Common Drug Review
Clinical Review Report

November 2016

Drug	rotigotine (Neupro) (transdermal patch)
Indication	Treatment of the signs and symptoms of idiopathic Parkinson disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa
Reimibursement request	List with similar criteria as pramipexole and ropinirole
Manufacturer	UCB Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in neurology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
APD	advanced Parkinson disease
COMT	catechol-O-methyltransferase
CI	confidence interval
EPD	early Parkinson disease
EQ-5D	EuroQol 5-dimensional scale
EU	European Union
FAS	full analysis set
HRQoL	health-related quality of life
LOCF	last observation carried forward
LS	least squares
MAO-A	monoamine oxidase A
MAO-B	monoamine oxidase B
MCID	minimal clinically important difference
MMSE	Mini Mental State Examination
NMA	network meta-analysis
NMDA	N-methyl-D-aspartate
PPS	per-protocol set
PD	Parkinson disease
PDHD	Parkinson disease home diaries
PDQ-39	Parkinson Disease Questionnaire 39
PDSS	Parkinson Disease Sleep Scale
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
UPDRS	Unified Parkinson's Disease Rating Scale
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Parkinson disease (PD) is a chronic and progressive neurodegenerative disorder, characterized by postural instability, tremor, rigidity, and slowness of movement.[1,2] Parkinson disease results from the death of the dopamine-containing cells of the substantia nigra,[3] and with no single known cause of PD, diagnosis based on etiology is unfeasible.[2] Rotigotine is a non-ergolinic dopamine agonist for the treatment of signs and symptoms of PD and idiopathic restless legs syndrome.[4] Rotigotine is currently available in the following transdermal patch doses in Canada: 2 mg per 24 hours, 4 mg per 24 hours, 6 mg per 24 hours, and 8 mg per 24 hours.[4] Rotigotine is applied once a day and should remain on the skin for 24 hours. In Canada, the maximum recommended dose for early Parkinson disease (EPD) is 8 mg per 24 hours and 16 mg per 24 hours for advanced Parkinson disease (APD). Multiple patches may be used to achieve doses higher than 8 mg per 24 hours.[4]

Indication under review
Treatment of the signs and symptoms of idiopathic Parkinson disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Listing criteria requested by sponsor
List in a similar manner to pramipexole and ropinirole.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of rotigotine for the treatment of the signs and symptoms of idiopathic PD.

Results and Interpretation

Included Studies

Four phase 3, multi-centre, randomized, parallel group, double-blind controlled studies met the inclusion criteria for this systematic review; two studies were conducted in patients with EPD[5,6] and two were conducted in patients with APD.[7,8]

SP512[5] (N = 277), a two-arm study, evaluated the efficacy and safety of rotigotine transdermal patches (starting at a dose of 2 mg per 24 hours titrated weekly up to 6 mg per 24 hours) compared with placebo transdermal patches over a duration of 38 weeks in patients with EPD. SP513[6] (N = 561), a three-arm study, evaluated the efficacy and safety of rotigotine transdermal patches, starting at a dose of 4 mg per 24 hours titrated weekly up to 8 mg per 24 hours, compared with placebo transdermal patches or capsules or ropinirole capsules (starting at a dose of 0.75 mg per day titrated to 24.0 mg per day) over a duration of 48 weeks in EPD patients. Rotigotine was assessed for superiority versus placebo and for non-inferiority compared with ropinirole in this study. SP515[7] (N = 506), a three-arm study, evaluated the efficacy and safety of rotigotine transdermal patches (starting at a dose of 4 mg per 24 hours titrated weekly up to 16 mg per 24 hours), compared with placebo transdermal patches or capsules or pramipexole capsules (starting at a dose of 0.375 mg per day titrated to 4.5 mg per day) over a duration of 32 weeks in patients with APD. Rotigotine was assessed for superiority versus placebo and for non-inferiority compared with pramipexole in this study. Lastly, SP650[8] (N = 351), a three-arm study, evaluated the efficacy and safety of rotigotine transdermal patches (target doses of 8 mg per 24 hours and 12 mg per 24 hours) compared with placebo transdermal patches for 38 weeks in APD patients. In

all included studies, two primary end points were used: a continuous end point for a US marketing application and a dichotomized response end point for a European Union marketing application. The primary outcomes in both EPD studies were change in Unified Parkinson's Disease Rating Scale (UPDRS) subscale score (parts II and III) from baseline visit to the end of the double-blind maintenance phase and response to therapy, defined as a ≥ 20% reduction in UPDRS (parts II and III) subtotal scores from baseline to end of maintenance. The primary outcomes in both APD studies were change in absolute time spent "off" from baseline to the end of the maintenance phase and response to therapy, defined as a ≥ 30% reduction in absolute "off" time from baseline to end of maintenance.

Efficacy

In the EPD studies, rotigotine was statistically significantly superior to placebo for changes in UPDRS subscale scores (parts II and III) from baseline to the end of the maintenance phase, with between-group mean differences of –5.28 (95% confidence interval [CI], −7.60 to −2.96) points in SP512 and –4.49 (95% CI, −6.64 to −2.35) points in SP513. A higher proportion of patients achieved a response to therapy (i.e., ≥ 20% reduction in UPDRS [parts II and III] subtotal scores from baseline to end of maintenance) with rotigotine (SP512: 48%; SP513: 52%) versus placebo (SP512: 19%; SP513: 30%), with between-group differences of 28.7% (95% CI, 18.0 to 39.4) in SP512 and 21.7% (95% CI, 11.1 to 32.4) in SP513. When compared with ropinirole in SP513, rotigotine did not demonstrate non-inferiority for both changes in UPDRS (parts II and III) and response to therapy. Results of this study were limited, as the clinical expert involved in this review noted that the ropinirole dose used was higher than would usually be used in practice for patients with EPD; hence, the comparison between rotigotine and ropinirole was not conducted using clinically similar doses.

Health-related quality of life in the EPD studies was evaluated using solely the visual analogue scale (VAS) portion of the EuroQol 5-dimensional scale (EQ-5D) questionnaire. Results were analyzed descriptively, with no between-group comparisons. Without a comparison to a control group, within-group change is difficult to interpret.

In the APD studies, rotigotine was statistically significantly superior to placebo for changes in time spent "off" from baseline to the end of the maintenance phase, with between-group mean differences of −1.58 (95% CI, −2.27 to −0.90) hours in SP515, and −1.8 (95% CI, –2.6 to –1.0) hours and –1.2 (95% CI, –2.0 to –0.4) hours among the rotigotine 8 mg per 24 hours and 12 mg per 24 hours groups versus placebo, respectively, in SP650. Rotigotine was statistically significantly superior to placebo for response to therapy (i.e., ≥ 30% reduction in absolute "off" time from baseline to end of maintenance). Sixty per cent of rotigotine-treated patients were responders versus 35% for placebo (between-group difference: 24.7% [95% CI, 13.2 to 36.3]) in SP515. Similarly, 57% and 55% of patients treated with rotigotine 8 mg per 24 hours and 12 mg per 24 hours, respectively, responded to treatment compared with 34% for placebo in SP650 (between-group differences: 22.2% [95% CI, 9.7 to 34.7] and 20.6% [95% CI, 7.9 to 33.3], respectively). In SP515, rotigotine demonstrated non-inferiority to pramipexole for changes in absolute "off" time (between-group mean difference of 0.44 hours [[95% CI, 0.15 to 1.03]; non-inferiority margin of 1.2), but not for difference in response to therapy (between-group difference: –7.3% [95% CI, –16 to 2.1]; non-inferiority margin of –15%).

In the APD studies, health-related quality of life was evaluated using the Parkinson Disease Questionnaire (PDQ-39) in SP515 and the EQ-5D in SP650. Similar to the EPD studies, results were analyzed descriptively, with no between-group comparisons. In SP515, PDQ-39 single index scores were −2.1 points, −5.0 points, and −6.1 points for the placebo, rotigotine, and pramipexole groups, respectively. In SP650, the mean change was –1.2 points, 4.3 points, and 3.6 points on the EQ-5D VAS

health state score for the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively. Nocturnal sleep was evaluated and analyzed descriptively with no between-group comparisons in SP515. There were improvements in nocturnal sleep in the rotigotine and pramipexole groups, with mean changes in Parkinson Disease Sleep Scale sum scores of 4.4 and 4.8, respectively, while the mean change in the placebo group was –2.9. Patient satisfaction was not measured in any of the included studies. Compliance (defined as > = 85% and < 115% compliant with dosing schedule) was high and similar among all treatment groups in all included studies, ranging from 93% to 100% among all treatment groups in the EPD studies and 93% to 98% in all treatment groups in the APD studies. The method used to assess compliance may not be the most accurate approach, as unreturned medication may not necessarily mean that the medication was used.

Harms

In all studies, the overall frequency of adverse events was generally high between-treatment groups: 77% to 90% and 66% to 93% among all treatment groups in the EPD and APD studies, respectively. The most common adverse event was application site reactions, which was most common in the rotigotine groups compared with placebo (38 % to 44% versus 11% to 12%, respectively, in the EPD studies and 21% to 46% versus 10% to 13%, respectively, in the APD studies). Serious adverse events occurred in fewer than 10% of patients treated with rotigotine, compared with fewer than 9% for placebo across all studies. Withdrawals due to adverse events generally occurred in a greater proportion of patients in the active treatment groups, most frequently because of application site reaction with rotigotine in the EPD studies, while reasons for withdrawals due to adverse events in the APD studies varied. Notable harms such as arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy occurred in fewer than 3% of patients in any treatment group across studies, and did not appear to differ between rotigotine and comparator treatment groups.

Pharmacoeconomic Summary

Rotigotine (Neupro) is a transdermal delivery system (patch) available in the following strengths: 2 mg per 24 hours, 4 mg per 24 hours, 6 mg per 24 hours, and 8 mg per 24 hours. The manufacturer submitted the following prices: $3.54 (2 mg), $6.50 (4 mg), and $7.27 (6 mg and 8 mg) per patch, or $3.54 to $7.27 per day for the treatment of EPD and $6.50 to $14.54 per day for APD. The manufacturer submitted a cost-minimization analysis, considering only drug costs, based on the assumption of similar efficacy among rotigotine, pramipexole, and ropinirole from the results of a network meta-analysis. The NMA showed that, for both EPD and APD, the efficacy of rotigotine, ropinirole, and pramipexole appeared similar at 11 to 16 weeks and 24 to 28 weeks after completion of the titration period. It is unclear if the findings of the NMA can be generalized to a longer time period, or to a population using different doses than those used in the clinical trials. Furthermore, the NMA did not assess the comparative safety profile of rotigotine with that of pramipexole and ropinirole.

At recommended doses, rotigotine (2 mg per 24 hours to 8 mg per 24 hours in EPD, and 4 mg per 24 hours to 16 mg per 24 hours in APD) is more expensive than generic pramipexole (1.5 mg to 4.5 mg daily, $0.79 to $2.37 per patient per day) and generic ropinirole (3 mg to 24 mg daily, $0.85 to $4.37 per patient per day), as well as other drugs used for the treatment of EPD and APD, such as oral levodopa-decarboxylase inhibitor combinations ($0.84 to $8.00 per patient per day), entacapone ($0.40 to $3.21 per patient per day), or monoamine oxidase B inhibitors ($1.00 to $7.00 per patient per day). Consequently, the listing of rotigotine would result in additional costs.

The expected average maintenance doses of rotigotine used in the manufacturer's base-case scenario were likely underestimated, especially in APD. A Common Drug Review analysis showed that the price of

rotigotine would need to be reduced by 51% to 88% to be equal to the average daily cost of generic pramipexole in EPD, and by 78% to 89% to be equal to the average daily cost of generic pramipexole in APD.

Conclusions

Based on two double-blind randomized controlled trials in patients with EPD, rotigotine resulted in statistically significant and clinically meaningful improvements in UPDRS subscale scores (parts II and III) and a greater proportion of responders when compared with placebo. The comparison of rotigotine with ropinirole failed to demonstrate non-inferiority and may have been limited by non-equivalence between rotigotine and ropinirole doses. Two double-blind randomized controlled trials in patients with APD also demonstrated statistically significant and clinically meaningful improvements in time spent "off" and a greater proportion of responders when patients were treated with rotigotine compared with placebo. The comparison of rotigotine with pramipexole was statistically non-inferior with regard to absolute differences in time spent "off," but not non-inferior for response to therapy. Without between-group comparisons, there is uncertainty regarding differences in health-related quality of life and nocturnal sleep between rotigotine and placebo or other active comparators (ropinirole and pramipexole). Compliance with study medication was high and similar in all treatment groups. Overall, rotigotine was generally well tolerated, though delivery of rotigotine with a transdermal patch was associated with application site reactions not experienced with oral dopamine agonists. The incidence of adverse events such as arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy with rotigotine did not appear to differ versus placebo, ropinirole, or pramipexole, although studies were not designed to identify between-group differences in these.

