study 243-06-001 N = 321
[redacted]

CDR = CADTH Common Drug Review.
[a] Re-translation by CDR clinical review team.
Source: Manufacturer's response to request for additional information, Aug. 4, 2015;[50] Clinical Study Report, 243-06-001.[48]

TABLE 55: ELECTROCARDIOGRAPHIC EVIDENCE OF QT PROLONGATION IN ADVANCED PARKINSON'S DISEASE OPEN-LABEL EXTENSION STUDIES

QT prolongation		
Parameter	**Study 243-08-002 N = 321**	**Study 243-06-001 N = 130**
QTc ≥ 500 ms	[redacted]	QTcB: 1 (0.8%)
QTc M: > 450 msec or F: > 470 msec plus change in QTc > 30 msec	[redacted]	
QTc ≥ 60 msec	[redacted]	NR
QTc ≥ 30 msec	[redacted]	NR

F = female; M = male; msec = millliseconds; NR = not reported; QTcB = QT corrected for heart rate using Bazett's formula; QTcF = QT corrected for heart rate using Fridericia's formula.
Source: Clinical Study Report, 243-08-002;[17] Study 243-06-001 clinical trials.gov.[48]

TABLE 56: ELECTROCARDIOGRAPHIC ABNORMALITIES IN STUDY 243-08-002

ECG abnormalities in Study 243-08-002		
Parameter	**n (%)**	**Description of abnormality**
Normal ECG at baseline and abnormal ECG during treatment	[redacted]	[redacted]
Abnormal insignificant ECG at baseline and significant changes during treatment	[redacted]	[redacted]

ECG = electrocardiogram [redacted]

Source: Clinical Study Report, 243-08-002.[17]

Efficacy

[redacted] (Table 57).

TABLE 57: EFFICACY OUTCOMES AT WEEK 52, FULL ANALYSIS SET

Parameter	243-08-002 N = 321			243-05-002 N = 130
Time point	Open-Label Extension Phase			
	Week 12 titration/ maintenance period	Week 12 maintenance treatment (= week 24)	Week 40 maintenance treatment (= week 52)	Week 40 maintenance treatment (= week 52)
Time spent off (hours) change from baseline (SD) (95% CI), n	[redacted]	[redacted]	[redacted]	–1.9 (3.0) (NR) n = 84
Responder rates ≥ 30% reduction in *off* time n/N (%)	[redacted]	[redacted]	[redacted]	NR
UPDRS Part III (on) sum score[a] change from baseline mean (SD) (95% CI)	[redacted]	[redacted]	[redacted]	–8.3 (9.8) (NR) n = 129
UPDRS Part II (mean of on and off)[a] sum score change from	[redacted]	[redacted]	[redacted]	–1.9 (4.7) (NR)

Parameter	243-08-002 N = 321			243-05-002 N = 130
Time point	Open-Label Extension Phase			
	Week 12 titration/ maintenance period	Week 12 maintenance treatment (= week 24)	Week 40 maintenance treatment (= week 52)	Week 40 maintenance treatment (= week 52)
baseline mean (SD) (95% CI)	[redacted]	[redacted]	[redacted]	n = 129
UPDRS Part I	[redacted]	[redacted]	[redacted]	NR
UPDRS Part IV	[redacted]	[redacted]	[redacted]	NR

CI = confidence interval; NR = not reported; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] Study 243-08-002: Full analysis set with last observation carried forward analysis for UPDRS scores; not specified for time spent *off*.
Note: For Study 243-08-002, week 12 titration and maintenance period is the end point of the initial period of the open-label (OL) extension phase. In this phase, once a maintenance dose was achieved, it was not to be changed. This was followed by a 40-week OL "maintenance treatment" period during which medications could be modified, as indicated in the text. Week 12 of the maintenance treatment period = week 24 of the OL extension study; week 40 of the maintenance treatment period = week 52 of the OL extension. For Study 243-05-002, week 40 of the maintenance period = week 52 of the OL extension study, because it followed a 12-week titration period.
Source: Clinical Study Report, 243-08-002; clinicaltrials.gov.

2.6 Extension Studies on Mixed Populations (Advanced and Early Parkinson's Disease)

2.6.1 SP915

SP915 is a one-year extension of the DB RCT SP889, and assessed the longer-term safety and efficacy of rotigotine in patients with APD.[10,19] This study was not included in the systematic review because it was a single-group, open-label extension phase.

a) Study characteristics

At the end of the DB RCT, all patients underwent de-escalation in 2 mg/24 h increments over a period of up to 14 days. Within two days of the end of the de-escalation period, the dose-titration of the open-label extension was started. The titration period lasted up to eight weeks, during which the dose of open-label rotigotine was increased in weekly 2 mg increments to a maximum of 16 mg/24 h. The optimal or maximal dose was maintained for up to 10 months. However, dose adjustments could be made. Clinic visits were weekly during dose-titration, at the start of maintenance, four weeks later, and then at 13-week intervals. A 14-day dose escalation followed, with a safety follow-up 28 days later. Entry criteria included completion of the prior DB RCT, absence of any ongoing SAEs deemed related to study medication, and investigator opinion that the patient would benefit from long-term treatment and be compliant. Participants were thus highly selected. Permitted medications were levodopa (in combination with benserazide or carbidopa), MAO-B inhibitors, anticholinergic drugs, NMDA antagonists, entacapone, certain atypical neuroleptics, and modafinil. Antiemetics without central anti-dopaminergic activity were permitted to treat nausea and vomiting.

Enrolment in this study was compromised because of a change in the manufacturing process for rotigotine patches. To prevent the need to switch to the new manufacturing process, the trial was stopped. Eighty-four of the 246 patients who completed SP889 were enrolled, and 66 (79%) completed one year.

Sixty-eight per cent of patients were male, predominantly Caucasian (86%), and the average age was 66 years, with 25% of patients 75 years or older. The average time since diagnosis was 4.9 years. The population was mixed, and comprised a range of severity of PD (Hoehn and Yahr stage 1 to 4). However, the majority of patients had APD; only 12% had EPD. Of the 84 participants in the open-label extension, 66 had previously received rotigotine and 23 had received placebo.

TABLE 58: BASELINE (DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL) CHARACTERISTICS FOR STUDY SP915, SAFETY SET

SP915 Baseline Characteristics N = 84	
Characteristic	**n (%) or Mean (SD)**
Stage of PD (levodopa use)	Early PD: 10 (11.9%) Advanced PD: 74 (88.1%)
UPDRS Part III sum score, mean (SD) Median (range)[a]	28.1 (13.7) 27.0 (range 5 to 68)
PDSS-2 sum score, mean (SD) Median (range)	19.7 (9.7) 19.5 (4 to 45)

PD = Parkinson's disease; PDSS = Parkinson's Disease Sleep Scale; SD = standard deviation.
[a] Measured at first titration visit of open-label extension study, whereas the other characteristics were measured at baseline of the double-blind RCT SP889.
Source: Trenkwalder 2012.[128]

TABLE 59: PATIENT DISPOSITION IN STUDY SP915

SP915 Patient Disposition	
Parameter	**n (%)**
Enrolled in open-label extension	[redacted]
Patients completing the study	[redacted]
Premature discontinuations, n (%)	[redacted]
AE	[redacted]
Lack of efficacy	[redacted]
Withdrew consent	[redacted]
Lost to follow-up	[redacted]

AE = adverse event.
Source: Clinical Study Report, SP915.[19]

2.6.2 Results

a) Rotigotine exposure

Patients received doses ranging from 2 mg/24 h to 16 mg/24 h for a mean duration of 321 days (range: 42 to 397 days). The mean dose over the maintenance phase was 11.5 mg/24 h ± 3.8 mg/24 h (range: 2 mg/24 h to 16 mg/24 h). Overall, 71% of patients took at least one concomitant anti-Parkinson drug. The proportion of compliant patients was 77% (with adherence defined as taking 85% to 115% of the medication).

TABLE 60: ROTIGOTINE EXPOSURE AND CONCOMITANT ANTI-PARKINSON MEDICATION DURING OPEN-LABEL EXTENSION, STUDY SP915 (SAFETY SET)

SP915 Drug Exposure in OL Extension N = 84	
Rotigotine	
Rotigotine dose entering maintenance phase, median	12 mg/24 h
Rotigotine dose over maintenance phase, mean (SD) Range	11.5 (3.8) Range 2 mg/24 h to 16 mg/24 h
Levodopa	
On levodopa at baseline of OL extension, n (%)	[redacted]
Initiating levodopa during OL extension, n (%)	[redacted]
Not on levodopa during OL extension, n (%)	[redacted]
Levodopa at start of OL extension (titration week 1), mean (SD)	[redacted]
Levodopa at EOM, mean (SD)	[redacted]
Other concomitant medications for PD[a]	
Anticholinergics	[redacted]
L-dopa and dopa derivatives	[redacted]
MAO-B inhibitors	[redacted]
Adamantane derivatives	[redacted]
Dopamine agonists	[redacted]
Other dopaminergic drugs	[redacted]
Unknown	[redacted]
Prior treatment in double-blind RCT	[redacted]

EOM = end of maintenance; NR = not reported; OL = open-label; PD = Parkinson's disease; RCT = randomized controlled trial; SD = standard deviation.
[a] Reported for treatment period defined as titration period, maintenance period, and de-escalation period.
Source: Clinical Study Report, SP915;[19] Trenkwalder 2012.[128]

2.6.3 Safety

Overall, 81% of patients experienced one or more AE. The most common AEs were application site reactions, which occurred in 24% of patients — a somewhat higher incidence than reported in the RCT. Although direct comparisons cannot be made, the investigators suggest this might be due to the longer duration of treatment (SP889 had a four-week maintenance period only) as well as new patients who had been on placebo. However, the number of patients who developed application site reactions who had previously received placebo in the RCT are not reported. Other common AEs (occurring in more than 10% of patients) were somnolence, hallucination, nausea, fall, dizziness, and dyskinesia.

Fourteen per cent of patients withdrew due to an AE (Table 59) and 19% reported at least one SAE (Table 61). One death occurred in a patient with diabetes and cardiovascular disease; this was described as sudden death. The death was deemed unlikely to be related to the study medication. The AE profile was similar to that previously reported for DAs, and generally consistent with transdermal patch use, dopamine receptor stimulation, and PD. Notable harms include valvular regurgitation in two patients (2.4%) (not thought to be attributable to rotigotine), sleep attacks in three (3.6%) patients, orthostatic hypotension and depression each in two patients (2.4%), and obsessive-compulsive disorder and syncope occurring in one patient (1.2%). [redacted]

[redacted][19]

Assessment of laboratory parameters indicated that there were three patients (3.6%) each with increased bilirubin and increased gamma-glutamyl transferase. Other laboratory abnormalities occurred in one or two patients and included one patient with eosinophilia, categorized as an SAE, which resolved with dose reduction. One patient had a QTc interval of ≥ 500 milliseconds plus an increase in QTc of ≥ 60 milliseconds.