TABLE 1: SUMMARY OF RESULTS FOR EARLY PARKINSON DISEASE STUDIES

Outcome	SP512 (27 weeks)		SP513 (37 weeks)		
	Placebo (n = 96)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
UPDRS (Subtotal Part II and III) from Baseline to End of Maintenance Phase					
Baseline mean (SD)	30.0 (10.67)	29.9 (12.22)	31.3 (12.63)	33.2 (12.58)	32.2 (12.41)
LS mean change[a] (SE)	1.31 (0.96)	−3.98 (0.71)	−2.33 (0.88)	−6.83 (0.66)	−10.78 (0.64)
Rotigotine – placebo difference (95% CI)	−5.28 (−7.60 to −2.96)		−4.49 (−6.64 to −2.35)		
Ropinirole – placebo difference (95% CI)	NA		−8.45 (−10.57 to −6.34)		
Rotigotine – ropinirole difference[b] (95% CI)	NA		3.96 (2.18 to 5.73)		
Response to Therapy (%)					
Responders,[c] n (%)	18 (19)	84 (48)	35 (30)	110 (52)	155 (68)
Rotigotine – placebo difference (95% CI)	28.7 (18.0, to 39.4)		21.7 (11.1 to 32.4)		
Ropinirole – placebo difference (95% CI)	NA		38.4 (28.1 to 48.6)		

Outcome	SP512 (27 weeks)		SP513 (37 weeks)		
	Placebo (n = 96)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
Rotigotine – ropinirole difference[d] (95% CI)	NA		−16.6 (−25.7 to −7.6)		
EQ-5D Health State VAS Score from Baseline to End of Maintenance Phase					
Mean (SD) at baseline	[redacted]		[redacted]		
Mean change (SD)	[redacted]		[redacted]		
Median change (min, max)	[redacted]		[redacted]		
Compliance					
Compliant (patches) (> = 85% and < 115%), n/N (%)	96/96 (100)	177/180 (98)	116/118 (98)	207/215 (96)	213/227 (93)
Compliant (capsules) (> = 85% and < 115%), n/N (%)	NA		115/118 (97)	206/215 (96)	212/227 (93)
AEs					
n (%)	85 (89)	163 (90)	91 (77)	183 (85)	188 (82)
SAEs					
n (%)	4 (4)	13 (7)	10 (8)	22 (10)	29 (13)
WDAEs					
n (%)	6 (6)	25 (14)	6 (5)	37 (17)	29 (13)
Notable Harm(s), n (%)					
Arrhythmias	1 (1)	1 (< 1)	3 (3)	0	1 (< 1)
Impulsive/asocial behaviour	0	0	0	0	0
Sudden onset of sleep	0	2 (1)	0	6 (3)	4 (2)
Syncope	1 (1)	2 (1)	4(2)	2 (< 1)	7 (3)
Valvulopathy	0	0	0	0	0

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D = EuroQol 5-dimensional scale; LS = least squares; NA = not applicable; SAEs = serious adverse events; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analogue scale; WDAE = withdrawal due to adverse events.
[a]Adjusted for geographic region and baseline UPDRS by means of a main effects ANCOVA model.
[b]Test of non-inferiority with predefined non-inferiority margin (2.9).
[c]Participants with a 20% reduction or greater in UPDRS (II and III) subtotal from baseline to end of maintenance are "responders."
[d]Test of non-inferiority with predefined non-inferiority margin (–15%).

TABLE 2: SUMMARY OF RESULTS FOR ADVANCED PARKINSON DISEASE STUDIES

Outcome	SP515 (23 weeks)			SP650 (29 weeks)		
	Placebo N = 100	Rotigotine N = 201	Pramipexole N = 200	Placebo N = 119	Rotigotine 8 mg/ 24 hours N = 113	Rotigotine 12 mg/ 24 hours N = 109
Absolute "Off" Time (Hours/Day) from Baseline to End of Maintenance Phase						
Baseline mean (SD)	6.5 (2.8)	6.3 (2.5)	6.0 (2.5)	6.4 (2.6)	6.7 (2.5)	6.3 (2.6)
LS mean change[a] (SE)	–0.9 (0.29)	–2.5 (0.20)	–2.8 (0.20)	–0.9 (2.83)	–2.7 (0.32)	–2.1 (0.32)
Rotigotine – placebo difference (95% CI)	−1.58 (−2.27 to −0.90)			8 mg/24 hours −1.8 (–2.6 to –1.0) 12 mg/24 hours –1.2 (–2.0 to –0.4)		
Pramipexole – placebo difference (95% CI)	–1.94 (–2.63 to –1.25)			NA		
Rotigotine – Pramipexole difference[b] (95% CI)	0.35 (–0.21 to 0.92)			NA		
Response to Therapy[c] (%)						
Responders n (%)	35 (35)	120 (60)	134 (67)	41 (34)	64 (57)	60 (55)
Rotigotine – placebo difference (95% CI)	24.7 (13.2 to 36.3)			8 mg/24 hours 22.2 (9.7, to 34.7) 12 mg/24 hours 20.6 (7.9 to 33.3)		
Pramipexole – placebo difference (95% CI)	32.0 (20.6 to 43.4)			NA		
Rotigotine – Pramipexole difference[d] (95% CI)	–7.3 (–16.7 to 2.1)			NA		
EQ-5D Health State Score from Baseline to End of Maintenance Phase						
Mean (SD) at baseline	[redacted]			[redacted]	[redacted]	[redacted]
Mean change (SD)				[redacted]	[redacted]	[redacted]
Median change (min, max)				[redacted]	[redacted]	[redacted]
PDQ-39 Single Index Score Mean Change from Baseline Values						
Mean (SD) at baseline	34.8 (13.91)	32.9 (14.87)	32.9 (14.02	NA		
Mean change (SD)	–2.1 (9.52)	–5.0 (9.07)	–6.1 (9.45			
Median change (min, max)	–2.0 (–29.6 to 21.0)	–4.7 (–34.1 to 21.3)	–5.5 (–27.3 to 23.1)			

Outcome	SP515 (23 weeks)			SP650 (29 weeks)		
	Placebo N = 100	Rotigotine N = 201	Pramipexole N = 200	Placebo N = 119	Rotigotine 8 mg/ 24 hours N = 113	Rotigotine 12 mg/ 24 hours N = 109
Nocturnal Sleep (PDSS Sum Score) Mean Change from Baseline Values						
Mean (SD) at baseline	95.3 (22.48)	93.2 (24.44)	96.2 (22.99)	NA		
Mean change (SD)	–2.9 (21.78)	4.4 (21.07)	4.8 (19.30)			
Median change (min, max)	–2.9 (–86.8 to 62.1)	1.8 (–69.6 to 69.3)	3.6(–60.6 to 84.6)			
Compliance						
Compliant (patches) (> = 85% and < 115%), n/N (%)	92/99 (93)	196/205 (96)	195/202 (97)	113/120 (94)	116/118 (98)	108/111 (97)
Compliant (capsules) (> = 85% and < 115%), n/N (%)	92/99 (93)	194/205 (95)	189/202 (94)	NA		
AEs						
n (%)	65 (66)	141 (69)	140 (69)	109 (91)	110 (93)	103 (93)
SAEs						
n (%)	9 (9)	19 (9)	15 (7)	10 (8)	8 (7)	11 (10)
WDAEs						
n (%)	5 (5)	11 (5)	15 (7)	10 (8)	19 (16)	17 (15)
Notable Harm(s), n (%)						
Arrhythmias	3 (3)	4 (2)	6 (3)	1 (< 1)	1 (< 1)	0
Impulsive/asocial behaviour	0	0	1 (0.5)	0	0	1 (< 1)
Sudden onset of sleep	0	0	1 (<1)	0	0	1 (< 1)
Syncope	1 (1)	3 (2)	2 (1)	1 (< 1)	0	0
Valvulopathy	0	1 (< 1)	0	0	0	0

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D = EuroQol 5-dimensional scale; LS = least squares; PDQ-39 = Parkinson's Disease Questionnaire-39; PDSS = Parkinson's Disease Sleep Scale; SAEs = serious adverse events; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

[a]Adjusted for geographic region and baseline "time off" by means of a main effects ANCOVA model.

[b]Test of non-inferiority with predefined non-inferiority margin (1.2).

[c]Participants with a 30% reduction or greater in absolute "off" time from baseline to end of maintenance are "responders."

[d]Test of non-inferiority with predefined non-inferiority margin (–15%).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Parkinson disease (PD) is a chronic and progressive neurodegenerative disorder, resulting from death of the dopamine-containing cells of the substantia nigra,[3] and is characterized by postural instability, tremor, rigidity, and slowness of movement.[1,2] With no single known cause of PD, diagnosis is based on history of symptoms and neurologic examination by a neurologist.[2] Although Parkinson disease is predominantly a movement disorder, it has been associated with psychiatric, cognitive, and sleep complications, as well as autonomic disorders (e.g., hypotension).[3] Data from the Canadian Community Health Survey in 2004 revealed that the estimated population prevalence of PD in the community was 0.2%.[9] The majority (85%) of diagnosed patients are older than 65 years.[10]

1.2 Standards of Therapy

For the treatment of early Parkinson disease (EPD), dopamine agonists, levodopa, and monoamine oxidase B (MAO-B) inhibitors have been established as effective symptomatic treatment options.[2] Based on discussions with the clinical expert involved with the review, levodopa is the mainstay treatment for managing PD symptoms, regardless of severity. It is a precursor of dopamine that is converted to dopamine in the substantia nigra, thereby offsetting the deficit of dopamine. An alternative approach to treating PD involves using direct agonists of dopamine (i.e., pramipexole, ropinirole, rotigotine). Dopamine agonists have shown efficacy in improving PD symptoms with the advantage of longer duration of action (six to eight hours) compared with levodopa, which has a shorter half-life and has only three to four hours' duration of effectiveness.[2] Levodopa, therefore, is typically administered with decarboxylation inhibitors, such as carbidopa, to reduce levodopa decarboxylation in the periphery and thereby increase the amount of active drug reaching the central nervous system. Additionally, the clinical expert involved in the review noted that levodopa requires active dopamine neurons for conversion to active form. Therefore, as the disease progresses, leading to further neuron loss, the effectiveness of levodopa reduces. Hence, the addition of direct dopamine agonists may compensate for the progressive neurotransmitter shortfall. Dopamine agonists are typically titrated to a clinically efficacious dose and should be replaced by another agonist or drug from another class if titration is not possible due to adverse effects.

For the treatment of advanced Parkinson disease (APD), evidence suggests that pramipexole, ropinirole, entacapone, and rasagiline are able to reduce "off" time among patients with motor fluctuation despite receiving levodopa.[2] Modified-release levodopa preparations can reduce motor fluctuations among patients with APD. Surgical treatment can be an option for APD, usually through deep brain stimulation of the subthalamic nucleus to reduce motor fluctuations, dyskinesia, and medication usage.[2]

1.3 Drug

In Canada, rotigotine, a non-ergolinic dopamine agonist, has an approved indication for the treatment of signs and symptoms of PD and may be used both as monotherapy (i.e., treatment of early stage PD) and as a combination therapy with levodopa (i.e., treatment of advanced PD). Rotigotine is also approved for the symptomatic treatment of moderate to severe idiopathic restless leg syndrome in adults.[4] Rotigotine is currently available in the following transdermal patch doses in Canada: 2 mg per 24 hours, 4 mg per 24 hours, 6 mg per 24 hours, and 8 mg per 24 hours.[4] Rotigotine is applied once a day and should remain on the skin for 24 hours. In Canada, the maximum approved dose for EPD is 8 mg per 24 hours, and 16 mg per 24 hours for APD. Multiple patches may be used to achieve doses higher than 8 mg per 24 hours.[4] Although the exact mechanism of action of rotigotine for the treatment of PD is unknown, it is believed to increase activity of D_1, D_2, and D_3 dopamine receptors.

Indication under review
The treatment of the signs and symptoms of idiopathic Parkinson disease. Neupro may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.
Listing criteria requested by sponsor
List in a similar manner to pramipexole and ropinirole.

TABLE 3: KEY CHARACTERISTICS OF TREATMENTS USED IN INCLUDED EARLY PARKINSON DISEASE AND ADVANCED PARKINSON DISEASE STUDIES

	Rotigotine	Ropinirole	Pramipexole	Levodopa/ Carbidopa	Levodopa/ Benserazide
Mechanism of action	Non-ergolinic dopamine agonist for the treatment of signs and symptoms of Parkinson disease and idiopathic restless legs syndrome. It is believed to reduce the symptoms of Parkinson disease by increasing the activities of the D_3, D_2, and D_1 receptors of the caudate putamen in the brain.	Non-ergolinic dopamine agonist, which activates post-synaptic dopamine receptors.	Non-ergolinic dopamine agonist with high in vitro specificity at the D_2 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, which 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, which makes more levodopa available for transport to the brain.
Indication[a]	Treatment of the signs and symptoms of idiopathic Parkinson disease. 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 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 Parkinson disease. Can be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.	Treatment of Parkinson disease.	Treatment of Parkinson Disease, with the exception of drug-induced Parkinsonism.
Route of	Transdermal	Oral			

	Rotigotine	Ropinirole	Pramipexole	Levodopa/ Carbidopa	Levodopa/ Benserazide
administration					
Recommended dose	Transdermal system 1 mg/24 hours, 2 mg/24 hours 3 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, 8 mg/24 hours rotigotine. The recommended maximal dose for is 8 mg/24 hours for EPD, and 16 mg/24 hours 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 18 mg/day in patients receiving regular dialysis.	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 per day and is not recommended at the 6 mg per day dose as the incidence of some adverse reactions is higher.	Immediate release: tablets 100 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). 100 mg/25 mg (patients without prior levodopa therapy)	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.
Serious side effects/ safety issues	Sudden onset of sleep				

APD = Advanced Parkinson disease; EPD = Early Parkinson disease.
Source: Health Canada product monographs.[4,11-15]
[a]Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of rotigotine for the treatment of the signs and symptoms of idiopathic PD.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years of age) with idiopathic EPD and APD **Subgroups of Interest** • Patients with severe 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: • Dopamine agonists (pramipexole, ropinirole) • Levodopa[a] • Placebo APD (all in combination with levodopa[a]): • Dopamine agonists (pramipexole, ropinirole) • Entacapone • MAO-B inhibitors (rasagiline, selegiline) • Placebo
Outcomes	**Key Efficacy Outcomes** EPD: • UPDRS subscale score (parts II + III) • Response to therapy[b] • HRQoL measured with a validated scale • Compliance • 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 • Compliance • Patient's satisfaction with therapy • Nocturnal sleep **Other Efficacy Outcomes** • Motor symptoms (UPDRS III score only) • Activities of daily living (UPDRS II score only)

	Harms Outcomes • Mortality • AEs, SAEs, WDAEs • AEs of interest: arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy
Study Design	Published and unpublished double-blind RCTs ≥ 16 weeks in duration[d]

AEs = adverse events; APD = advanced Parkinson disease; DB = double blind; EPD = early Parkinson disease; GI = gastrointestinal; HRQoL = health-related quality of life; MAO-B = monoamine oxidase B; RCT = randomized controlled trial; SAEs = serious adverse events; WDAE = withdrawal due to adverse event; 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 and 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.
[d]Defined from start of dose titration phase to final end point assessment during the maintenance phase.

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 through Ovid; Embase (1974–) through 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 concept was rotigotine (Neupro).

No methodological filters were applied to limit retrieval to 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.

The initial search was completed on September 6, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on February 19, 2014. 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 Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters). 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 manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Figure 1; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in Figure 1.

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

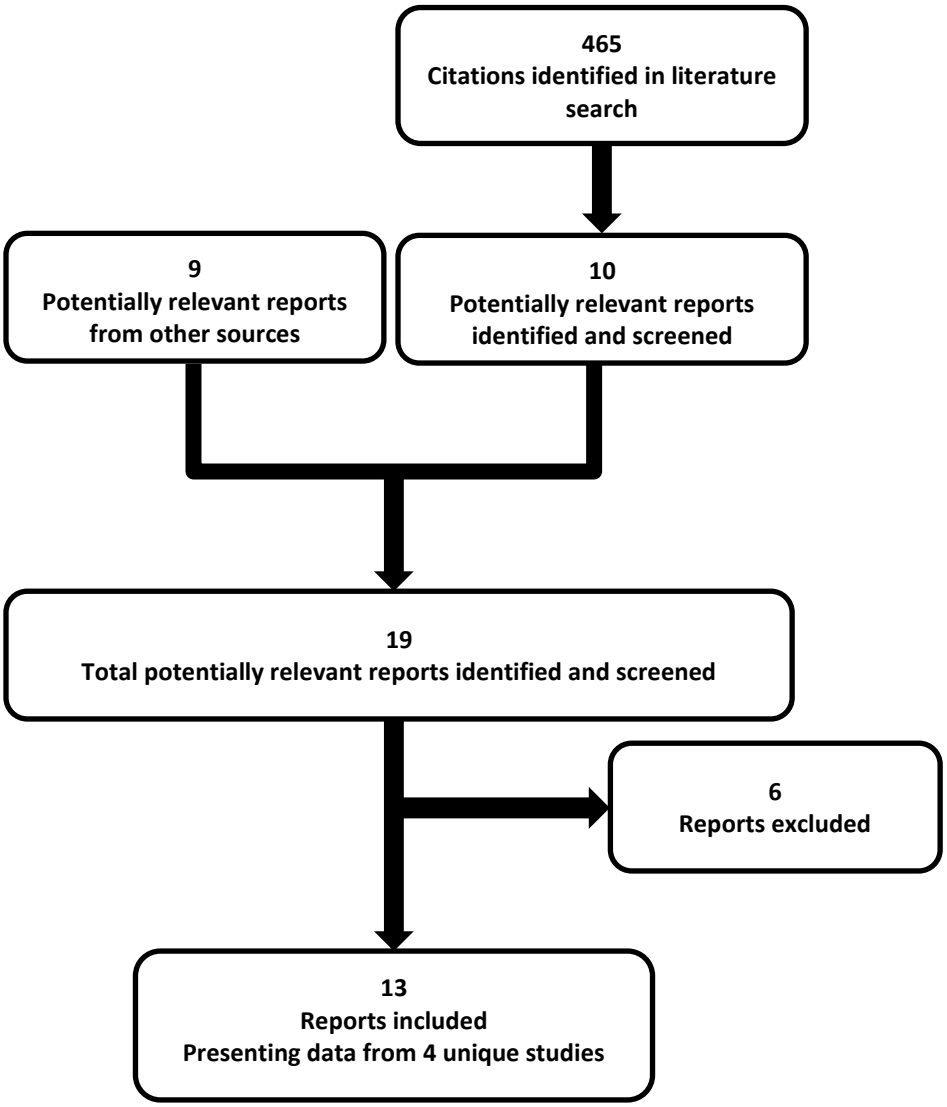


TABLE 5: DETAILS OF INCLUDED STUDIES FOR EARLY PARKINSON DISEASE STUDIES

		SP512	SP513
DESIGNS & POPULATIONS	Study design	DB RCT	DB RCT
	Locations	[redacted]	[redacted]
	Randomized (N)	277	561
	Inclusion criteria	• aged ≥ 30 years • diagnosed with idiopathic PD of ≤ 5 years in duration • had a UPDRS motor score (part III) of ≥ 10 at baseline • had a Hoehn and Yahr stage ≤ III • had at least 2 or more of the following cardinal signs: bradykinesia, resting tremor, rigidity, postural instability • were without any other known or suspected cause of Parkinsonism • if the participant had been receiving an anticholinergic drug, a MAO-B inhibitor, or an NMDA-antagonist, he/she must have been on a stable dose for at least 28 days prior to baseline and be maintained on that dose for the duration of the trial	• aged ≥ 30 years • diagnosed with idiopathic PD of ≤ 5 years in duration • had a UPDRS motor score (part III) of • ≥ 10 at baseline • had a Hoehn & Yahr stage ≤ III [redacted]
	Exclusion criteria	• had prior or concurrent therapy with a dopamine agonist within 28 days of the baseline visit • had prior therapy with carbidopa/levodopa within 28 days of baseline • had received carbidopa/levodopa for more than 6 months since diagnosis [redacted] • within 3 months prior to the baseline visit • had clinically relevant hepatic dysfunction • had clinically relevant renal dysfunction • had clinically relevant cardiac dysfunction and/or myocardial infarction within the last 12 months [redacted]	• had prior or concurrent therapy with a dopamine agonist within 28 days of the baseline visit • had prior therapy with carbidopa/levodopa within 28 days of baseline • had received carbidopa/levodopa for more than 6 months since diagnosis [redacted] • had clinically relevant hepatic dysfunction • had clinically relevant renal dysfunction • had clinically relevant cardiac dysfunction and/or myocardial infarction within the last 12 months • [redacted] the patient has an average QTc interval

		SP512	SP513
		[redacted] • was pregnant or nursing, or is of child-bearing potential but not surgically sterile or not using adequate birth control methods (including at least one barrier method) [redacted] • [redacted] • had a current diagnosis of epilepsy, has a history of seizures as an adult, has a history of stroke, or has had a transient ischemic attack within 1 year before pre-treatment [redacted]	• ≥ 450 msec for males and ≥ 470 msec for females at the baseline [redacted] • had a history of symptomatic orthostatic hypotension [redacted]

		SP512	SP513
DRUGS	Intervention	Rotigotine: 2 mg/24 hours, 4 mg/24 hours, and 6 mg/24 hours transdermal system (patch)	Rotigotine: 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours transdermal system (patch)
	Comparator(s)	Placebo transdermal patches	Placebo transdermal patches Placebo capsules Ropinirole: 0.75, 1.5, 2.25, 3.0, 4.5, 6.0, 7.5, 9.0, 12.0, 15.0, 18.0, 21.0 or 24.0 mg/day capsules PO
DURATION	Phase		
	Run-in	[redacted]	[redacted]
	Double-blind	[redacted]	[redacted]
	Follow-up	[redacted]	[redacted]
OUTCOMES	Primary end point	• [redacted] change in the sum of scores from the ADL and the Motor Examination sections in the UPDRS (parts II+III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase. • [redacted] participant's response to therapy. A "responder" was a patient with a 20% or greater decrease in the sum of scores from the ADL and Motor Examination sections in the UPDRS (parts II+III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase.	• [redacted] change in the sum of scores from the ADL and the Motor Examination sections in the UPDRS (parts II+III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase. • [redacted] participant's response to therapy. A "responder" was a patient with a 20% or greater decrease in the sum of scores from the ADL and Motor Examination sections in the UPDRS (parts II+III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase.
	Other end points	[redacted]	• change from the baseline visit to the end of the double-blind maintenance phase in UPDRS part II • change from the baseline visit to the end of the double-blind maintenance phase in UPDRS part III [redacted]
NOTES	Publications	Watts et al. 2007[16] Watts et al. 2007[17]	Giladi et al. 2007[18]

ADL = activities of daily living; COMT = catechol-O-methyltransferase; DB RCT = double-blind randomized controlled trial; MAO-B = monoamine oxidase B; msec = millisecond; NMDA = N-methyl-D-aspartate; PD = Parkinson disease; PO = oral; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Study SP512,[5] SP513.[6]
Note: 4 additional reports were included.[19-22]