TABLE 61: TREATMENT-EMERGENT ADVERSE EVENTS IN STUDY SP915 (SAFETY SET)

SP915 Adverse Events N = 84	
AEs	
Patients with ≥ 1 AE n (%)	68 (81%)
Common AEs Reported in 5% or More of Patients	
Application site reactions	20 (23.8%)
Somnolence	[redacted]
Hallucination	[redacted]
Nausea	10 (11.9%)
Vomiting	[redacted]
Dizziness	9 (10.7%)
Dyskinesia	9 (10.7%)
Fall	[redacted]
PD	[redacted]
Peripheral edema	[redacted]
Disturbances in initiating and maintaining sleep	[redacted]
UTI	[redacted]
Nasopharyngitis	[redacted]
Deaths	
n (%)	[redacted][a]
SAEs	
N (%)	[redacted][c]
femoral neck fracture	[redacted]
application site vesicles	[redacted]
atrial fibrillation	[redacted]
atrioventricular heart block, third degree	[redacted]
eosinophil count increased	[redacted]
chest pain	[redacted]
emphysema, malignant melanoma	[redacted]
bladder cancer	[redacted]
inguinal hernia	[redacted]
osteomyelitis	[redacted]
osteoarthritis	[redacted]
trigger finger	[redacted]

SP915 Adverse Events N = 84	
WDAEs	
n (%)	[redacted]
application site reactions	[redacted]
skin reaction	[redacted]
peripheral edema	[redacted]
confusional state, dementia, pitting edema	[redacted]
dyskinesia, eating disorder, economic problem, obsessive-compulsive disorder	[redacted]
Notable Harms	
sleep attacks	3 (3.6%)
syncope	[redacted]
obsessive-compulsive disorder	[redacted]
valvulopathy	[redacted][b]
arrhythmia	[redacted]
Additional Harms Identified by Investigators as Notable	
parasomnia (abnormal dreams, REM abnormal)	[redacted]
depression	[redacted]
dizziness postural	[redacted]
orthostatic hypotension	[redacted]
ECG	
QT interval increase ≥ 500 ms	[redacted]
QT increase ≥ 60ms	[redacted]
QT interval ≥ 500 ms plus increase ≥ 60 ms	[redacted]

AE = adverse event; ECG = electrocardiography; ms = milliseconds; PD = Parkinson's disease; QTcB = QT corrected for heart rate using Bazett's formula; QTcF = QT corrected for heart rate using Fridericia's formula; REM = rapid eye movement; SAE = serious adverse event; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.
[a] Sudden death in 71-year-old black male with history of diabetes and cardiovascular disease, including bypass.
[b] Mitral valve and aortic valve regurgitation in one patient each was noted in the prior trial SP889.
[c] Value reported from Clinical Study Report, SP915.
Source: Clinical Study Report, SP915;[19] Trenkwalder 2012.[128]

2.6.4 Efficacy

Efficacy end points indicated improvement over up to one year in UPDRS Part III sum score. From baseline (start of the extension phase) to the end of the maintenance period, UPDRS Part III sum score was reduced by 5.8 points, an amount within the range of available MCIDs. The study investigators noted that the observed improvement diminished slightly over the year in UPDRS Part III scores (e.g., time points week 11 and week 52, n = 76 at each time point), but a statistical analysis was not conducted. Conclusions cannot be drawn on these data, although study investigators suggested that the phenomenon may be due to disease progression. Sleep disturbances were assessed by the PDSS-2, which improved by about six points. There is no published MCID for the PDSS-2 scale.

TABLE 62: EFFICACY OUTCOMES FOR SP915, FULL ANALYSIS SET

SP915 Efficacy Outcomes N = 87	
Parameter	**Value**
UPDRS Part III (*On* state) Sum Score (Points)	
OL extension baseline mean (SD)	28.1 (13.7) N = 83
End-of-maintenance mean (SD)	22.0 (13.7) N = 76
Change from baseline mean (SD)	–5.8 (9.4)
30% responders	25 (32.9%)
PDSS-2 Sum Score (Points)	
OL extension baseline mean (SD)	19.9 (9.6)
End-of-maintenance mean (SD)	14.1 (9.4)
Change from baseline	–5.8 (7.8)
Other Outcomes Change from Baseline (Points)	
UPDRS Part II + III	[redacted]
UPDRS Part II	–1.2 (4.6)
NADCS	–1.5 (2.1)
Nocturia	–0.4 (1.2)
PDQ-8	–6.7 (15.0)
BDI-II	–3.3 (6.7)
PDNMS	–13.4 (31.2)
Likert Pain Scale	–0.7 (3.0)

BDI-II = Beck Depression Inventory (second edition); NADCS = Nocturnal Akinesia, Dystonia, and Cramps Score; Parkinson's Disease Non-Motor Symptom Scale; PDQ-8 = Parkinson's Disease Questionnaire; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Clinical Study Report, SP915;[19] Trenkwalder 2012.[128]

2.6.5 Summary

In three open-label extension studies of up to 54 weeks' duration (N = 535 in total), AEs experienced by patients with APD or a mixed population (EPD + APD) were similar to those already reported for non-ergolinic DAs and generally consistent with transdermal patch use, dopamine receptor stimulation, and PD. Among the most common AEs reported were application site reactions, dyskinesia, somnolence, hallucinations or delusion, nausea, fall, dizziness, and (reported in one study) feeling abnormal. The number of patients experiencing SAEs ranged from 6% to 19%, and 13% to 19% withdrew because of AEs. Gastric ulcer hemorrhage occurred as an SAE in three patients (0.9% of the total study population) in the largest study (N = 321 patients with APD), which was conducted in Japan, a region with a higher incidence of peptic ulcer disease than North America. Different dopamine receptors may have opposite effects on gastric and duodenal ulcers (either protective or pro-ulcerogenic), based on a preclinical study (Desai 1999), and the clinical significance of these events in relation to rotigotine is not known. In the three open-label extension phases, the frequency of sudden onset of sleep was 0.8% to 3.6%; syncope, 0% to 1.2% (two studies); impulse control disorder, 0.8% to 1.2%; arrhythmias, 0% to 0.3% (two studies); no valvulopathy events were reported.

There was one sudden death in each open-label extension (incidence 0.3% to 1.2%). Two of the patients were known to have underlying cardiovascular disease, one of whom was diabetic and had undergone aortocoronary bypass. In the latter patient, the death was judged unrelated to treatment. The death in Study 243-08-002 was evaluated as related to rotigotine.[30] There are no further details on the third death, which occurred in Study 243-06-001. There was no autopsy information available for any patient.

The open-label extension studies are primarily designed to evaluate safety and tolerability, and the reported uncontrolled efficacy data cannot be used to draw conclusions about efficacy. For some outcomes, the observed improvement in efficacy diminished slightly over time, but no statistical analyses were conducted.

The only new supplementary information on rotigotine use in patients with EPD was a recently published, post hoc analysis that pooled two open-label extension studies of up to six years' duration (N = 596) and reported an overall pooled incidence of 19% for dyskinesia.[21] Of the patients who were not taking levodopa (N = 173), 15% developed dyskinesia, with a median onset of ~2.5 years earlier than those on levodopa. It is unknown whether these patients have any distinguishing features that would confer susceptibility to dyskinesia. In the absence of levodopa, dyskinesia has also been reported for pramipexole and ropinirole. In a five-year trial comparing ropinirole versus levodopa in EPD, 5% of patients (9 out of 177) taking ropinirole developed dyskinesia before the addition of levodopa was allowed, and in a four-year trial comparing pramipexole with levodopa, 7% of patients (10 out of 151) developed dyskinesia in the absence of levodopa. Seven of the 10 patients in the latter trial had no prior history of levodopa. The open-label extension study summarized in this appendix does not provide comparative data to evaluate whether any particular DA is associated with less dyskinesia.

APPENDIX 7: SUMMARY AND CRITICAL APPRAISAL OF MULTIPLE TREATMENT COMPARISON ANALYSIS

1. Aim

In early Parkinson's disease (EPD) and advanced Parkinson's disease (APD), non-ergolinic dopamine receptor agonists (DAs) have been evaluated in both placebo-controlled and direct head-to-head comparison randomized controlled trials (RCTs). In the previous Neupro submission, the manufacturer submitted an unpublished multiple treatment comparison (MTC) network meta-analysis (NMA) that examined the comparative efficacy of rotigotine, ropinirole, and pramipexole (DAs) in patients with EPD and APD.[129] The NMA has subsequently been published.[85] This summary reviews the findings of the published report and highlights any differences between the published and unpublished versions.

2. Summary of Multiple Treatment Comparison Network Meta-analyses

The MTC NMAs were performed to compare the efficacy of rotigotine to ropinirole and pramipexole in patients with EPD and APD based on key efficacy outcomes at both early (11 to 16 weeks) and late (24 to 28 weeks) time points following dose titration.

The report was based on a systematic review of the literature that was conducted using standard methods. Inclusion criteria were open-label or blinded RCTs in adults over 18 years of age with either EPD or APD (as defined by the individual trials). Experimental interventions included rotigotine, ropinirole, and pramipexole with the following control interventions: levodopa (with and without decarboxylase inhibitors), bromocriptine, cabergoline, piribedil, pergolide, and placebo (for patients with EPD only). Extended release (ER) and regular release formulations of ropinirole and pramipexole were considered equivalent. Key efficacy outcomes included the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (activities of daily living [ADL]), UPDRS Part III (motor functioning), UPDRS Parts II + III subtotal score (for EPD only), and "off" time reduction (for APD only).

In the published NMA, 23 trials were included for EPD: 20 trials informing the analysis for the 11- to 16-week post-titration time point and 11 trials informing the analysis for the 24- to 28-week post-titration time point. Twenty-two trials were included for APD: 13 trials informing the analysis for the 11- to 16-week post-titration time point and 13 trials informing the analysis for the 24- to 28-week post-titration time point. The studies included in the published NMA were different from those in the unpublished version, but the reasons for these changes were unclear, as the published report did not provide a list of excluded studies and reasons for exclusion. Two new clinical trials (Study 243-08-001 and Study 243-05-001)[6,8] submitted as part of this submission[5] were not included in the NMA; however, the maintenance phase of these trials may not have met the inclusion criteria for the systematic review.