TABLE 6: DETAILS OF INCLUDED STUDIES FOR ADVANCED PARKINSON DISEASE STUDIES

		SP515	SP650
DESIGNS & POPULATIONS	Study design	DB RCT	DB RCT
	Locations	Europe, [redacted] South Africa, Australia, New Zealand	US and Canada
	Randomized (N)	506	351
	Inclusion criteria	• aged ≥ 30 years (and ≤ 80 years in South Africa only) • diagnosed with idiopathic Parkinson disease for > 3 years, as defined by the cardinal sign bradykinesia, plus the presence of at least 1 of the following: resting tremor, rigidity, impairment of postural reflexes, and without any other known or suspected cause of Parkinsonism • Hoehn & Yahr stage II through IV in both the "on" and the "off" state and has an MMSE score of ≥ 25 • on stable dose of levodopa, either short-acting or sustained release (in combination with benserazide or carbidopa), for at least 28 days prior to baseline of at least 300 mg/day, administered in at least 3 intakes • [redacted]	• aged ≥ 30 years • diagnosed with idiopathic Parkinson disease for > 3 years, as defined by the cardinal sign bradykinesia, plus the presence of at least one of the following: resting tremor, rigidity, impairment of postural reflexes, and without any other known or suspected cause of Parkinsonism • Hoehn & Yahr stage II through IV in both the "on" and "off" state, and has MMSE score of ≥ 25 • on a stable dose of levodopa, either short-acting or sustained release (in combination with benserazide or carbidopa), for at least 28 days prior to baseline of at least 200 mg/day, administered in at least 2 intakes [redacted]
	Exclusion criteria	• suspicion of atypical Parkinsonism (multiple system atrophy, progressive supranuclear palsy, or other) • previous surgery for Parkinson disease • MMSE score < 25 • concurrent hallucination or psychosis • history of orthostatic hypotension 6 months before baseline • history of myocardial infarction over past 12 months.	[redacted]

		SP515	SP650
		• QTc interval > 450 msec (men) or > 470 msec (women) • history of skin hypersensitivity to adhesives or other transdermals • intake of investigational drug within 4 weeks before pre-treatment visit • concomitant treatment with dopamine agonists, MAO-A inhibitors, dopamine-releasing drugs, tolcapone, neuroleptics, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, or quinine to participate in the trial.	[redacted]
DRUGS	Intervention	Rotigotine: 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours, 10 mg/24 hours, 12 mg/24 hours, 14 mg/24 hours, 16 mg/24 hours transdermal system (patch)	Rotigotine: 8 mg/24 hours and 12 mg/24 hours transdermal system (patch)
	Comparator(s)	Placebo transdermal patches Placebo capsules Pramipexole: 0.375, 0.75, 1.5, 2.25, 3.0, 3.75, or 4.5 mg/day capsules PO	Placebo transdermal patches

		SP515	SP650
DURATION	Phase		
	Run-in	[redacted]	[redacted]
	Double-blind	[redacted]	[redacted]
	Follow-up	[redacted]	[redacted]
OUTCOMES	Primary end point	• change from baseline to end of the double-blind maintenance period in absolute time spent off, as assessed by patient diaries and patient's response to therapy. A "responder" was a patient with a 30% or more reduction in absolute off time from baseline to end of maintenance.	• change from baseline to end of treatment in absolute and relative time spent "off" • change in the sum of scores in UPDRS parts II, III, and IV during "on" periods from baseline to end of treatment
	Other end points	[redacted] • UPDRS II and III scores during on periods [redacted]	[redacted] • UPDRS II and III scores during on periods change from baseline to the end of the [redacted]
NOTES	Publications	Poewe et al. 2007[23]	LeWitt et al. 2007[24]

ADL = activities of daily living; COMT = catechol-O-methyltransferase; DB RCT = double-blind randomized controlled trial; L-DOPA = levodopa; MAO-A = monoamine oxidase A; MAO-B = monoamine oxidase B; MMSE = Mini Mental State Examination; msec = millisecond; PDQ-39 = Parkinson's Disease Questionnaire-39; PDSS = Parkinson's Disease Sleep Scale; PO = oral; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: SP515,[7] SP650.[8]

3.2 Included Studies

3.2.1 Description of Studies

a) Early Parkinson Disease

For EPD, two phase 3, multi-centre, randomized, parallel group, double-blind, controlled studies met the inclusion criteria for this systematic review. SP512 (N = 277), a two-arm superiority study, evaluated the efficacy and safety of rotigotine transdermal patches, starting at a dose of 2 mg per 24 hours and titrated weekly up to 6 mg per 24 hours, compared with placebo transdermal patches over a duration of 38 weeks (four-week pre-treatment washout period, a three-week dose-escalation period, a 24-week dose-maintenance period, and a four-week follow-up period). Participants were randomized in a 2:1 ratio to receive either rotigotine or placebo. SP512 consisted of 12 visits: pre-treatment (visit 1), baseline (visit 2), dose escalation (visits 3 to 4), maintenance (visits 5 to 11), and safety follow-up (visit 12). SP513 (N = 561), a three-arm study, evaluated the efficacy and safety of rotigotine transdermal patches, starting at a dose of 4 mg per 24 hours titrated weekly up to 8 mg per 24 hours, compared with placebo transdermal patches or capsules or ropinirole capsules (starting at 0.75 mg per day titrated weekly up to 24.0 mg per day) over 48 weeks (pre-treatment washout period of up to four weeks, a

dose-escalation period of up to 13 weeks, a 24-week dose-maintenance period, a mandatory dose de-escalation phase of up to 12 days, and a four-week safety follow-up period). Participants were randomized in a 2:2:1 ratio to receive rotigotine, ropinirole, or placebo. The study assessed the superiority of rotigotine over placebo and non-inferiority of rotigotine versus ropinirole. SP513 consisted of 18 visits: pre-treatment (visit 1), baseline (visit 2), dose escalation (visits 3 to 10), maintenance (visits 11 to 17), and safety follow-up (visit 18).

b) Advanced Parkinson Disease

For APD, two phase 3, multi-centre, randomized, three-arm parallel group, double-blind, controlled studies met the inclusion criteria for this systematic review. SP515 (N = 506), a three-arm study, evaluated the efficacy and safety of rotigotine transdermal patches, starting at a dose of 4 mg per 24 hours titrated weekly up to 16 mg per 24 hours, compared with placebo transdermal patches or capsules or pramipexole capsules (0.375 mg per day titrated weekly up to 4.5 mg per day) over a duration of up to 32 weeks (pre-treatment washout period of up to four weeks, a dose-escalation period of up to seven weeks, a 16-week dose-maintenance period, a dose de-escalation phase of six days, and a four-week safety follow-up period). Participants were randomized in a 2:2:1 ratio to receive rotigotine, pramipexole, or placebo. The study assessed the superiority of rotigotine versus placebo and non-inferiority of rotigotine versus pramipexole. SP515 consisted of 15 visits: pre-treatment (visit 1), baseline (visit 2), dose escalation (visits 3 to 8), maintenance (visits 9 to 14), and safety follow-up (visit 15). SP650 (N = 351), a three-arm superiority study, evaluated the efficacy and safety of rotigotine transdermal patches with target doses of 8 mg per 24 hours and 16 mg per 24 hours compared with placebo transdermal patches over 38 weeks (pre-treatment washout period of up to four weeks, a dose-escalation period of up to five weeks, a 24-week dose-maintenance period, a dose–de-escalation phase of up to eight days, and a four-week safety follow-up period). Participants were randomized in a ratio of 1:1:1 to receive rotigotine 8 mg per 24 hours, rotigotine 12 mg per 24 hours, or placebo. SP650 also consisted of 15 visits: pre-treatment (visit 1), baseline (visit 2), dose escalation (visits 3 to 6), maintenance (visits 7 to 14), and safety follow-up (visit 15). In both APD studies, patients were considered not well controlled on levodopa, yet continued levodopa treatment during the studies.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Early Parkinson Disease

The inclusion criteria in SP512 and SP513 were patients 30 years of age or older with idiopathic PD, less than or equal to five years in duration, with at least two or more of the following signs: bradykinesia, resting tremor, rigidity, postural instability; and without any other known or suspected cause of Parkinsonism. Patients must have been Hoehn and Yahr stage ≤ III, had a Mini Mental State Examination (MMSE) score of ≥ 25, and a UPDRS motor score (part III) of ≥ 10 at baseline. In addition, patients receiving an anticholinergic drug (i.e., benztropine, trihexyphenidyl, parsitan, procyclidine, biperiden), a MAO-B inhibitor (e.g., selegiline), or a N-methyl-D-aspartate (NMDA) antagonist (e.g., amantadine) must have been on a stable dose for at least 28 days prior to baseline and be maintained on that dose for the duration of the study. Exclusion criteria comprised prior or concurrent therapy with a dopamine agonist, prior therapy with carbidopa/levodopa within 28 days of the baseline visit, or received carbidopa/levodopa for more than six months since diagnosis. Patients with atypical Parkinson syndrome(s) due to drugs (e.g., metoclopramide, flunarizine), metabolic neurogenetic disorders (e.g., Wilson's disease), encephalitis, cerebrovascular disease, or degenerative disease (e.g., progressive supranuclear palsy) were excluded. Patients with a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant were also excluded.

Advanced Parkinson Disease

The inclusion criteria in SP515 and SP650 were patients with idiopathic PD of more than three years in duration; who had a Hoehn and Yahr stage II through IV, as observed in both the "on" and "off" state; and who had the cardinal Parkinsonian sign of bradykinesia, plus the presence of at least one of the following cardinal features: resting tremor, rigidity, and impairment of postural reflexes. Additionally, patients were without any other known or suspected cause of Parkinsonism; were on a stable dose of levodopa of at least 300 mg per day (in SP515) or 200 mg per day (in SP650) for at least 28 days prior to baseline, and administered in at least three daily intakes; and were not adequately controlled on anti-Parkinson medication (including levodopa and entacapone) as judged by the treating investigator. Also, patients had to be willing and needed to be able to complete a diary over a six-day period and clearly differentiate between the "on" and "off" state as confirmed by four of the six diaries being "valid," as determined by the investigator. In order to be classified as "valid," diaries also needed to confirm an average of 2.5 hours per day or more spent in the "off" state and needed to confirm that the patient was on a stable dose of all anti-Parkinsonian medications for at least 20 days prior to completing the six diaries. If the patient had been receiving an anticholinergic drug (i.e., benztropine, trihexyphenidyl, parsitan, procyclidine, biperiden), the MAO-B inhibitor selegiline, or a NMDA-antagonist (amantadine or memantine), he or she must have been on a stable dose for at least 28 days prior to baseline and be maintained on that dose for the duration of the study.

b) Baseline Characteristics

Early Parkinson Disease

Baseline characteristics (Table 7) were generally well balanced across treatment groups in both studies, with the exception of the number of males seen in each treatment arm in both studies. Patients had a mean age of approximately 62 years, had had a diagnosis of PD for approximately 1.3 years, and had a mean baseline UPDRS subtotal (parts II and III) score ranging from 29.9 to 33.2 in both studies. The majority of patients were male (~60%) and Caucasian (~96%). According to the clinical expert involved in the review, the male to female ratio is reflective of clinical practice.

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS FOR EARLY PARKINSON DISEASE STUDIES

Characteristics	SP512		SP513		
	Placebo (n = 96)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
Age, year (SD)	64.5 (10.47)	62.0 (10.29)	60.4 (9.98)	61.1(9.84)	61.6 [redacted]
Male, n (%)	[redacted] (60)	[redacted] (68)	[redacted] (58)	[redacted] (55)	[redacted] (40)
Weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Years since first diagnosis (SD)	1.4 (1.25)	1.3 (1.30)	1.2 [redacted]	1.4 [redacted]	1.3 [redacted]
Diseases of the digestive system at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)					
Caucasian	[redacted] (96)	[redacted] (97)	[redacted] (97)	[redacted] (96)	[redacted] (96)
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline UPDRS Part II (Activities of Daily Living) Score					
Mean (SD)	8.7 (4.02)	8.3 (4.62)	8.7 [redacted]	9.3 [redacted]	9.1 [redacted]
Baseline UPDRS Part III (Motor Exam) Score					
Mean (SD)	[redacted]	[redacted]	22.6 [redacted]	23.8 [redacted]	23.2 [redacted]
Baseline UPDRS Subtotal (Parts II and III) Score					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Study SP512,[5] SP513.[6]

Advanced Parkinson Disease

Baseline characteristics (Table 8) were generally well balanced across treatment groups in both studies, with the exception that more patients in rotigotine groups in SP650 had diseases of the digestive system at baseline compared with the placebo group, and the proportion of males varied widely between-treatment groups in SP515. Patients had a mean age of approximately 65 years, had had a diagnosis of PD for approximately 8.1 years, and had a mean baseline absolute "off" time ranging from 6.0 to 6.7 hours in both studies. The majority of patients were male (~64%) and Caucasian (~95%). In SP515, baseline nocturnal sleep scores were similar in all treatment groups and, according to the clinical expert, were low for patients with APD, suggested that patients likely did not have sleep disturbances. In SP515, baseline nocturnal sleep scores were similar in all treatment groups and, according to the clinical expert, were representative of patients with APD who likely had sleep disturbances.

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS FOR ADVANCED PARKINSON DISEASE STUDIES

Characteristics	SP515			SP650		
	Placebo (n = 99)	Rotigotine (n = 205)	Pramipexole (n = 202)	Placebo (n = 119)	Rotigotine 8 mg/24 h ours (n = 113)	Rotigotine 12 mg/24 h ours (n = 109)
Age, year mean (SD)	64.7(10.1)	64.3 (8.9)	63.3 (9.7)	66.3 (9.6)	66.5 (10.0)	65.8 (10.0)
Male, n (%)	71 (71)	132 (66)	112 (56)	74 [redacted]	78 [redacted]	71 [redacted]
Weight, kg (SD)	74.2 (13.1)	74.5 (14.4)	71.9 (12.8)	[redacted]	[redacted]	[redacted]
Years since first diagnosis, mean (SD)	8.3 (4.9)	8.8 (4.4)	8.4 (4.7)	[redacted]	[redacted]	[redacted]
Diseases of the digestive system at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline UPDRS Part II (Activities of Daily Living) Score						
Mean (SD)	12.8 (6.2)	12.3 (5.8)	12.1 (6.0)	12.4 (6.2)	13.2 (6.5)	13.6 (6.7)
Baseline UPDRS III (Motor Exam) Score						
Mean (SD)	26.8 (11.4)	26.3 (11.4)	26.4 (11.6)	26.3 (13.9)	26.3 (14.7)	27.0 (12.2)
Baseline Nocturnal Sleep PDSS Score						
Mean (SD)	[redacted]	[redacted]	[redacted]		[redacted]	
Daily Absolute "Off" Time (Hours)						
Mean (SD)	6.5 (2.8)	6.3 (2.5)	6.0 (2.5)	6.4 (2.6)	6.7 (2.5)	6.3 (2.6)

SD = standard deviation; PDSS = Parkinson's Disease Sleep Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: SP515,[7] SP650.[8]

3.2.3 Interventions

a) Early Parkinson Disease

In SP512, the treatments included rotigotine 2 mg per 24 hours titrated weekly up to 6 mg per 24 hours by transdermal application, and matching placebo transdermal patches that were identical in appearance. Patients were provided with rotigotine 2 mg per 24 hours dose patches at baseline and were titrated to the 4 mg per 24 hours dose at week 2 and 6 mg per 24 hours dose at week 3. Patients were instructed to apply the patches for 24 hours, although it was not stated whether patients were directed on where to apply the patch or about rotating the application site. Titration continued for patients until either the optimal dose (defined following discussions between the investigator and participant, considering efficacy and his or her adverse event [AE] profile) was identified or the titration period was complete.

In SP513, the treatments included rotigotine 4 mg per 24 hours titrated weekly up to 8 mg per 24 hours by transdermal application, matching placebo transdermal patches with no rotigotine that were identical in appearance, encapsulated ropinirole taken orally at doses starting at 0.25 mg titrated weekly up to 5 mg, and matching placebo capsules identical in appearance without the active ingredient. All participants received their respective treatments in a double-blind and double-dummy fashion. A 13-week titration schedule was used to accommodate the titration schedule of ropinirole. Titration of rotigotine increased by a dose of 2 mg per 24 hours weekly, starting from 2 mg per 24 hours. Patients in the ropinirole group received 0.25 mg at week one and were titrated by weekly increments of 0.25 mg from week one to four, weekly increments of 0.5 mg from weeks five to eight, and weekly increments of 1.0 mg from weeks nine to 13. Titration continued for patients until either the optimal dose (defined following discussions between the investigator and participant, considering efficacy and his or her AE profile) was identified or the titration period was complete. In SP513, the 8 mg per 24 hours dose was achieved by using two 4 mg per 24 hours patches. Patches were applied for 24 hours while capsules were taken three times a day.

In both studies, the following concomitant medications were permitted, provided the dose was stable (no change in dose and/or frequency of daily intake) and had been stable for at least 28 days prior to baseline: MAO-B inhibitors (e.g., selegiline), anticholinergic drugs (e.g., benztropine, trihexyphenidyl, parsitan, procyclidine, biperiden), and NMDA antagonists (e.g., amantadine).

b) Advanced Parkinson Disease

In SP515, the treatments included rotigotine starting at a dose of 4 mg per 24 hours titrated weekly up to 16 mg per 24 hours by transdermal application, matching placebo transdermal patches with no rotigotine that were identical in appearance, encapsulated pramipexole taken orally at a starting dose of 0.375 mg titrated weekly up to 4.5 mg, and matching placebo capsules identical in appearance without the active ingredient. Patients in the rotigotine group were provided with one 4 mg per 24 hours patch at week 1. Titration increased by a dose of 2 mg per 24 hours weekly. Patients in the pramipexole group received 0.125 mg at week one and were titrated by weekly increments of 0.125 mg from week one to two, and weekly increments of 0.25 mg from weeks two to seven. Titration continued for patients until either the optimal dose was identified or the titration period was complete. All participants received their respective treatments in a double-blind and double-dummy fashion.

In SP650, the treatments included rotigotine 8 mg per 24 hours and 12 mg per 24 hours by transdermal application and matching placebo transdermal patches with no rotigotine that were identical in appearance. Patients were provided with the rotigotine 4 mg per 24 hours dose patches at week one. Titration increased by a dose of 2 mg per 24 hours weekly. Patients in the rotigotine groups were started at the same dosage, though patients in the higher target dose group received an additional 2 mg per 24 hours at week four and an additional 4 mg per 24 hours at week five to achieve the study dose of 12 mg per 24 hours. Patients were instructed to apply the patches for 24 hours. Titration continued for patients until either the optimal dose was identified or the titration period was complete.

In both studies, the following concomitant medications were permitted in both APD studies, provided the dose was stable (no change in dose and/or frequency of daily intake) and had been stable for at least 28 days prior to baseline: MAO-B inhibitors (e.g., selegiline), anticholinergic drugs (e.g., benztropine, trihexyphenidyl, ethopropazine, biperiden), NMDA antagonists (e.g., amantadine or memantine), and levodopa (in combination with benserazide or carbidopa). Patients were permitted to reduce their levodopa dose if required due to dopaminergic AEs during the first two weeks of the maintenance phase. Patients whose doses were reduced during this period were permitted to be up-

titrated to their original levodopa dose if required. Patients' levodopa doses were otherwise to remain stable throughout the trial.

3.2.4 Outcomes

In all included studies, two primary end points were used: a continuous end point (change in UPDRS [parts II and III] subtotal scores from baseline and change in absolute time spent "off" from baseline) for a US marketing application and a dichotomized response end point (≥ 20% decrease in the sum of the UPDRS [parts II and III] subtotal scores from baseline and a ≥ 30% decrease in absolute time spent "off" from baseline) for a European Union (EU) marketing application. Two separate primary analyses were performed for each end point.

a) UPDRS Subscale Sore (Parts II and III)

Change in UPDRS subscale score (parts II and III) from baseline visit to the end of the double-blind maintenance phase was a primary outcome in the EPD studies SP512 and SP513. The UPDRS is a measure of disability and impairment in PD. Part II (activities of daily living [ADL]) of the UPDRS comprises 13 items, with scores ranging from 0 to 52. Part III (Motor Examination) of the UPDRS comprises 14 items, with scores ranging from 0 to 56. For both parts II and III, each scale item is scored 0 to 4 and then summed to create an overall score, with lower scores representing less disability. The minimal clinically important difference (MCID) for the combined part II and III subscale scores is uncertain, though other trials that included patients with varying PD severity have concluded a MCID range from 3.5 to 8 points for UPDRS total score for subscales of parts I, II, and III[25-27] (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).

UPDRS assessments were performed at each visit, where patients were asked about their general state during the week prior to the scheduled visit. The UPDRS assessment was delivered by experienced trial staff. Patients were assessed by the same individuals where possible in order to avoid interindividual rating differences. Although change in UPDRS subscale score (parts II and III) from baseline visit to the end of the double-blind maintenance phase was measured only in the EPD studies, measures of the individual scales and ADL (part II) and Motor Examination sections in the UPDRS (part III) were measured in both EPD studies and both APD studies (Table 9). In the APD studies, measurement of UPDRS took place when patients were in the "on" state.

b) Time Spent "Off"

The reduction in absolute time spent "off" from baseline to the end of the double-blind maintenance phase was a primary outcome in the APD studies SP515 and SP650. Reduction in absolute time spent "off" was measured by self-completed Parkinson disease home diaries (PDHD). The PDHD is a validated tool that assesses the amount of "on" and "off" time that patients experience in a 24-hour period.[28] Patients viewed a training video showing different motor stages of APD patients and how to complete the diaries. At the pre-treatment visit (visit 1), patients were provided with a set of six daily diaries to be completed prior to the baseline visit (visit 2) for six consecutive pre-specified days. Diaries were only considered "valid" if at least 22 of the 24 hours were completed with not more than two hours of data missing, and patients needed a total of at least four of six diaries to be "valid," determined by the investigator. Patients completed the baseline assessment (visit 2) only if the diaries were determined to be valid. At baseline through to visit 13, patients were provided with three diaries at each visit to be completed for three consecutive days prior to the following visit. Patients were required to have two out of the three diaries determined to be "valid" by the investigator. Patients recorded time spent "on without troublesome dyskinesias," "on with troublesome dyskinesias," "off," sleep, and time of anti-Parkinson medication intake. The status of "off" was defined between the investigator and patient on an

individual basis and the symptoms that appeared were recorded in the diaries. A patient was considered "off" when he or she began to lose the optimum effects of his or her current anti-Parkinson medication. The MCID for off time for APD patients has not been formally derived; however, one trial reported an MCID of one hour of reduction in "off time" for EPD patients (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).[27] The clinical expert involved in the review confirmed that a decrease in off time of one to two hours is a clinically meaningful goal.

c) Response to Therapy

Response to therapy in the EPD studies was defined as a 20% or greater decrease in the sum of the UPDRS (parts II+III) subtotal scores from the baseline visit to the end of the double-blind maintenance phase. Response to therapy in the APD studies was defined as a 30% or greater decrease in absolute time spent "off" from baseline to the end of the double-blind maintenance phase. Response to therapy from the baseline visit to the end of the double-blind maintenance phase was considered the primary end point for the EU. The predefined cut points of 20% and 30% in the respective EPD and APD studies were selected and deemed clinically meaningful by the investigators. The clinical significance of these cut points was confirmed by the clinical expert consulted on this review.

d) Health-related Quality of Life

Health-related quality of life (HRQoL) was measured with the EuroQol 5-dimensional scale (EQ-5D) in SP512, SP513, and SP650, which was completed at baseline and at the end of the maintenance phase or withdrawal assessment. Health state scores were derived from the EQ-5D VAS, a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. In SP515, HRQoL was measured by the Parkinson's Disease Questionnaire 39 (PDQ-39), which was completed at baseline and at the end of the maintenance phase or withdrawal assessment. Like the EQ-5D, the PDQ-39 is a tool designed for self-completion by the study patients, which describes health status and provides scores in eight dimensions: mobility, ADL, emotions, stigma, social support, cognition, communication, and bodily discomfort. The PDQ-39 consists of 39 items graded on a 5-point scale (0 = never; 4 = always), with higher scores indicating worse quality of life. A summary index score derived from eight domains consisting of 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) was transformed to have a range of 0 to 100. The MCID of the PDQ-39 instrument is uncertain (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).

e) Compliance

Compliance with the treatment dosing regimen was calculated as the ratio of actual days under treatment and theoretical days under treatment. This was determined by counting the number of treatment medications handed out and the number of treatment medications returned. Patients were considered compliant if the calculated duration was between 85% and 115%.

f) Nocturnal Sleep

Nocturnal sleep was measured in SP515 by the Parkinson's Disease Sleep Scale (PDSS) at baseline and at the end of the maintenance phase or withdrawal assessment. The PDSS is a self-completion tool that consists of a simple scale, utilizing VASs, to assess sleep and nocturnal disability in PD. Addressed 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 through 13), sleep refreshment (item 14), and daytime dozing

(item 15)."[29] Patients or caregivers (as a proxy) 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).[29,30] The PDSS is a validated tool with a total score of 120 points being suggested as the cut-off point to detect sleep disturbances in patients with PD (APPENDIX 5: VALIDITY OF OUTCOME MEASURES).[31]

g) Adverse Events

AEs were defined as any adverse, noxious, or pathological change in a patient or clinical investigation patient compared with pre-existing conditions that occurred during any phase of the clinical trial including pre-treatment run-in, washout, or follow-up periods. Serious adverse events (SAEs) were defined as any untoward medical occurrence that at any dose was fatal (resulted in death), was life-threatening, resulted in persistent or significant disability or incapacity, required in-patient hospitalization, prolonged existing in-patient hospitalization, was a congenital anomaly or birth defect, or was considered to be an important medical event. Other safety outcomes of interest included arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy.