TABLE 63: NUMBER OF STUDIES INCLUDED IN THE PUBLISHED AND UNPUBLISHED NETWORK META-ANALYSIS REPORTS

Population/ Analysis	Unpublished NMA	Published NMA	Comments
EPD	[redacted]	23	Published report excluded Adler 1997;[130] included Mizuno 2013[99]
11 weeks to 16 weeks	[redacted]	20	Published report included Mizuno 2013[99]
24 weeks to 28 weeks	[redacted]	11	
APD	[redacted]	22	Published report excluded Mizuno 2011;[130] Guttman 1997[63] may have been counted twice in the unpublished report
11 weeks to 16 weeks	[redacted]	13	Published report excluded Mizuno 2011[131]
24 weeks to 28 weeks	[redacted]	13	Published report excluded Mizuno 2011;[131] Guttman 1997[63] may have been counted twice in the unpublished report

APD = advanced Parkinson's disease; EPD = early Parkinson's disease.
Source: Thorlund Confidential Report,[129] Thorlund 2014.[85]

The number of trials included in the three efficacy outcomes for patients with EPD and APD is listed in Table 64.

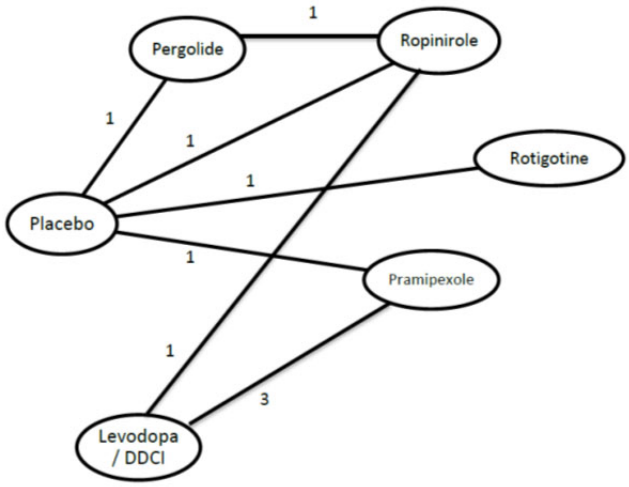
TABLE 64: NUMBER OF STUDIES INCLUDED IN EFFICACY OUTCOMES IN THE PUBLISHED NETWORK META-ANALYSIS

Outcome	EPD		APD	
	11 Weeks to 16 Weeks	24 Weeks to 28 Weeks	11 Weeks to 16 Weeks	24 Weeks to 28 Weeks
UPDRS Part II	10	10	7	6
UPDRS Part III	16	7	8	10
UPDRS Part II + III	14	10	NR	NR
"Off" time	NA	NA	10	9

APD = advanced Parkinson's disease; EPD = early Parkinson's disease; NA = not applicable; NR = not reported; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Thorlund 2014.[85]

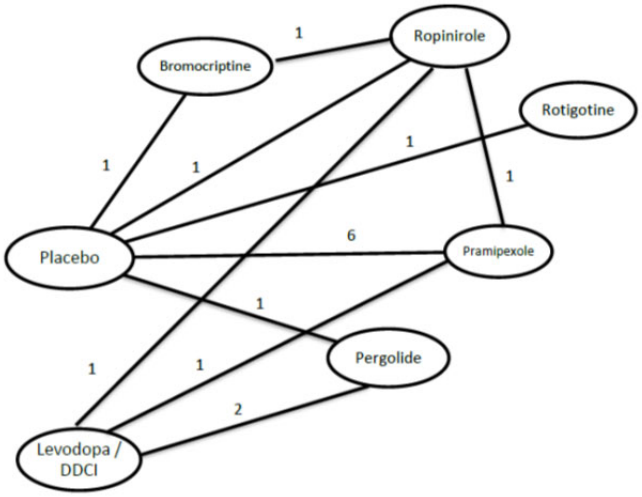
Network diagrams for the outcomes evaluated at the 11-week to 16-week time point are presented in Figure 2, Figure 3, and Figure 4 for NMAs in EPD, and in Figure 5, Figure 6, and Figure 7 for analyses in APD. Network diagrams for the outcomes reported at 24 weeks to 28 weeks were similar except for the exclusion of pergolide for UPDRS Part II, and pergolide and bromocriptine for UPDRS Part III in EPD. For APD, the UPDRS Part III and *off* time NMAs also included cabergoline.

FIGURE 2: NETWORK DIAGRAM FOR UNIFIED PARKINSON'S DISEASE RATING SCALE PART II AT 11 WEEKS TO 16 WEEKS IN EARLY PARKINSON'S DISEASE



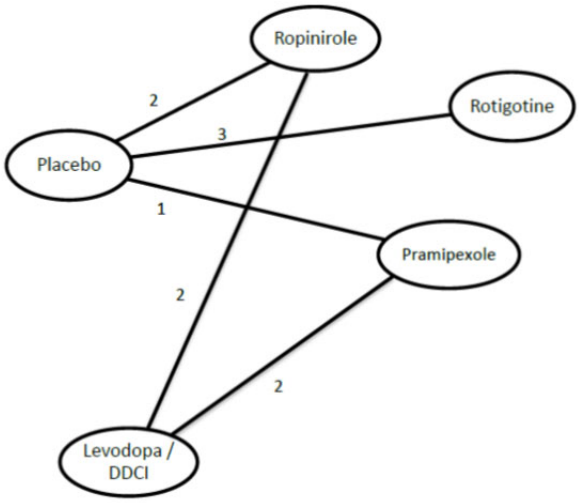
DDCI = dopa decarboxylase inhibitor.

FIGURE 3: NETWORK DIAGRAM FOR UNIFIED PARKINSON'S DISEASE RATING SCALE PART III AT 11 WEEKS TO 16 WEEKS IN EARLY PARKINSON'S DISEASE



DDCI = dopa decarboxylase inhibitor.

FIGURE 4: NETWORK DIAGRAM FOR UNIFIED PARKINSON'S DISEASE RATING SCALE PARTS II + III AT 11 WEEKS TO 16 WEEKS IN EARLY PARKINSON'S DISEASE



DDCI = dopa decarboxylase inhibitor.

FIGURE 5: NETWORK DIAGRAM FOR UNIFIED PARKINSON'S DISEASE RATING SCALE PART II AT 11 WEEKS TO 16 WEEKS IN ADVANCED PARKINSON'S DISEASE

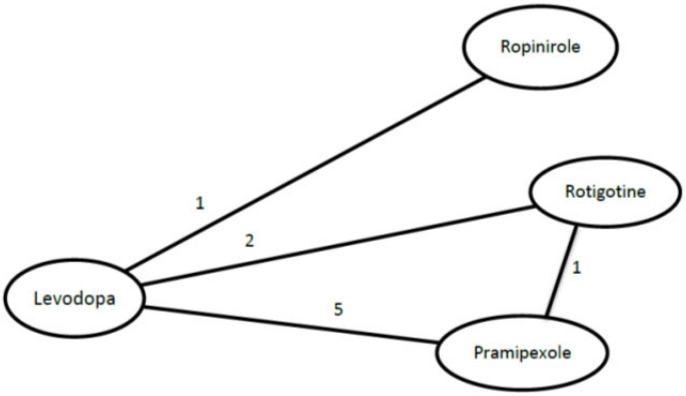


FIGURE 6: NETWORK DIAGRAM FOR UNIFIED PARKINSON'S DISEASE RATING SCALE PART III AT 11 WEEKS TO 16 WEEKS IN ADVANCED PARKINSON'S DISEASE

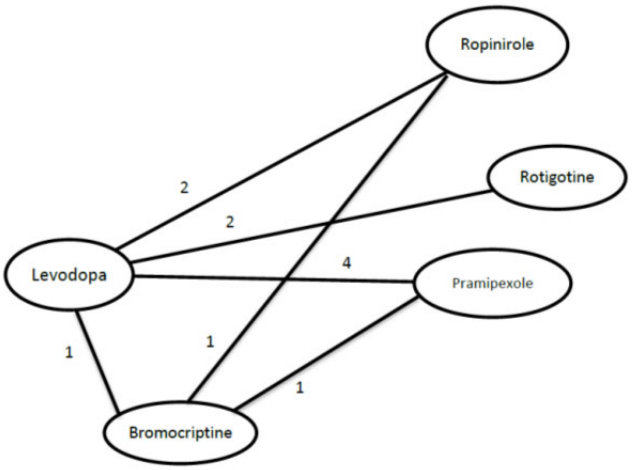
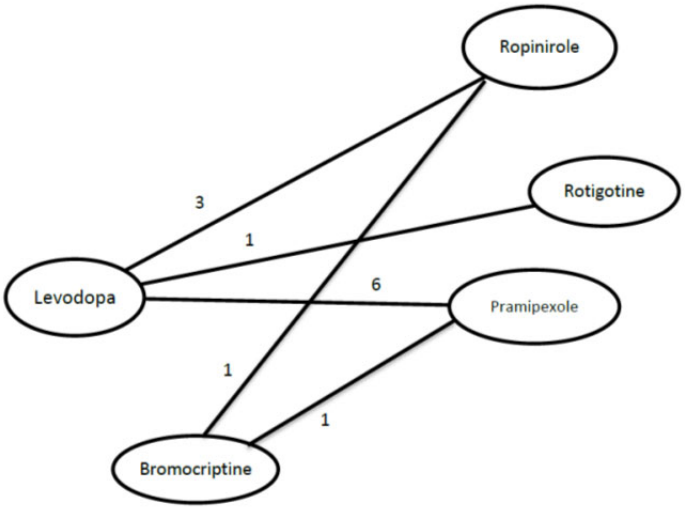


FIGURE 7: NETWORK DIAGRAM FOR *OFF* TIME AT 11 WEEKS TO 16 WEEKS FOR ADVANCED PARKINSON'S DISEASE



2.1 Methods

2.1.1 Description of the Bayesian Multiple Treatment Comparison

Bayesian NMAs were performed in EPD and APD for both "short duration" (defined as results reported after 11 to 16 weeks of treatment, excluding the titration period) and "longer duration" (defined as results reported 24 to 28 weeks post-titration).

In the EPD analysis, the NMAs were performed on the change from baseline for the UPDRS Part II (ADL), UPDRS Part III (motor functioning), and UPDRS Parts II + III outcome scores. In APD, the analyses were performed on the change from baseline for the UPDRS Part II and UPDRS Part III scores, and the change

from baseline in *off* time. The effect measure in the Bayesian NMA models was the mean difference (i.e., the difference between the mean change from baseline values in the two intervention groups) with 95% credible intervals (CrI). Missing intervention group standard errors were imputed if not reported in the individual studies. A shared-parameter model was used so that originally reported data from the trials could be used in the analysis (i.e., either intervention group mean responses or calculated mean differences). Non-informative prior distributions were used in the Bayesian random effects model.

The rotigotine versus ropinirole trial by Giladi et al. (Study SP513)[3] was excluded from the primary analysis of the 24- to 28-week UPDRS Parts II + III outcome because the ropinirole response was substantially higher than in other similar ropinirole trials, and thus was a source of heterogeneity. Sensitivity analyses were conducted that included the Giladi trial[3] and excluded trials with missing intervention group standard errors (i.e., any trial where all standard error values were imputed using data from other studies).

2.1.2 Patient and Treatment Characteristics

a) Early Parkinson's disease

The authors reported that the included trials were similar in terms of key patient characteristics, such as age, disease duration, and disease severity. The average age was approximately 60 to 65 years (estimated range: 50 to 75 years) with an average duration of Parkinson's disease (PD) between one and two years (estimated range: less than one year to six years). In addition, disease severity was measured at a Hoehn and Yahr staging of 1 or 2 for the majority or patients, with < 15% classified as stage 3 in most trials.

Allowed background medications and the proportions of patients receiving them varied between trials and, in some trials, were not well reported. Additionally, dosing was somewhat different for the concomitant levodopa and non-ergolinic DAs:

- Levodopa range of mean doses: 364 mg/day to 753 mg/day
- Pramipexole range of mean doses: 1.0 mg/day to 4.5 mg/day
- Ropinirole range of mean doses: 10 mg/day to ≤ 24 mg/day
- Rotigotine range of median doses: 4.5 mg/24 h to 18 mg/24 h

b) Advanced Parkinson's disease

Several key patient characteristics were similar between the included trials for APD, as stated by the review's authors. Patients were between 60 and 65 years of age (estimated range: 50 to 75 years), with an average PD duration between four and 10 years (standard deviation indicated a range of two to 20 years). The authors reported that in general, disease severity was measured at a Hoehn and Yahr stage greater than 2.5; however, the proportions of patients in each stage were not reported for the individual studies, so it was not possible to verify these data.

Allowed background medications and the proportions of patients receiving them varied between trials and, in some trials, were not well reported. Additionally, dosing was somewhat different between backbone levodopa and the following non-ergolinic DAs. In the trials, all patients were receiving levodopa, except in two studies, where 81% to 95% of patients were on levodopa. The range mean doses of levodopa and DAs were as follows:

- Levodopa: 319 mg/day to 1,092 mg/day
- Pramipexole: 2.7 mg/day to 4.6 mg/day

- Ropinirole: 3.3 mg/day to 18.8 mg/day
- Rotigotine: 7.2 mg/24 h to 12.9 mg/24 h

2.2 Results

The results of the NMA of patients with EPD are presented in Table 65 and Table 66, and for APD in Table 67 and Table 68. Negative values for the mean differences favour the experimental treatment versus control, and 95% CrI that do not include the null value (i.e., do not cross 0) were interpreted as statistically significant.

2.2.1 Early Parkinson's Disease

a) 11 weeks to 16 weeks post-titration

For UPDRS Part II (ADL), Part III (motor impairment), and Parts II + III outcomes at 11 to 16 weeks, the NMA showed statistically significant differences favouring levodopa, pramipexole, ropinirole, and rotigotine compared with placebo. The only exception was for UPDRS Part II, where ropinirole versus placebo did not reach statistical significance (Table 65). The differences between active drugs and placebo were within the range of the minimal clinically important difference (MCID) values reported in the literature for UPDRS Part II (MCID: –0.7 to –2.0; treatment effects mean difference [MD]: –1.0 to –1.8) and UPDRS Part III (MCID: –2.5 to –6.1; treatment effects MD: –2.9 to –6.1). The differences between active treatments and placebo were less than the MCID value reported in the literature (–8.1) for the UPDRS Parts II + III outcome, except for levodopa versus placebo (MD: –8.6).

No statistically significant differences were observed with any UPDRS outcome when rotigotine was compared with either pramipexole or ropinirole; however, statistically significant improvements in the UPDRS Part III and UPDRS Parts II + III total scores were reported favouring levodopa when compared with rotigotine (Table 65). The treatment differences between rotigotine and levodopa were small and did not exceed the MCID for the UPDRS Parts II + III outcome.

TABLE 65: EFFICACY COMPARISONS AT 11 WEEKS TO 16 WEEKS POST-TITRATION IN PATIENTS WITH EARLY PARKINSON'S DISEASE

Comparison	UPDRS II, MD (95% CrI)	UPDRS III, MD (95% CrI)	UPDRS II + III, MD (95% CrI)
Placebo Comparisons[a]			
Levodopa vs. placebo	**–1.77 (–3.15 to –0.38)**	**–6.09 (–8.29 to –3.89)**	**–8.59 (–10.8 to –6.26)**
Pramipexole vs. placebo	**–1.15 (–1.77 to –0.38)**	**–3.40 (–4.56 to –2.44)**	**–4.33 (–5.35 to –3.32)**
Ropinirole vs. placebo	–1.28 (–3.44 to 0.87)	**–2.85 (–5.09 to –0.89)**	**–4.18 (–6.15 to –2.26)**
Rotigotine vs. placebo	**–1.01 (–1.68 to –0.33)**	**–3.34 (–4.99 to –1.71)**	**–4.52 (–5.70 to –3.29)**
Active Comparisons[b]			
Rotigotine vs. levodopa	–0.76 (–0.57 to 2.16)	**2.76 (0.18 to 5.33)**	**4.08 (1.56 to 6.58)**
Rotigotine vs. pramipexole	0.14 (–0.97 to 0.70)	0.06 (–2.77 to 2.10)	–0.17 (–1.61 to 1.40)
Rotigotine vs. ropinirole	0.28 (–2.41 to 1.98)	–0.50 (–3.01 to 2.30)	0.32 (–2.00 to 2.58)

CrI = credible interval; MD = mean difference; UPDRS = Unified Parkinson's Disease Rating Scale; vs. = versus.
[a] A negative MD indicates superiority of the active intervention. Statistically significant differences in bold.
[b] A negative result would favour rotigotine; a positive result favours control. Statistically significant differences in bold.
Source: Thorlund 2014.[85]

b) 24 weeks to 28 weeks post-titration

The findings for active treatments versus placebo at 24 to 28 weeks were similar to those in the 11- to 16-week analyses. All treatments were statistically significantly different from placebo for all UPDRS outcomes, except for ropinirole for UPDRS Part II (Table 66). The differences between DA drugs and placebo were within the range of the MCID values for the UPDRS Part II and UPDRS Part III outcomes, but less than the MCID value for UPDRS Parts II + III. For all outcomes, the difference between levodopa and placebo exceeded the MCID values reported in the literature. No statistically significant differences were found for rotigotine versus ropinirole, pramipexole, or levodopa, for any outcome (Table 66).

TABLE 66: EFFICACY COMPARISONS AT 24 WEEKS TO 28 WEEKS POST-TITRATION IN PATIENTS WITH EARLY PARKINSON'S DISEASE

Comparison	UPDRS II, MD (95% CrI)	UPDRS III, MD (95% CrI)	UPDRS II + III, MD (95% CrI)
Placebo Comparisons[a]			
Levodopa vs. placebo	**–2.76 (–4.77 to –0.81)**	**–7.26 (–10.7 to –3.86)**	**–9.15 (–13.2 to –4.83)**
Pramipexole vs. placebo	**–1.67 (–2.64 to –0.72)**	**–4.37 (–6.16 to –2.63)**	**–6.05 (–8.84 to –3.19)**[b]
Ropinirole vs. placebo	–2.39 (–4.71 to 0.12)	**–5.08 (–7.28 to –2.85)**	**–6.32 (–10.4 to –2.00)**[c]
Rotigotine vs. placebo	**–1.70 (–2.91 to –0.45)**	**–3.78 (–6.20 to –1.23)**	**–5.35 (–9.33 to –1.43)**[d]
Active Comparisons[e]			
Rotigotine vs. levodopa	1.06 (–1.23 to 3.43)	3.46 (–0.03 to 7.17)	3.78 (–2.00 to 9.40)
Rotigotine vs. pramipexole	–0.03 (–1.55 to 1.54)	0.61 (–2.32 to 3.69)	0.70 (–4.07 to 5.46)
Rotigotine vs. ropinirole	0.69 (–2.11 to 3.31)	1.34 (–1.94 to 4.62)	0.97 (–4.82 to 6.58)

CrI = credible interval; MD = mean difference; UPDRS = Unified Parkinson's Disease Rating Scale; vs. = versus.
[a] A negative MD indicates superiority of the active intervention. Statistically significant differences in bold.
[b] Sensitivity analysis including Giladi et al. MD –6.18 (–8.79 to –3.50).
[c] Sensitivity analysis including Giladi et al. MD –7.11 (–10.1 to –4.00).
[d] Sensitivity analysis including Giladi et al. MD –5.02 (–8.52 to –1.50).
[e] A negative result would favour rotigotine; a positive result favours control. Statistically significant differences in bold.
Source: Thorlund 2014.[85]

The authors reported that the sensitivity analyses that excluded trials with fully imputed variance data, or that included the Giladi trial, showed similar results to the primary analyses at 11 weeks to 16 weeks and 24 weeks to 28 weeks (incomplete data reported in Thorlund et al. 2014[85]).

2.2.2 Advanced Parkinson's Disease

a) 11 weeks to 16 weeks post-titration

Rotigotine, ropinirole, and pramipexole were all statistically significant different from placebo in UPDRS Part II and UPDRS Part III scores, and in the amount of *off* time at 11 weeks to 16 weeks post-titration (Table 67). The differences between DA drugs and placebo (MD: –3.8 to –5.0) were less than the MCID value (–6.5) for UPDRS Part III, as well as the UPDRS Part II outcome (treatment effects MD: –1.7 to –2.0; MCID: –2.3 to –3.0). The differences in *off* time ranged from –1.4 to –1.5 hours for DA drugs versus placebo, which was considered a clinically relevant change and was within the range of MCID values (–1.3 to –1.9 hours) reported in the literature. The estimated differences in the UPDRS Part II or UPDRS Part III scores and *off* time were not statistically significant between rotigotine and pramipexole or ropinirole (Table 67).