TABLE 9: EFFICACY OUTCOMES IN INCLUDED STUDIES

Efficacy Outcomes[a]	EPD		APD	
	SP512	SP513	SP515	SP650
UPDRS subscale score (Parts II and III)	X	X		
Time spent "off"			X	X
Response to therapy	X	X	X	X
EQ-5D	X	X		X
PDQ-39			X	
Compliance	X	X	X	X
Patient's satisfaction with therapy				
Nocturnal sleep (PDSS)			X	
Motor symptoms (UPDRS III score only)	X	X	X	X
Activities of daily living (UPDRS II score only)	X	X	X	X

APD = Advanced Parkinson disease; EPD = Early Parkinson disease; EQ-5D = EuroQol 5-dimensional scale; PDQ-39 = Parkinson's Disease Questionnaire-39; PDSS = Parkinson's Disease Sleep Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
[a]According to the protocol (Table 4).

3.2.5 Statistical Analysis

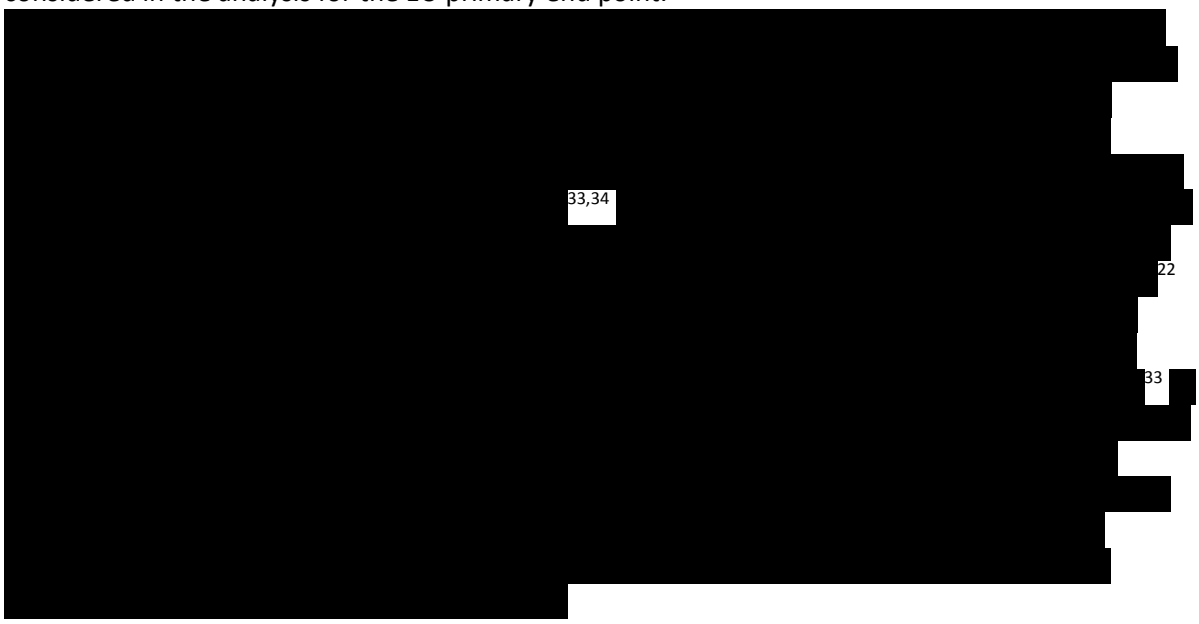
a) Early Parkinson Disease

- The primary analysis for the all primary end points (mean change in UPDRS parts II and III subtotal from baseline to the end of the maintenance phase [US primary end point] and difference in response to therapy [EU primary end point]) was performed using the full analysis set (FAS) population.
- Secondary end points in both studies were analyzed descriptively, with no between-group comparisons.
- Missing data for both primary end points were imputed using the last observation carried forward (LOCF).
- According to the investigators, adjustments for multiplicity for the primary end points were not required, as the two different primary efficacy end points that correspond to the US and EU reviewing agencies did not affect the type I error rate for participants in each region.

SP512

- An analysis of covariance model (ANCOVA), with adjustment terms for geographic region of investigational centre (blocking factor) and baseline UPDRS (a covariate), was used to compare the superiority of rotigotine to placebo for change from baseline to the end of the double-blind maintenance phase in the sum of the UPDRS parts II and III subtotal (US primary end point). Fisher's exact test was used to compare the superiority of rotigotine to placebo for responder status at the end of the maintenance phase (EU primary end point).
- For the US primary end point, change in UPDRS parts II and III subtotal, 160 participants in the rotigotine group and 80 participants in the placebo group (2:1 randomization) were expected to be sufficient to achieve 95% power for the group comparison, assuming a standard deviation (SD) of approximately 7 points, as seen in SP506.[32]
- For the EU primary end point (i.e., differences in response to therapy), 160 participants in the rotigotine group and 80 participants in the placebo group were expected to be sufficient to achieve 80% power using a two-sided Fisher's exact test. This calculation assumed a maximum response rate for placebo of 30% and a minimum response rate for rotigotine of 50% (as seen in SP506).[32]

SP513

- A closed-test procedure for each primary end point (i.e., mean change in UPDRS parts II and III subtotal from baseline to the end of the maintenance phase [US primary end point] and response to therapy [EU primary end point]) was used, which included the following steps:
  1) a two-sided test (alpha = 5%) of superiority of rotigotine versus placebo
  2) a one-sided test (alpha = 2.5%) for non-inferiority was used to compare rotigotine with ropinirole if the estimate of rotigotine was larger than the placebo estimate
  3) a one-sided test (alpha = 2.5%) of superiority was performed if the estimator of rotigotine was larger than the ropinirole estimator.
- Point estimates of mean treatment differences were based on least-square means with standard errors and *P* values. Baseline value of UPDRS (parts II and III) subtotal score was considered as a covariate. Baseline was used as a covariate in the model of the US primary end point analysis. Given that responder end point was already a baseline adjusted end point, the baseline score was not considered in the analysis for the EU primary end point.
- 

- For the EU primary end point (i.e., difference in response to therapy), 180 participants in each active group and a lower limit of the observed one-sided 97.5% CI were expected to exceed the non-inferiority margin of –15% and achieve 80% power when the proportion of responders for ropinirole and rotigotine were 50%. Ninety patients in the placebo group would achieve 85% power using an expected placebo response rate of 30% at the 5% alpha level.
- For the US primary end point (i.e., UPDRS parts II and III subtotal), the sample size was calculated on the analysis as it was performed for the EU.

b) Advanced Parkinson Disease

- The primary analysis for all the primary end points (mean change in absolute "off" time from baseline to the end of the maintenance phase [US primary end point] and response to therapy [EU primary end point]) was performed using the FAS population.
- Secondary end points in both studies were analyzed descriptively, with no between-group comparisons.
- Missing data for both primary end points were imputed using the LOCF.
- According to the investigators, adjustments for multiplicity for the primary end points were not required, as the two different primary efficacy end points that correspond to the US and EU reviewing agencies did not affect the type I error rate for participants in each region.

SP515

- The US primary end point (i.e., mean change in absolute time spent "off" from baseline to the end of the maintenance phase) was analyzed using an ANCOVA model, with treatment and grouped region as factors and baseline "off" time score as a covariate. The EU primary end point (change in patient's response to treatment, defined as ≥ 30% decrease in absolute time spent "off" from baseline to the end of the maintenance phase) was analyzed using CIs according to the test of 2 proportions using normal approximation to obtain estimates of the responder rate in each of the treatment groups.
- A closed-test procedure for each primary end point (change in absolute time spent "off" from baseline to the end of the maintenance phase [US primary end point] and response to therapy [EU primary end point]) was used, which included the following steps:
  1) a two-sided test (alpha = 5%) of superiority of rotigotine versus placebo
  2) a one-sided test (alpha = 2.5%) for non-inferiority was used to compare rotigotine with pramipexole if the estimate of rotigotine was larger than the placebo estimate
  3) a two-sided test (alpha = 5%) of superiority was performed if the estimator of rotigotine was larger than the pramipexole estimator.
- [redacted]
- For the EU end point, a total of 180 participants in each active group and a lower limit of the observed one-sided 97.5% CI were expected to exceed the non-inferiority margin of –15% and achieve 80% power when the proportion of responders for rotigotine and pramipexole were 50%. The comparison of 180 patients receiving active treatments compared with 90 patients receiving placebo (based on the 2:2:1 ratio between the groups) was sufficient to obtain 85% power using a two-sided normal approximation test at an alpha level of 5% when assuming a rotigotine responder rate of 50% and difference between active and placebo of 20%.

SP650

- The US primary end point (mean change in absolute time spent "off" from baseline to the end of the maintenance phase) was analyzed using an ANCOVA model, with geographic region as factors and baseline "off" time score as adjustment factors.
- A closed-test procedure for each primary end point (mean change in absolute time spent "off" from baseline to the end of the maintenance phase [US primary end point] and difference in response to therapy [EU primary end point]) was used, which included the following steps:
  1) a one-sided test (alpha = 2.5%) of superiority of rotigotine 12 mg per 24 hours rotigotine versus placebo using least squares means difference from ANCOVA
  2) a one-sided test (alpha = 2.5%) of superiority of rotigotine 8 mg per 24 hours versus placebo if 12 mg per 24 hours rotigotine proved significant against placebo. If the comparison of 12 mg per 24 hours rotigotine versus placebo did not demonstrate statistical significance, the comparison between 8 mg per 24 hours versus placebo was declared statistically non-significant with no *P* value calculated.
- The EU primary end point (change in patient's response to treatment, defined as a ≥ 30% decrease in absolute time spent "off" from baseline to the end of the maintenance phase) was analyzed using CIs according to the test of 2 proportions using normal approximation to obtain estimates of the responder rate in each of the treatment groups.
- A response rate of 60% was assumed for the highest dose of rotigotine. With a sample size of 100 patients in each group, 80% power would be achieved with a 5% two-sided significance level, assuming true proportion of 60% and 40% in the active and placebo groups, respectively.
- The expected 20% difference, as given in the responder end point, corresponded to 1.5 hours' reduction in absolute "off" time. The power would be greater than 95% when assuming a difference of 1.5 hours and an SD of approximately 2.48 (as observed in SP511).[35]

Analysis Populations

The following data sets were defined in the both EPD and APD studies:

Full analysis set: includes all double-blind, randomized patients having a baseline and at least one post-baseline measurement for the primary variable under treatment. In the APD studies, patients in the FAS were also required to have at least four out of six valid diary days and have at least one valid set of diary data post-baseline. The FAS was used for the primary analyses in all included studies.

Per-protocol set: subset of the FAS by excluding all patients with fewer than eight weeks of exposure to the trial medication in the maintenance phase or who had a major protocol deviation.

Safety data set: all randomized patients receiving at least one dose of trial medication.

3.3 Patient Disposition

Patient disposition is summarized in Table 10. For the EPD studies, a total of 302 patients in SP512 and 561 patients in SP513 were randomized. Overall, the number of premature discontinuations in both studies was high, ranging from 16% to 30%. In SP512, discontinuation was lower among the placebo group (16%) compared with the rotigotine group (22%). In SP513, discontinuation was lower among the ropinirole group (24%) and similar among the rotigotine (30%) and placebo groups (29%). AEs were the most frequent reasons for discontinuation and were most prevalent in the rotigotine treatments groups in SP512 and SP513. For the APD studies (Table 11), a total of 506 patients in SP515 and 351 patients in SP650 were randomized. Overall, the number of discontinuations in both studies was high, ranging from 11% to 28%. In SP515, discontinuation was lowest among the rotigotine group (11%) compared with the

pramipexole (15%) and placebo (26%) groups. In SP513, discontinuation was lowest among the placebo group (23%), and similar among the rotigotine 8 mg per 24 hours (28%) and rotigotine 12 mg per 24 hours (27%) groups. AEs were the most common reason for discontinuation in the rotigotine group (17%) and were less frequent in the ropinirole (13%) and placebo groups (5%) in SP515 and SP650.