TABLE 67: EFFICACY COMPARISONS AT 11 WEEKS TO 16 WEEKS POST-TITRATION IN PATIENTS WITH ADVANCED PARKINSON'S DISEASE

Comparison	UPDRS II, MD (95% CrI)	UPDRS III, MD (95% CrI)	*Off* Time (hours), MD (95% CrI)
Placebo Comparisons[a]			
Pramipexole vs. placebo	**–2.03 (–2.69 to –1.37)**	**–5.03 (–6.73 to –3.39)**	**–1.53 (–2.11 to –0.95)**
Ropinirole vs. placebo	**–1.84 (–3.22 to –0.44)**	**–5.01 (–8.43 to –1.63)**	**–1.44 (–2.06 to –0.79)**
Rotigotine vs. placebo	**–1.71 (–2.62 to –0.78)**	**–3.84 (–6.94 to –0.89)**	**–1.52 (–2.46 to –0.47)**
Active Comparisons[b]			
Rotigotine vs. pramipexole	0.32 (–0.68 to 1.35)	1.21 (–1.77 to 4.11)	–0.01 (–0.99 to 1.06)
Rotigotine vs. ropinirole	0.13 (–1.51 to 1.74)	1.20 (–3.49 to 5.65)	0.06 (–1.13 to 1.19)

CrI = credible interval; MD = mean difference; UPDRS = Unified Parkinson's Disease Rating Scale; vs. = versus.
[a] A negative MD indicates superiority of the active intervention. Statistically significant differences in bold.
[b] A negative result would favour rotigotine; a positive result favours control. Statistically significant differences in bold.
Source: Thorlund 2014.[85]

b) 24 weeks to 28 weeks post-titration

The differences between pramipexole, ropinirole, and rotigotine versus placebo were statistically significantly different for all outcomes measured at 24 to 28 weeks post-titration, with the UPDRS Part II differences (MD: –2.2 to –2.3) and *off* time (MD: –1.2 to –1.6 hours) within the MCID values (Table 68). No statistically significant differences were detected between rotigotine and the non-ergolinic DAs, pramipexole and ropinirole, at 24 to 28 weeks (Table 68).

For all analyses in APD, the sensitivity analyses that excluded trials with fully imputed standard deviation data showed similar results as the primary analyses (data not reported in Thorlund et al. 2014[85]).

TABLE 68: EFFICACY COMPARISONS AT 24 WEEKS TO 28 WEEKS POST-TITRATION IN PATIENTS WITH ADVANCED PARKINSON'S DISEASE

Comparison	UPDRS II, MD (95% CI)	UPDRS III, MD (95% CI)	*Off* Time, MD (95% CI)
Placebo Comparisons[a]			
Pramipexole vs. placebo	**–2.18 (–2.96 to –1.42)**	**–4.22 (–6.31 to –2.37)**	**–1.60 (–3.27 to –0.59)**
Ropinirole vs. placebo	**–2.20 (–3.24 to –1.14)**	**–4.84 (–7.33 to –2.55)**	**–1.17 (–2.49 to –0.31)**
Rotigotine vs. placebo	**–2.25 (–3.71 to –0.78)**	**–4.28 (–7.63 to –1.12)**	**–1.49 (–2.91 to –0.05)**
Active Comparisons[b]			
Rotigotine vs. pramipexole	0.06 (–1.62 to 1.77)	–0.07 (–3.87 to 3.73)	0.10 (–1.68 to 1.79)
Rotigotine vs. ropinirole	0.05 (–1.71 to 1.91)	0.64 (–3.41 to 4.60)	–0.33 (–1.98 to 1.42)

CI = confidence interval; MD = mean difference; UPDRS = Unified Parkinson's Disease Rating Scale; vs. = versus.
[a] A negative MD indicates superiority of the active intervention. Statistically significant differences in bold.
[b] A negative result would favour rotigotine; a positive result favours control. Statistically significant differences in bold.
Source: Thorlund 2014.[85]

2.2.3 Critical Appraisal of Indirect Comparison

TABLE 67: APPRAISAL OF THE INDIRECT COMPARISON ANALYSES USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility for the RCTs was stated, the search strategy was provided, the study selection process was reported, and the method of data extraction was provided. • The validity of the individual trials was not reported, nor were the study selection flow chart or reasons for exclusions.
3.	Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis were stated. No harms data were analyzed.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A Bayesian NMA was used, and the rationale for using this method was reported; however, no justification for using random versus fixed effects models was discussed. It appears there were limited assessments of heterogeneity and potential biases, and no assessment of the consistency of direct and indirect evidence.
5.	Are sensitivity analyses presented?	• Two sensitivity analyses were conducted and general statements regarding their findings were reported. Complete data from the NMA were not provided.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• The selection process of included studies was reported using PICO. • Patient characteristics were provided, but numbers of patients in individual trials were omitted. • Some trial characteristics were provided. Raw outcome data used in the analyses were not reported. • Figures of the networks were provided. • No results of any direct pairwise comparisons were reported.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• Model fit not reported. No evaluation of alternate models.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the primary analyses were clearly reported; however, data were incomplete for the sensitivity analyses.

NMA = network eta-analysis; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial.
Source: Jansen et al.[132]

a) Strengths and Limitations

The MTC NMAs were based on a systematic review of the available RCTs. The methods for the systematic review included a literature search of multiple databases, pre-defined inclusion criteria, duplicate screening, and extraction; however, no critical appraisal of the included studies was conducted and no flowchart of the study selection process or list of excluded studies was reported.

In terms of the methods used for the statistical analysis, the Bayesian method appeared appropriate for this NMA; however, no justification for selecting a random versus fixed effects model was provided. Furthermore, no information was provided to justify the prior distributions selected, nor was any sensitivity analyses conducted on these parameters. Considering that some networks were sparse, the use of non-informative priors for between-study variance may have produced overly wide credible intervals.[133] Reporting of the model was incomplete, as no information on model fit, convergence diagnostics, or burn-in period were provided. It appears there was no assessment of consistency between direct and indirect evidence.

The internal validity of these NMAs may have been compromised by the heterogeneity between the included trials and the inclusion of open-label trials. As there was no quality assessment of individual trials reported, it appears that the risk of bias was not considered in the analyses. The lack of blinding is associated with a higher risk of bias in trials with subjective outcome measures. As previously reported, there were some between-trial differences in the dosing of the DAs and levodopa, yet all doses were pooled in the analyses, and there was no exploration of treatment dose or use of concomitant medications as a source of heterogeneity. Although the dose ranges for the non-ergolinic DAs and levodopa may be in line with clinical practice, the clinical relevance of pooled dosage data may be diminished. It appears there was some variability across trials in the proportion of patients at different Hoehn and Yahr stages, and it is unclear if the definitions of EPD versus APD used in the individual studies were consistent. Other than the heterogeneity issues raised with regards to the Giladi trial,[3] and the sensitivity analyses for studies with imputed variance data, no other subgroup, sensitivity, or meta-regression analyses were conducted.

The NMAs did not assess the comparative efficacy for other outcomes, such as responder rate, nor did it assess the comparative safety of the non-ergolinic DAs. Because no analyses for these outcomes were included, there is risk of excluding potentially relevant information that would help to strengthen the overall meta-analyses. In addition, there was no analysis performed on the comparative safety between the non-ergolinic DAs.

The discordance between the results of the NMA and the direct evidence from Giladi et al.[3] was of concern. This trial was reported to be an outlier because the mean decrease from baseline with ropinirole for the UPDRS Part II + III subtotal (11.0) was larger than changes observed in other ropinirole trials whose results were more homogeneous (range: 5.20 to 7.52).[85] For this reason, analyses were performed that included or excluded Giladi et al. The mean differences for ropinirole versus placebo were similar in both analyses, and fell within the ranges observed in the other included trials versus placebo: at –6.32 (95% CrI, –10.4 to –2.00) with the Giladi study excluded and –7.11 (95% CrI, –10.1 to –4.00) with it included. In the Giladi trial,[85] rotigotine was not non-inferior to ropinirole; however, in the NMA, no statistically significant difference between treatments was found in the primary analysis, excluding the Giladi trial. The NMA results for the analysis including Giladi et al. were not reported. Nonetheless, the design of the Giladi et al. study (i.e., higher ropinirole dose, longer duration) may have contributed to the discordance in the direct and indirect comparison between ropinirole and rotigotine.

The individual RCTs appeared to contain appropriately representative populations of patients living with EPD and APD, which enhances the generalizability of the results. Although the analysis included comparators that are relevant to the Canadian context, it also included medications that were not available in Canada (e.g., long-acting ropinirole and pramipexole, cabergoline, piribedil, and pergolide). It is not clear if the results of the NMAs — which were conducted for time intervals of 11 weeks to 16 weeks and 24 weeks to 28 weeks after initiation of treatment — can be extrapolated to beyond 28

weeks. PD is a progressive condition and it is possible that the maintenance doses needed over time will increase, especially in advanced disease.

In EPD, monotherapy with levodopa/carbidopa is considered the standard of care by many clinicians and, therefore, should be considered an appropriate comparator. In the NMA, rotigotine was inferior to levodopa for change from baseline in UPDRS Part III and UPDRS Parts II + III subtotal scores at 11 weeks to 16 weeks. The mean difference compared with levodopa was 2.8 (95% CrI, 0.2 to 5.3) for UPDRS Part III and 4.1 (95% CrI, 1.6 to 6.6) for UPDRS Parts II + III. Point estimates were similar for both outcomes at 24 weeks to 28 weeks (UPDRS Part III: 3.5; UPDRS Parts II + III: 3.8), but did not reach statistical significance.

2.2.4 Summary

In EPD and APD, all three non-ergolinic DAs of interest (pramipexole, ropinirole, and rotigotine) were associated with statistically significant reductions in UPDRS scores for ADL (Part II) and motor functioning (Part III), as well as reductions in *off* time (APD only), compared with placebo at both the 11-week to 16-week and 24-week to 28-week time points. The exception was ropinirole in EPD, which was not associated with significant differences in UPDRS Part II scores.

In patients with EPD, the treatment effects for DA drugs versus placebo were small and within the range of MCID values reported in the literature for the UPDRS Part II and UPDRS Part III individual scores, but the combined score (UPDRS Parts II + III) did not exceed the MCID. In contrast, the differences between levodopa and placebo consistently exceeded the MCID for all outcomes in patients with EPD. In APD, the clinical importance of DA treatment effects was less clear, because differences between DA drugs and placebo were less than the MCID for UPDRS Part II and Part III scores in some analyses. The differences in *off* time between DA drugs and placebo were generally within the reported MCID values.

When pramipexole, ropinirole, and rotigotine were compared with each other, their effect estimates were similar, and did not reach statistical significance in EPD and APD. However, levodopa in EPD was found to be more efficacious than rotigotine in improving motor function and UPDRS Parts II + III total scores at the 11-week to 16-week time point, although treatment differences were small.

The findings should be interpreted in the context of the NMA's limitations, which included possible clinical heterogeneity between trials and the absence of an assessment of the risk of bias in individual studies. Also, the comparative safety of PD treatments was not assessed. The authors did not provide justification for using a random effects model, and there was no exploration of alternate models or prior distributions. While pramipexole, ropinirole, and rotigotine appeared to have similar efficacy in improving some of the symptoms associated with PD, the reliability and validity of these results for these specific patient populations remains uncertain.

REFERENCES

1. Neupro (rotigotine) transdermal system [product monograph]. Oakville (ON): UCB Canada Inc.; 2013 Mar 19.
2. Common Drug Review. CDEC final recommendation: rotigotine (Neupro — UCB Canada Inc.) [Internet]. Ottawa: CADTH; 2014 May 28. [cited 2015 Jul 31]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0344_complete_Neupro_May-30-14.pdf
3. Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, Schapira AH, et al. Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. Mov Disord. 2007 Dec;22(16):2398-404.
4. Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol. 2007 Jun;6(6):513-20.
5. CDR resubmission: Neupro (rotigotine) transdermal system (patch) Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): UCB Canada Inc.; 2015.
6. Mizuno Y, Nomoto M, Hasegawa K, Hattori N, Kondo T, Murata M, et al. Rotigotine vs ropinirole in advanced stage Parkinson's disease: a double-blind study. Parkinsonism Relat Disord. 2014 Dec;20(12):1388-93.
7. Clinical Trial Report: 243-08-001. A multi-centre, randomised, double blind, placebo and ropinirole-controlled comparative study to confirm superiority to the placebo and non-inferiority to ropinirole of repeated transdermal administration of SPM 962 once a day at doses of 4.5 - 36.0 mg (16-week dose escalation and maintenance period) in Parkinson's disease patients in coadministration with L-dopa. (phase III study) [**CONFIDENTIAL** internal manufacturer's report]. Osaka: Otsuka Pharmaceutical Co., Ltd.; 2015 Jul 20.
8. Nomoto M, Mizuno Y, Kondo T, Hasegawa K, Murata M, Takeuchi M, et al. Transdermal rotigotine in advanced Parkinson's disease: a randomized, double-blind, placebo-controlled trial. J Neurol. 2014 Oct;261(10):1887-93.
9. Clinical Study Report: PRT No. 243-05-001. A Placebo-controlled Dose-finding Study for SPM 962 in Advanced Parkinson's Disease Patients with Concomitant Treatment of L-dopa [**CONFIDENTIAL** internal manufacturer's report]. Osaka: Otsuka Pharmaceutical Co., Ltd.; 2007 Jun 9.
10. Trenkwalder C, Kies B, Rudzinska M, Fine J, Nikl J, Honczarenko K, et al. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord [Internet]. 2011 Jan [cited 2015 Aug 19];26(1):90-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3072524
11. Swick TJ, Friedman JH, Chaudhuri KR, Surmann E, Boroojerdi B, Moran K, et al. Associations between severity of motor function and nonmotor symptoms in Parkinson's disease: a post hoc analysis of the RECOVER Study. Eur Neurol. 2014;71(3-4):140-7.
12. Kassubek J, Chaudhuri KR, Zesiewicz T, Surmann E, Boroojerdi B, Moran K, et al. Rotigotine transdermal system and evaluation of pain in patients with Parkinson's disease: a post hoc analysis of the RECOVER study. BMC Neurol [Internet]. 2014 [cited 2015 Jul 8];14:42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4016269/pdf/1471-2377-14-42.pdf
13. Ray CK, Martinez-Martin P, Antonini A, Brown RG, Friedman JH, Onofrj M, et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. Parkinsonism Relat Disord. 2013 Jul;19(7):660-5.

14. Ghys L, Surmann E, Whitesides J, Boroojerdi B. 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. 2011 Sep;12(13):1985-98.
15. Clinical Trial Report: SP889. RECOVER Randomized evaluation of the 24-hour coverage: efficacy of rotigotine [**CONFIDENTIAL** internal manufacturer's report]. Research Triangle Park (NC): Schwarx Biosciences; 2009 Nov 12.
16. LeWitt PA, Lyons KE, Pahwa R, SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology. 2007 Apr 17;68(16):1262-7.
17. Clinical study report: a long-term extension study of the Phase 3 study (243-08-001) of SPM 962 in patients with Parkinson's disease using concomitant L-dopa (a long-term study) [**CONFIDENTIAL** internal manufacturer's report]. Tokyo: Otsuka Pharmaceutical Co., Ltd.; 2014.
18. Clinical Study Report: SPM 962 Synopsis of study protocol 243-06-001. A long-term extention study of 243-05-001 study for SPM 962 in patient with advanced Parkinson's disease with concomitant use of L-dopa [**CONFIDENTIAL** internal manufacturer's report]. Osaka: Otsuka Pharmaceutical Co; 2006 Aug 25.
19. Clinical Trial Report: SP915. A multicenter, multinational, Phase 3b, open-label extension trial to evaluate the long-term effect of the 24-hour transdermal delivery of rotigotine on motor function, sleep quality, and nocturnal and non-motor symptoms in subjects with idiopathic Parkinson's disease. [**CONFIDENTIAL** internal manufacturer's report]. Monheim, Germany: Schwarz Biosciences, GmbH; 2010 Feb 16.
20. Yuan Y, Padol IT, Hunt RH. Peptic ulcer disease today. Nat Clin Pract Gastroenterol Hepatol. 2006 Feb;3(2):80-9.
21. Giladi N, Ghys L, Surmann E, Boroojerdi B, Jankovic J. Effects of long-term treatment with rotigotine transdermal system on dyskinesia in patients with early-stage Parkinson's disease. Parkinsonism Relat Disord. 2014 Dec;20(12):1345-51.
22. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med. 2000 May 18;342(20):1484-91.
23. Holloway RG, Shoulson I, Fahn S, Kieburtz K, Lang A, Marek K, et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol. 2004 Jul;61(7):1044-53.
24. Clinical Study Report: 243-05-001. A placebo-controlled dose-finding study for SPM 962 in advanced Parkinson's disease patients with concomitant treatment of L-dopa [**CONFIDENTIAL** internal manufacturer's report]. Osaka: Otsuka Pharmaceutical Co.; 2009 Feb 2.
25. Calabresi P, Ghiglieri V, Mazzocchetti P, Corbelli I, Picconi B. Levodopa-induced plasticity: a double-edged sword in Parkinson's disease? Philos Trans R Soc Lond B Biol Sci [Internet]. 2015 Jul 5 [cited 2015 Aug 21];370(1672). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455753
26. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Apr 17.
27. Kalf JG, de Swart BJ, Bloem BR, Munneke M. Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. Parkinsonism Relat Disord. 2012 May;18(4):311-5.
28. Kim JS, Sung HY. Gastrointestinal autonomic dysfunction in patients with Parkinson's Disease. J Mov Disord [Internet]. 2015 May [cited 2015 Aug 21];8(2):76-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4460543

29. Wong SL, Gilmour H, Ramage-Morin PL. Parkinson's disease: prevalence, diagnosis and impact. Health Rep. 2014 Nov 19;25(11):10-4.

30. Grimes D, Gordon J, Snelgrove B, Lim-Carter I, Fon E, Martin W. Canadian guidelines on Parkinson's disease. Can J Neurol Sci. 2012;39(4):S1-S30. Supplement 4.

31. [Pr]Sinemet© (levodopa and cardidopa) tablets; 100 mg levodopa and 10 mg carbidopa, 100 mg levodopa and 25 mg carbidopa, 250 mg levodopa and 25 mg carbidopa [product monograph]. Kirkland (QC): Merck Canada Inc.; 2013 May 23.

32. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol. 2006 Aug;5(8):677-87.

33. Schaeffer E, Pilotto A, Berg D. Pharmacological strategies for the management of levodopa-induced dyskinesia in patients with Parkinson's disease. CNS Drugs. 2014 Dec;28(12):1155-84.

34. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA. 2014 Apr 23;311(16):1670-83.

35. Suchowersky O, Reich S, Perlmutter J, Zesiewicz T, Gronseth G, Weiner WJ, et al. Practice Parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66(7):968-75.

36. National Institute for Health and Clinical Excellence. Parkinson's disease: diagnosis and management in primary and secondary care [Internet]. London: NICE; 2006. [cited 2015 Aug 21]. (NICE clinical guideline 35). Available from: http://www.nice.org.uk/nicemedia/pdf/cg035niceguideline.pdf

37. Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, et al. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part I: early (uncomplicated) Parkinson's disease. Eur J Neurol. 2006 Nov;13(11):1170-85.

38. Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, et al. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: late (complicated) Parkinson's disease. Eur J Neurol. 2006 Nov;13(11):1186-202.

39. Trenkwalder C, Chaudhuri KR, Garcia Ruiz PJ, LeWitt P, Katzenschlager R, Sixel-Doring F, et al. Expert Consensus Group report on the use of apomorphine in the treatment of Parkinson's disease - clinical practice recommendations. Parkinsonism Relat Disord. 2015 Jun 17.

40. Pahwa R, Factor SA, Lyons KE, Ondo WG, Gronseth G, Bronte-Stewart H, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006 Apr 11;66(7):983-95.

41. European Public Assessment Report (EPAR). Neupro (rotigotine). Scientific discussion [Internet]. London: European Medicines Agency; 2006. [cited 2015 Aug 21]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000626/WC500026394.pdf

42. [Pr]Mirapex® pramipexole dihydrochloride tablets 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg, 1.5 mg pramipexole dihydrochloride monohydrate [product monograph]. Burlington (ON): BoehringerIngelheim (Canada) Ltd.; 2012 Nov 27.