TABLE 10: PATIENT DISPOSITION FOR EARLY PARKINSON DISEASE STUDIES

	SP512		SP513		
	Placebo (n = 96)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
Screened, N	302		610		
Randomized, N (%)	277 (92)		561 (92)		
Discontinued, N (%)	15 (16)	39 (22)	34 (29)	64 (30)	54 (24)
Lack of efficacy	6 (6)	12 (7)	22 (19)	14 (7)	8 (4)
Adverse event	6 (6)	25 (14)	6 (5)	37 (17)	29 (13)
Withdrew consent	4 (4)	6 (3)	7 (6)	18 (8)	15 (7)
FAS, N	96 (100)	177 (98)	117 (99)	213 (99)	227 (99)
PP, N (%)	80 (83)	148 (82)	77(65)	145 (67)	157 (69)
Safety, N	96 (100)	180 (99)	118 (100)	215 (100)	228 (100)
Safety, as treated,[a] N	95 (99)	181 (100)	NA		

FAS = full analysis set; PP = per protocol.
Source: Study SP512,[5] SP513.[6]
[a]One patient who was randomized to the placebo group inadvertently received rotigotine during the first 3 months of the maintenance period. For this reason, the patient was included in the "Safety, as treated" population.

TABLE 11: PATIENT DISPOSITION FOR ADVANCED PARKINSON DISEASE STUDIES

	SP515			SP650		
	Placebo (n = 101)	Rotigotine (n = 204)	Pramipexole (n = 201)	Placebo (n = 120)	Rotigotine 8 mg/24 hours (n = 120)	Rotigotine 12 mg/24 hours (n = 111)
Screened, N	604			462		
Randomized, N (%)	506 (84)			351		
Discontinued, N (%)	26 (26)	23 (11)	30 (15)	28 (23)	33 (28)	30 (27)
Lack of efficacy	7 (7)	3 (2)	3 (2)	11 (9)	7 (6)	5 (5)
Adverse event	6 (6)	11 (6)	14 (7)	11 (9)	18 (15)	17 (15)
Withdrew consent	8 (8)	8 (4)	4 (2)	8 (7)	5 (4)	8 (7)
FAS, N	100 (99)	201 (99)	200 (99)	119 (>99)	113 (94)	109 (98)
PP, N	73 (72)	177 (87)	165 (82)	85(71)	84(70)	78 (70)
Safety, N	101 (100)	204 (100)	201 (100)	120 (100)	118 (98)	111 (100)

FAS = full analysis set; PP = per protocol.

3.4 Exposure to Study Treatments

Table 12 presents the mean and median amount of days patients were exposed to their respective study medication. In SP512, the majority of patients in the rotigotine group received a dose of 6 mg per 24 hours for greater than 27 weeks (71%) during the maintenance phase. In SP513, the majority of patients in the rotigotine group received a dose of 8 mg per 24 hours for greater than nine months (42%), while the majority of patients in the ropinirole group received a dose of 24 mg per day (80%) for greater than nine months during the maintenance phase. In SP515, the majority of patients in the rotigotine group received a dose of 16 mg per 24 hours for greater than 23 weeks (86%), while the majority of patients in the pramipexole group received a dose of 4.50 mg for greater than 23 weeks (86%) during the maintenance phase. In SP650, the majority of patients in the rotigotine group received a dose 12 mg per 24 hours for greater than 29 weeks (82%) during the maintenance phase (Table 13 to Table 16).

TABLE 12: TOTAL DAYS EXPOSURE OF STUDY MEDICATION — SAFETY ANALYSIS SET

	SP512 (27 weeks)		SP513 (37 weeks)			SP515 (23 weeks)			SP650 (29 weeks)		
Days	Placebo (n = 96)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)	Placebo (n = 99)	Rotigotine (n = 205)	Pramipexole (n = 202)	Placebo (n = 119)	Rotigotine 8 mg/ 24 hours (n = 113)	Rotigotine 12 mg/ 24 hours (n = 109)
Mean (SD)	[redacted]										
Median	[redacted]										
(Min, Max)	[redacted]										

SD = standard deviation.
Source: Study SP512,[5] SP513,[6] SP515,[7] SP650.[8]

TABLE 13: DURATION OF TRIAL MEDICATION EXPOSURE BY MAINTENANCE PHASE DOSE IN SP512

SP512 (N = 277)				
Weeks of Exposure	Placebo (N = 96)		Rotigotine (N = 180)	
	Placebo n (%)	2 mg/24 hours n (%)	4 mg/24 hours n (%)	6 mg/24 hours n (%)
0 to 3	[redacted]			
4 to 11	[redacted]			
12 to 19	[redacted]			
20 to 26	[redacted]			
≥ 27	[redacted]			

Source: Study SP512.[5]

TABLE 14: DURATION OF TRIAL MEDICATION EXPOSURE BY MAINTENANCE PHASE DOSE IN SP513

SP513 (N = 561)									
				Months of Exposure n (%)					
Treatment	Type	Dose	N	< 2	2 to 4	4 to < 6	6 to < 8	8 to < 9	≥ 9
Placebo	Patch	2 mg/24 hours							
		4 mg/24 hours							
		6 mg/24 hours							
		8 mg/24 hours							
	Capsule	0.75 mg/day							
		1.50 mg/day							
		2.25 mg/day							
		3.00 mg/day							
		4.50 mg/day							
		6.00 mg/day							
		7.50 mg/day							
		9.00 mg/day							
		12.00 mg/day							
		15.00 mg/day							
		18.00 mg/day							
		21.00 mg/day							
		24.00 mg/day							
Rotigotine	Patch	2 mg/24 hours							
		4 mg/24 hours							
		6 mg/24 hours							
		8 mg/24 hours							
Ropinirole	Capsule	0.75 mg/day							
		1.50 mg/day							
		2.25 mg/day							
		3.00 mg/day							
		4.50 mg/day							
		6.00 mg/day							
		7.50 mg/day							
		9.00 mg/day							
		12.00 mg/day							
		15.00 mg/day							
		18.00 mg/day							
		21.00 mg/day							
		24.00 mg/day							

Source: SP513.[6]

TABLE 15: DURATION OF TRIAL MEDICATION EXPOSURE BY MAINTENANCE PHASE DOSE IN SP515

SP515 (N = 506)									
				Weeks of Exposure n (%)					
Treatment	Type	Dose	N	< 7	7 to < 11	11 to < 15	15 to < 19	19 to < 23	≥ 23
Placebo	Patch	16 mg/24 hours							
		14 mg/24 hours							
		12 mg/24 hours							
		10 mg/24 hours							
		8 mg/24 hours							
		6 mg/24 hours							
		4 mg/24 hours							
	Capsule	4.50 mg							
		3.75 mg							
		3.00 mg							
		2.25 mg							
		1.50 mg							
		0.75 mg							
		0.375 mg							
Rotigotine	Patch	16 mg/24 hours							
		14 mg/24 hours							
		12 mg/24 hours							
		10 mg/24 hours							
		8 mg/24 hours							
		6 mg/24 hours							
		4 mg/24 hours							
Pramipexole	Capsule	4.50 mg							
		3.75 mg							
		3.00 mg							
		2.25 mg							
		1.50 mg							
		0.75 mg							
		0.375 mg							

Source: SP515.[7]

TABLE 16: DURATION OF TRIAL MEDICATION EXPOSURE BY MAINTENANCE PHASE DOSE IN SP650

SP650 (N = 349)						
Weeks of Exposure	Placebo (N = 120)	Rotigotine (N = 229)				
	Placebo n (%)	4 mg/24 hours n (%)	6 mg/24 hours n (%)	8 mg/24 hours n (%)	10 mg/ 24 hours n (%)	12 mg/ 24 hours n (%)
0 to 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 5 to 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 9 to 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 13 to 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 17 to 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 21 to 25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 25 to 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: SP650.[8]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Selection, Allocation, and Disposition of Patients

- All studies were randomized and double blinded.
- The studies employed appropriate methods of allocation concealment (central allocation via telephone-based interactive voice response system). Placebo interventions were identical in appearance to their respective active treatments (double dummy).
- Baseline characteristics of treatment groups were generally similar, with the exception of sex difference between-treatment groups in SP512, SP513, and SP515 and differences in the number of patients with diseases of the digestive system between-treatment groups in SP650.
- In SP513, based on discussion with the clinical expert, the dose used in the ropinirole group was higher than would usually be seen in practice. Therefore, the comparison between rotigotine and ropinirole was not based on clinically similar dosing of the two drugs and likely biases the efficacy results in favour of ropinirole. In the SP512 study, one patient was inadvertently treated with rotigotine during the first three months of the maintenance phase after being randomized to receive placebo; however, it is unlikely this influenced outcomes of the study.
- In all the studies, the proportion of patients who discontinued was relatively high, though similar in all treatment groups. The majority of patients discontinued due to treatment-related AEs.
- There is concern regarding the FAS population, as not all randomized participants were included in the analysis. With numerous dropouts, the FAS population results for both the superiority and non-inferiority analyses were reliant on the LOCF approach, which may not have been the most conservative approach.
- The per-protocol population was relatively small in comparison with the number of participants randomized and is particularly concerning for the accuracy of the non-inferiority tests.
- In all studies, application site reactions were far more common among patients receiving treatment with rotigotine transdermal patches, potentially affecting the blinding in each study.

b) Intervention and Comparator

- In all studies, secondary end points were analyzed descriptively and in an exploratory manner. Thus, without a comparison to a control group, within-group change is difficult to interpret.
- The interpretation of HRQoL results is limited in SP512, SP513, and SP650, as the investigators did not provide EQ-5D summary index scores.
- There is uncertainty regarding the appropriateness of the derivation of the non-inferiority margins used in SP513 and SP515.
    - For the responder analysis (EU primary end point), it is unclear if the non-inferiority margins used previously for other dopamine agonists were appropriately derived and applicable. It is also unclear whether the clinical relevance of the non-inferiority margin of –15% was considered.
    - For the derivation of the non-inferiority margin for the US primary end points (continuous change from baseline in UPDRS subtotal score and change from baseline in off time), these were based on results from the rotigotine phase II study versus placebo in patients with PD (SP506[22]). Fitting bell curves to the distribution of change scores from these studies is questionable, because these data are unlikely to be normally distributed. Hence, conversion to percentiles based upon a bell-shaped curve to non-normally distributed data are not valid. The manufacturer did not provide a clear explanation of how the derived non-inferiority margins of 2.9 and 1.2 points relate to SP506.
- The selected cut points and classification of responders in both EPD (≥ 20% reduction in UPDRS II and III) and APD (≥ 30% reduction in absolute "off" time) appear to be appropriate and clinically meaningful.
- In all studies, the use of LOCF in the context of the differential withdrawal rates could affect the FAS results of the primary end points among all treatment groups. However, this concern is mitigated to an extent by the fact that the per-protocol set (PPS) results were consistent with the FAS. The use of LOCF in non-inferiority trials is generally not a conservative approach.
- In all studies, the compliance rates among all treatment groups were high, though the methods used to assess compliance may not be the most accurate as unreturned medication may not necessarily mean that the medication was used.
- The SP650 study reported a greater reduction in "off" time for a lower dose (8 mg per 24 hours) of rotigotine than the higher dose (12 mg per 24 hours), which could lead to questions regarding the dose-response relationship, but the authors describe the difference as "not statistically significant in post hoc analysis." Differences in absolute "off" time were deemed clinically significant by the clinical expert.