43. [Pr]Requip® (ropinirole hydrochloride tablets 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg, 3.0 mg, 4.0 mg, 5.0 mg ropinirole) [product monograph]. Mississauga (ON): GlaxoSmithKline Inc; 2014 May 7.

44. [Pr]Prolopa® levodopa and benserazide combination capsules 50-12.5, 100-25, 200-50 [product monograph]. Burlington (ON): Hoffman-La Roche; 2015 Jul 3.

45. Clinical trial report [protocol no. sp513]: A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and ropinerole-controlled trial of the efficacy and safety of the rotigotine CDS patch in subjects with early-stage idiopathic Parkinson's disease (part I) (the open-label extension of the trial [part II] will be reported separately) [**CONFIDENTIAL** internal manufacturer's report]. Research Triangle Park (NC): Schwarz Biosciences; 2004.

46. Clinical trial report [protocol no. SP516]: A multi-center, multinational, phase 3, open-label extension trial to assess the safety and efficacy of rotigotine patch in subjects with advanced-stage, idiopathic Parkinson's disease who are not well controlled on levodopa [**CONFIDENTIAL** internal manufacturer's report]. Research Triangle Park (NC): Schwarz Biosciences; 2008.

47. Chaudhuri KR, Martinez-Martin P. Clinical assessment of nocturnal disability in Parkinson's disease: the Parkinson's Disease Sleep Scale. Neurology. 2004 Oct 26;63(8 Suppl 3):S17-S20.

48. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01631812, a long term extension trial from late phase II of SPM 962 in advanced Parkinson's disease patients; 2015 [cited 2015 Jul 31]. Available from: https://clinicaltrials.gov/ct2/show/NCT01631812?term=243-06-001&rank=1

49. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 -. Identifier NCT01628848, a placebo-controlled dose-finding study for SPM 962 in advanced Parkinson's disease patients with concomitant treatment of L-dopa; 2014 Feb 3 [cited 2015 Aug 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT01628848?term=243-05-001&rank=2

50. UCB Canada Inc. response to July 29 2015 CDR request for additional information regarding the Neupro resubmission CDR review: information on Nomoto 2014 and Mizuno 2014 [**CONFIDENTIAL** additional manufacturer's information]. Oakville (ON): UCB Canada Inc.; 2015 Aug 4.

51. UCB Canada Inc. response to July 28th 2015 CDR request for additional information regarding the Neupro resubmission CDR review: information on Nomoto 2014 [**CONFIDENTIAL** additional manufacturer's information]. Oakville (ON): UCB Canada Inc.; 2015 Aug 6.

52. UCB Canada Inc. response to August 7th 2015 CDR request for additional information regarding the Neupro resubmission CDR review: information on active comparator trial Mizuno 2014. [**CONFIDENTIAL** additional manufacturer's information]. Oakville (ON): UCB Canada Inc.; 2015 Aug 11.

53. Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. Mov Disord. 2003 Jul;18(7):738-50.

54. Hauser RA, Auinger P, Parkinson Study Group. Determination of minimal clinically important change in early and advanced Parkinson's disease. Mov Disord. 2011 Apr;26(5):813-8.

55. Hauser RA, Gordon MF, Mizuno Y, Poewe W, Barone P, Schapira AH, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis [Internet]. 2014 [cited 2015 Aug 21];2014:467131. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995302

56. Schrag A, Sampaio C, Counsell N, Poewe W. Minimal clinically important change on the unified Parkinson's disease rating scale. Mov Disord. 2006 Aug;21(8):1200-7.

57. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol. 2010 Jan;67(1):64-70.

58. Trenkwalder C, Kohnen R, Hogl B, Metta V, Sixel-Doring F, Frauscher B, et al. Parkinson's disease sleep scale--validation of the revised version PDSS-2. Mov Disord. 2011 Mar;26(4):644-52.

59. Luo N, Tan LC, Zhao Y, Lau PN, Au WL, Li SC. Determination of the longitudinal validity and minimally important difference of the 8-item Parkinson's Disease Questionnaire (PDQ-8). Mov Disord. 2009 Jan 30;24(2):183-7.

60. Mizuno Y, Abe T, Hasegawa K, Kuno S, Kondo T, Yamamoto M, et al. Ropinirole is effective on motor function when used as an adjunct to levodopa in Parkinson's disease: STRONG study. Mov Disord. 2007 Oct 15;22(13):1860-5.

61. Clinical trial report [protocol no. sp650]: A multi-center, multinational, phase 3, randomized, double-blind, parallel group, placebo-controlled trial of the efficacy and safety of the rotigotine CDS patch (2 target doses) in subjects with advanced-stage Parkinson's disease who are not well controlled on levodopa (part I) [**CONFIDENTIAL** internal manufacturer's report]. Research Triangle Park (NC): Schwarz Biosciences; 2005.

62. Barone P, Lamb J, Ellis A, Clarke Z. Sumanirole versus placebo or ropinirole for the adjunctive treatment of patients with advanced Parkinson's disease. Mov Disord. 2007 Mar 15;22(4):483-9.

63. Guttman M. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurology. 1997 Oct;49(4):1060-5.

64. Mizuno Y, Yanagisawa N, Kuno S, Yamamoto M, Hasegawa K, Origasa H, et al. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. Mov Disord. 2003 Oct;18(10):1149-56.

65. UCB Canada Inc. response to July 29 2015 CDR request for additional information regarding the Neupro resubmission CDR review: information on non-inferiority margin Mizuno 2014. [**CONFIDENTIAL** additional manufacturer's information]. Oakville (ON): UCB Canada Inc.; 2015 Aug 4.

66. Press release: EMEA recommends changes in the storage conditions for Neupro (rotigotine) [Internet]. London: European Medicines Agency; 2008 Jun 4. [cited 2015 Aug 4]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500008895.pdf

67. Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. [London]: The Cochrane Collaboration; 2011 Mar. [cited 2015 Jul 28]. Available from: http://handbook.cochrane.org/

68. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010 Aug;63(8):e1-37.

69. Pond GR. Statistical issues in the use of dynamic allocation methods for balancing baseline covariates. Br J Cancer [Internet]. 2011 May 24 [cited 2015 Aug 21];104(11):1711-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3111167

70. Brown S, Thorpe H, Hawkins K, Brown J. Minimization--reducing predictability for multi-centre trials whilst retaining balance within centre. Stat Med. 2005 Dec 30;24(24):3715-27.

71. Berkman ND, Santaguida PL, Viswanathan M, Morton SC. The empirical evidence of bias in trials measuring treatment differences [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Sep. (AHRQ Methods for Effective Health Care). Report No.: 14-EHC050-EF. [cited 2015 Aug 21]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK253181/

72. Christensen E. Methodology of superiority vs. equivalence trials and non-inferiority trials. J Hepatol. 2007 May;46(5):947-54.

73. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials [Internet]. 2011 [cited 2015 Aug 21];12:106. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113981

74. Cawello W, Kim SR, Braun M, Elshoff JP, Masahiro T, Ikeda J, et al. Pharmacokinetics, safety, and tolerability of rotigotine transdermal system in healthy Japanese and Caucasian subjects following multiple-dose administration. Eur J Drug Metab Pharmacokinet. 2015 Mar 13.

75. Cawello W, Kim SR, Braun M, Elshoff JP, Ikeda J, Funaki T. Pharmacokinetics, safety and tolerability of rotigotine transdermal patch in healthy Japanese and Caucasian subjects. Clin Drug Invest [Internet]. 2014 Feb [cited 2015 Aug 21];34(2):95-105. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3899448

76. Kimura M, Ieiri I, Mamiya K, Urae A, Higuchi S. Genetic polymorphism of cytochrome P450s, CYP2C19, and CYP2C9 in a Japanese population. Ther Drug Monit. 1998 Jun;20(3):243-7.

77. Ota T, Kamada Y, Hayashida M, Iwao-Koizumi K, Murata S, Kinoshita K. Combination analysis in genetic polymorphisms of drug-metabolizing enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A5 in the Japanese population. Int J Med Sci [Internet]. 2015 [cited 2015 Aug 21];12(1):78-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278879

78. Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry [Internet]. 2004 Apr [cited 2015 Aug 21];75(4):637-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1739032

79. UCB Canada Inc. response to July 28 2015 CDR request for additional information for the NEUPRO CDR review: Nomoto 2014 (Questions #4, #7) and Nomoto extension study 243-06-001 (Question #6) [**CONFIDENTIAL** additional manufacturer's information]. Oakville (ON): UCB Canada Inc.; 2015 Aug 5.

80. Suzuki K, Miyamoto M, Miyamoto T, Tatsumoto M, Watanabe Y, Suzuki S, et al. Nocturnal disturbances and restlessness in Parkinson's disease: using the Japanese version of the Parkinson's disease sleep scale-2. J Neurol Sci. 2012 Jul 15;318(1-2):76-81.

81. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: development and validation of a short-form parkinson's disease questionnaire. Psychology & Health. 1997;12(6):805-14.

82. Reichmann H, Odin P, Brecht HM, Koster J, Kraus PH. Changing dopamine agonist treatment in Parkinson's disease: experiences with switching to pramipexole. J Neural Transm Suppl. 2006;(71):17-25.

83. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Drug Approval Package Requip/Ropinirole Hydrochloride [Internet]. In: Requip/Ropinirole Hydrochloride. Company: SmithKline Beecham. Application no.: 20658. Approval date: 09/09/1997. Rockville (MD): FDA; 2007 [cited 2015 Aug 10]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020658_requip_toc.cfm.

84. LeWitt PA, Boroojerdi B, MacMahon D, Patton J, Jankovic J. Overnight switch from oral dopaminergic agonists to transdermal rotigotine patch in subjects with Parkinson disease. Clin Neuropharmacol. 2007 Sep;30(5):256-65.

85. Thorlund K, Wu P, Druyts E, Eapen S, Mills EJ. Nonergot dopamine-receptor agonists for treating Parkinson's disease - a network meta-analysis. Neuropsychiatr Dis Treat [Internet]. 2014 [cited 2015 Jun 24];10:767-76. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019622/pdf/ndt-10-767.pdf

86. Zhou CQ, Lou JH, Zhang YP, Zhong L, Chen YL, Lu FJ, et al. Long-acting versus standard non-ergolinic dopamine agonists in Parkinson's disease: a meta-analysis of randomized controlled trials. CNS Neurosci Ther. 2014 Apr;20(4):368-76.

87. Stowe R, Ives N, Clarke CE, Deane K, van Hilten, Wheatley K, et al. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications. Cochrane Database Syst Rev. 2010;(7):CD007166.

88. Stowe R, Ives N, Clarke CE, Handley K, Furmston A, Deane K, et al. Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease. Mov Disord. 2011 Mar;26(4):587-98.

89. Antonini A, Bauer L, Dohin E, Oertel WH, Rascol O, Reichmann H, et al. Effects of rotigotine transdermal patch in patients with Parkinson's disease presenting with non-motor symptoms - results of a double-blind, randomized, placebo-controlled trial. Eur J Neurol. 2015 Jun 22.

90. Korczyn AD, Thalamas C, Adler CH. Dosing with ropinirole in a clinical setting. Acta Neurol Scand. 2002 Oct;106(4):200-4.

91. Kim JM, Chung SJ, Kim JW, Jeon BS, Singh P, Thierfelder S, et al. Rotigotine transdermal system as add-on to oral dopamine agonist in advanced Parkinson's disease: an open-label study. BMC Neurol [Internet]. 2015 [cited 2015 Jun 24];15:17. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364324/pdf/12883_2015_Article_267.pdf

92. Reichmann H, Herting B, Miller A, Sommer U. Switching and combining dopamine agonists. J Neural Transm. 2003 Dec;110(12):1393-400.

93. Chitnis S, Jaffery M, Dewey RB. Outcomes from switching from rotigotine patch to alternate therapies in Parkinson's disease. Int J Neurosci. 2012 Jan;122(1):22-5.

94. Clinical trial report [protocol no. sp515]: A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and pramipexole-controlled trial of the efficacy and safety of the rotigotine patch in subjects with advance-stage Parkinson's disease who are not well controlled on levodopa [**CONFIDENTIAL** internal manufacturer's report]. Research Triangle Park (NC): Schwarz Biosciences; 2006.

95. Nicholas AP, Borgohain R, Chana P, Surmann E, Thompson EL, Bauer L, et al. A randomized study of rotigotine dose response on 'off' time in advanced Parkinson's disease. J Parkinsons Dis [Internet]. 2014 [cited 2015 Jul 22];4(3):361-73. Available from: http://content.iospress.com/download/journal-of-parkinsons-disease/jpd130320?id=journal-of-parkinsons-disease%2Fjpd130320

96. Chung SJ, Kim JM, Kim JW, Jeon BS, Singh P, Thierfelder S, et al. Switch from oral pramipexole or ropinirole to rotigotine transdermal system in advanced Parkinson's disease: an open-label study. Expert Opin Pharmacother. 2015 May;16(7):961-70.

97. Kim BH, Yu KS, Jang IJ, Soo LK, Kim JR, Elshoff JP, et al. Pharmacokinetic properties and tolerability of rotigotine transdermal patch after repeated-dose application in healthy korean volunteers. Clin Ther. 2015 Apr 1;37(4):902-12.

98. Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. Arch Neurol. 2003 Dec;60(12):1721-8.

99. Mizuno Y, Nomoto M, Kondo T, Hasegawa K, Murata M, Takeuchi M, et al. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Mov Disord. 2013 Sep;28(10):1447-50.

100. Fahn S, Elton R, Members of the UPDRS Development Committee. Unified Parkinson's Rating Scale. In: Recent developments in Parkinson's disease. Florham Park (NJ): MacMillan Health Care Information; 1987. p. 153-63, 292-304.

101. Hauser RA, Deckers F, Lehert P. Parkinson's disease home diary: further validation and implications for clinical trials. Mov Disord. 2004 Dec;19(12):1409-13.

102. Suzuki K, Miyamoto T, Miyamoto M, Suzuki S, Numao A, Watanabe Y, et al. Evaluation of cutoff scores for the Parkinson's disease sleep scale-2. Acta Neurol Scand. 2015 Jun;131(6):426-30.

103. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967 May;17(5):427-42.

104. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004 Sep;19(9):1020-8.

105. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002 Sep;17(5):867-76.

106. Siderowf A, McDermott M, Kieburtz K, Blindauer K, Plumb S, Shoulson I, et al. Test-retest reliability of the unified Parkinson's disease rating scale in patients with early Parkinson's disease: results from a multicenter clinical trial. Mov Disord. 2002 Jul;17(4):758-63.

107. Forjaz MJ, Martinez-Martin P. Metric attributes of the unified Parkinson's disease rating scale 3.0 battery: part II, construct and content validity. Mov Disord. 2006 Nov;21(11):1892-8.

108. Seidel SE, Tilley BC, Huang P, Palesch YY, Bergmann KJ, Goetz CG, et al. Subject-investigator reproducibility of the Unified Parkinson's Disease Rating Scale. Parkinsonism Relat Disord [Internet]. 2012 Mar [cited 2015 Aug 21];18(3):230-3. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288816

109. Goetz CG, Stebbins GT. Assuring interrater reliability for the UPDRS motor section: utility of the UPDRS teaching tape. Mov Disord. 2004 Dec;19(12):1453-6.

110. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. 1995 Jun;4(3):241-8.

111. Katsarou Z, Bostantjopoulou S, Peto V, Kafantari A, Apostolidou E, Peitsidou E. Assessing quality of life in Parkinson's disease: can a short-form questionnaire be useful? Mov Disord. 2004 Mar;19(3):308-12.

112. Jenkinson C, Fitzpatrick R. Cross-cultural evaluation of the short form 8-item Parkinson's Disease Questionnaire (PDQ-8): results from America, Canada, Japan, Italy and Spain. Parkinsonism Relat Disord. 2007 Feb;13(1):22-8.

113. Huang TT, Hsu HY, Wang BH, Chen KH. Quality of life in Parkinson's disease patients: validation of the Short-Form Eight-item Parkinson's Disease Questionnaire (PDQ-8) in Taiwan. Qual Life Res. 2011 May;20(4):499-505.

114. Tan LC, Lau PN, Au WL, Luo N. Validation of PDQ-8 as an independent instrument in English and Chinese. J Neurol Sci. 2007 Apr 15;255(1-2):77-80.

115. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry [Internet]. 2002 Dec [cited 2015 Aug 21];73(6):629-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1757333

116. Uemura Y, Nomura T, Inoue Y, Yamawaki M, Yasui K, Nakashima K. Validation of the Parkinson's disease sleep scale in Japanese patients: a comparison study using the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale and Polysomnography. J Neurol Sci. 2009 Dec 15;287(1-2):36-40.

117. Pellecchia MT, Antonini A, Bonuccelli U, Fabbrini G, Ferini SL, Stocchi F, et al. Observational study of sleep-related disorders in Italian patients with Parkinson's disease: usefulness of the Italian version of Parkinson's disease sleep scale. Neurol Sci. 2012 Jun;33(3):689-94.

118. Hogl B, Arnulf I, Comella C, Ferreira J, Iranzo A, Tilley B, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. Mov Disord. 2010 Dec 15;25(16):2704-16.

119. Martinez-Martin P, Visser M, Rodriguez-Blazquez C, Marinus J, Chaudhuri KR, van Hilten JJ, et al. SCOPA-sleep and PDSS: two scales for assessment of sleep disorder in Parkinson's disease. Mov Disord. 2008 Sep 15;23(12):1681-8.

120. Wang G, Cheng Q, Zeng J, Bai L, Liu GD, Zhang Y, et al. Sleep disorders in Chinese patients with Parkinson's disease: validation study of a Chinese version of Parkinson's disease sleep scale. J Neurol Sci. 2008 Aug 15;271(1-2):153-7.

121. Horvath K, Aschermann Z, Acs P, Deli G, Janszky J, Karadi K, et al. Test-retest validity of Parkinson's disease sleep scale 2nd version (PDSS-2). J Parkinsons Dis. 2014;4(4):687-91.

122. Elmer LW, Surmann E, Boroojerdi B, Jankovic J. 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. 2012 Jun;18(5):488-93.

123. Giladi N, Boroojerdi B, Surmann E. The safety and tolerability of rotigotine transdermal system over a 6-year period in patients with early-stage Parkinson's disease. J Neural Transm. 2013 Sep;120(9):1321-9.

124. LeWitt PA, Boroojerdi B, Surmann E, Poewe W, SP716 Study Group, SP715 Study Group. 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 [Internet]. 2013 Jul [cited 2015 Aug 21];120(7):1069-81. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3687107

125. Clinical trial report [protocol no. SP512OL]: A multi-center, multinational, phase III, randomized, double-blind, placebo-controlled trial, of the efficacy and safety of the rotigotine CDS patch in subjects with early stage idiopathic Parkinson's disease (part I) and an open-label extension to assess the safety of long-term treatment of rotigotine CDS (part II) [**CONFIDENTIAL** internal manufacturer's report]. Research Triangle Park (NC): Schwarz Biosciences; 2010 Feb 3.

126. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. JAMA. 2000 Oct 18;284(15):1931-8.

127. Clinical Study Report: 243-06-001. A long-term extension study of 243-05-001 study for SPM 962 in patient with advanced Parkinson's disease with concomitant use of L-dopa [**CONFIDENTIAL** internal manufacturer's report]. Osaka: Otsuka Pharmaceutical Co.; 2010 Jun 30.

128. Trenkwalder C, Kies B, Dioszeghy P, Hill D, Surmann E, Boroojerdi B, et al. Rotigotine transdermal system for the management of motor function and sleep disturbances in Parkinson's disease: results from a 1-year, open-label extension of the RECOVER study. Basal Ganglia. 2012;2:79-85.

129. Thorlund K, Mills E. Multiple treatment comparison meta-analysis Neupro (rotigotine) versus other non-ergolinic dopamine receptor agonists for the treatment of Parkinson's disease. In: CDR submission binder: Neupro (rotigotine) transdermal system (patch); Company: UCB Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): UCB Canada Inc.; 2013 Jul.

130. Adler CH, Sethi KD, Hauser RA, Davis TL, Hammerstad JP, Bertoni J, et al. Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group. Neurology. 1997 Aug;49(2):393-9.

131. Mizuno Y, Kozul TK, Hasegawa K, Murata M, Hattori N, Nomoto M, et al. A randomized, double-blind, double-dummy, placebo- and ropinirole-controlled trial of rotigotine in patients with advanced Parkinson's disease in Japan. Abstract presented at: 15th International Congress of Parkinson's Disease and Movement Disorders; 2011 Jun; Toronto.

132. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.

133. Lambert PC, Sutton AJ, Burton PR, Abrams KR, Jones DR. How vague is vague? A simulation study of the impact of the use of vague prior distributions in MCMC using WinBUGS. Stat Med. 2005 Aug 15;24(15):2401-28.