3.5.2 External Validity

a) Patient Characteristics

- The generalizability of the EPD studies is somewhat limited, as patients with prior or concomitant use of levodopa were excluded. Levodopa is considered a first-line therapy for PD in Canada.
- In SP512, rotigotine was only titrated up to 6 mg per 24 hours, which is below the maximum recommended dose of 8 mg per 24 hours in EPD.
- The long-term efficacy and safety of rotigotine are yet to be determined. Although extension data exist, these studies have several limitations, such as select populations that are usually not comparative, single-arm designs, and results that are subject to confounding. Portions of the exclusion criteria involving inability to meet diary entry requirements and restricted use of certain classes of medication makes the generalizability of the APD study findings indeterminate. Several APD patients may not have been able to keep up with the rigour of documenting their condition

every 30 minutes for 24 hours, and they may have had genuine need to use the restricted medications to control their APD and/or other comorbid conditions.
- All studies included different durations for dose-escalation and dose-maintenance phases; thus, results and comparisons between studies should be interpreted with caution.
- There is overlap in the definitions of EPD and APD patients in both practice and in the included studies; hence, misclassification of PD stage may have occurred.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Early Parkinson Disease

a) Unified Parkinson's Disease Rating Scale Subscale Score (Parts II and III)

Results for mean change in UPDRS subscale scores from baseline to the end of the maintenance phase are summarized in Table 17 for the FAS population. In both studies, rotigotine was statistically significantly superior to placebo for improvement in UPDRS parts II and III subtotal score, with a mean difference of –5.28 (95% CI, −7.60 to −2.96) points in SP512 and –4.49 (95% CI, −6.64 to −2.35) points in SP513. In SP513, with a mean difference of 3.96 (95% CI, 2.18 to 5.73), rotigotine was not non-inferior to ropinirole in the FAS population for differences in UPDRS subscale scores at the end of the maintenance phase, as the upper and lower bounds of the 95% CI crossed the non-inferiority margin of 2.9 (statistical test for non-inferiority was not statistically significant). Results were consistent with the PPS population (Table 26 and Figure 2).

b) Response to Therapy

Results for difference in response to therapy from baseline to the end of the maintenance phase are summarized in Table 17 for the FAS population. In both studies, rotigotine was statistically significantly superior to placebo for response to therapy with a mean difference of 28.7% (95% CI, 18.0% to 39.4%) in SP512 and 21.7% (95% CI, 11.1% to 32.4%) in SP513. In SP513, with a difference of −16.6 (95% CI, −25.7 to −7.6), rotigotine was not non-inferior to ropinirole in the FAS population for differences in response to therapy at the end of the maintenance phase, as the upper and lower bounds of the 95% CI crossed the non-inferiority margin of −15% (statistical test for non-inferiority was not statistically significant). Results were consistent with the PPS population shown in Table 26 and Figure 3.

c) Health-related Quality of Life

Results for mean change in HRQoL from baseline to the end of the maintenance phase are summarized in Table 19 for the safety analysis population and were measured using the EQ-5D VAS. The mean change was –1.2 points and 0.0 points for the placebo and rotigotine groups, respectively, in SP512, and –0.08 points, 3.6 points, and 5.5 points for the placebo, rotigotine, and ropinirole groups, respectively, in SP513. Changes in the EQ-5D were descriptive; no between-group statistical comparisons were performed for this outcome.

d) Compliance

Results for compliance from baseline to the end of the maintenance phase are summarized in Table 19 for the safety analysis population. Compliance rates were 100% and 98% for the placebo and rotigotine groups, respectively, in SP512. Compliance rates were 98%, 96%, and 93% for patients receiving transdermal patches, and 97%, 96%, and 93% for patients receiving capsules in the placebo, rotigotine, and ropinirole groups, respectively, in SP513.

e) Patient's Satisfaction with Therapy

Patient's satisfaction with therapy was not evaluated in in SP512 and SP513.

f) Nocturnal Sleep

Nocturnal sleep was not evaluated in SP512 and SP513.

3.62 Advanced Parkinson Disease

a) Time Spent "Off"

Results for mean change in time spent off from baseline to the end of the maintenance phase are summarized in Table 18 for the FAS population. In both studies, rotigotine was statistically significantly superior to placebo for improvement in time spent "off," with a mean difference of −1.58 (95% CI, −2.27 to −0.90) hours in SP515, and −1.8 (95% CI, –2.6 to –1.0) hours and –1.2 (95% CI, –2.0 to –0.4) hours among the rotigotine 8 mg per 24 hours and 12 mg per 24 hours, respectively, in SP650. In SP515, with a mean difference of 0.35 (95% CI, –0.21 to 0.92) hours, rotigotine demonstrated non-inferiority to pramipexole in the FAS population for differences in time spent "off" at the end of the maintenance phase, as the upper bound of the 95% CI did not cross the non-inferiority margin of 1.2 (statistical test for non-inferiority was statistically significant). Results were consistent with the PP analysis population (Table 27 and Figure 4).

b) Response to Therapy

Results for mean change in response to therapy from baseline to the end of the maintenance phase are summarized in Table 18 for the FAS population. In both studies, rotigotine was statistically significantly superior to placebo for improvement in response to therapy, with a difference of 24.7% (95% CI, 13.2 to 36.3) in SP515, and 22.2% (95% CI, 9.7 to 34.7) hours and 20.6% (95% CI, 7.9 to 33.3) hours among the rotigotine 8 mg per 24 hours and 12 mg per 24 hours, respectively, in SP650. In SP515, with a between-group difference of –7.3 (95% CI, –16.7 to 2.1), rotigotine was not non-inferior to pramipexole in the FAS population for differences in response to therapy at the end of the maintenance phase, as the lower bound of the 95% CI crossed the non-inferiority margin of −15% (statistical test for non-inferiority was not statistically significant). Results were consistent with the PP analysis population (Table 27 and Figure 5).

c) Health-related Quality of Life

Results for mean change in HRQoL from baseline to the end of the maintenance phase are summarized in Table 20 for the safety analysis population. In SP515, the mean within-groups change on the PDQ-39 single index score were –2.1 points, –5.0 points, –6.1 points for the placebo, rotigotine, and pramipexole groups, respectively. In SP650, the mean change was 1.2 points, 4.3 points, and 3.6 points on the EQ-5D VAS for the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively. No statistical analysis of the difference in change between groups was performed for the HRQoL outcomes.

d) Compliance

Results for compliance from baseline to the end of the maintenance phase are summarized in Table 20 for the safety analysis population. Compliance rates were 93%, 96%, and 97% for patients receiving transdermal patches and 93%, 95%, and 94% for patients receiving capsules in the placebo, rotigotine, and pramipexole groups, respectively, in SP515. Compliance rates were 94%, 98%, and 97% for the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively, in SP650.

e) Patient's Satisfaction with Therapy

Patient's satisfaction with therapy was not evaluated in SP512 and SP513.

f) Nocturnal Sleep

Results for nocturnal sleep from baseline to the end of the maintenance phase are summarized in Table 21 for the safety analysis population. There were small improvements in the rotigotine and pramipexole groups, with mean changes in PDSS sum scores of 4.4 and 4.8, respectively, while the mean change in the placebo group was –2.9; however, no statistical analysis of the difference in change between groups was performed.

g) Other Efficacy Outcomes

Results for mean change in UPDRS parts II and III scores from baseline to the end of the maintenance phase are summarized for the FAS population in Table 22 for EPD studies, and Table 23 for the APD studies. In the EPD studies, the mean change in UPDRS part III scores from baseline to the end of the maintenance phase were 0.5 and –1.1 for the placebo and rotigotine groups, respectively, in SP512, and –2.1, –5.3, and –8.0 for the placebo, rotigotine, and ropinirole groups, respectively, in SP513. The mean change in UPDRS part II scores from baseline to the end of the maintenance phase were 1.0 and –0.3 for the placebo and rotigotine groups, respectively, in SP512, and –0.2, –2.0, and –3.0 for the placebo, rotigotine, and ropinirole groups, respectively, in SP513. No statistical analysis of the difference in change between groups was performed.

In the APD studies, the mean change in UPDRS part III scores from baseline to the end of the maintenance phase were –4.3, –8.7, and –10.3 for the placebo, rotigotine, and pramipexole groups, respectively, in SP515, and –3.4, –6.8, and –8.7 for the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively, in SP650. The mean change in UPDRS part II scores from baseline to the end of the maintenance phase were –2.0, –4.2, and –4.6 for the placebo, rotigotine, and pramipexole groups, respectively, in SP515, and –0.5, –3.1, and –3.2 for the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively, in SP650. No statistical analysis of the difference in change between groups was performed.

TABLE 17: KEY EFFICACY OUTCOMES (BASELINE TO END OF MAINTENANCE PHASE) FOR EARLY PARKINSON DISEASE STUDIES — FULL ANALYSIS SET

	SP512 (27 weeks)		SP513 (37 weeks)		
Outcome	**Placebo (n = 96)**	**Rotigotine (n = 177)**	**Placebo (n = 117)**	**Rotigotine (n = 213)**	**Ropinirole (n = 227)**
UPDRS (Subtotal Parts II and III)					
Baseline mean (SD)	30.0 (10.67)	29.9 (12.22)	31.3 (12.63)	33.2 (12.58)	32.2 (12.41)
LS mean change (SE) from baseline to end of maintenance phase	1.31 (0.96)	−3.98 (0.71)	−2.33 (0.88)	−6.83 (0.66)	−10.78 (0.64)
Rotigotine – placebo difference (95% CI) *P* value[a]	−5.28 (−7.60 to −2.96) < 0.0001		−4.49 (−6.64 to −2.35) < 0.0001		
Ropinirole – placebo difference (95% CI) *P* value	NA		−8.45 (−10.57 to −6.34) NA		

	SP512 (27 weeks)		SP513 (37 weeks)		
Outcome	**Placebo (n = 96)**	**Rotigotine (n = 177)**	**Placebo (n = 117)**	**Rotigotine (n = 213)**	**Ropinirole (n = 227)**
Response to Therapy (%)					
Responders[b, c] N (%)	18 (19)	84 (48)	35 (30)	110 (52)	155 (68)
Rotigotine – placebo difference (95% CI) *P* value	28.7 (18.0 to 39.4) < 0.0001		21.7 (11.1 to 32.4) < 0.0001		
Ropinirole – placebo difference (95% CI) *P* value	NA		38.4 (28.1, 48.6) NA		

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; NA = not applicable; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.
Study SP512,[5] SP513[6]
[a]Treatment effect results adjusted for geographic region and baseline UPDRS by means of a main effects ANCOVA model.
[b]Patients with a 20% reduction or greater in UPDRS (II and III) subtotal from baseline to end of maintenance are "responders."
[c]Response rates analyzed using asymptotic normal approximation methodology.

FIGURE 2: UPDRS ROTIGOTINE VERSUS ROPINIROLE IN SP513 NON-INFERIORITY ANALYSIS-ADJUSTED MEAN CHANGE IN UPDRS SUBTOTAL FROM BASELINE TO END OF MAINTENANCE PHASE

Figure 2 contained confidential data and was removed at the manufacturer's request.

FIGURE 3: ROTIGOTINE VERSUS ROPINIROLE IN SP513 NON-INFERIORITY ANALYSIS-RESPONDER ANALYSIS TEST RESULTS

Figure 3 contained confidential data and was removed at the manufacturer's request.

TABLE 18: KEY EFFICACY OUTCOMES (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON DISEASE STUDIES — FULL ANALYSIS SET

	SP515 (23 weeks)			SP650 (29 weeks)		
Outcome	**Placebo N = 100**	**Rotigotine N = 201**	**Pramipexole N = 200**	**Placebo N = 119**	**Rotigotine 8 mg/ 24 hours N = 113**	**Rotigotine 12 mg/ 24 hours N = 109**
Absolute "Off" Time (hours/day)						
Baseline mean (SD)[a]	6.5 (2.8)	6.3 (2.5)	6.0 (2.5)	6.4 (2.6)	6.7 (2.5)	6.3 (2.6)
LS mean change (SE) from baseline to end of maintenance phase	–0.9 (0.29)	–2.5 (0.20)	–2.8 (0.20)	–0.9 (2.83)	–2.7 (0.32)	–2.1 (0. 32)
Rotigotine – placebo difference (95% CI) *P* value	−1.58 (−2.27, −0.90) < 0.001			8 mg/24 hours −1.8 (–2.6,–1.0) < 0.001 12 mg/24 hours –1.2 (–2.0,–0.4) 0.003		

	SP515 (23 weeks)			SP650 (29 weeks)		
Outcome	**Placebo N = 100**	**Rotigotine N = 201**	**Pramipexole N = 200**	**Placebo N = 119**	**Rotigotine 8 mg/ 24 hours N = 113**	**Rotigotine 12 mg/ 24 hours N = 109**
Pramipexole – placebo difference (95% CI) *P* value	–1.94 (–2.63, –1.25) NA			NA		
Response to Therapy (%)						
Responders[b,c] N (%)	35 (35)	120 (60)	134 (67)	41 (34)	64 (57)	60 (55)
Rotigotine – placebo difference (95% CI) *P* value	24.7 (13.2, 36.3) < 0.0001			8 mg/24 hours 22.2 (9.7, 34.7) < 0.001 12 mg/24 hours 20.6 (7.9, 33.3) < 0.001		
Pramipexole – placebo difference (95% CI) *P* value	32.0 (20.6,43.4) NA			NA		

CI = confidence interval; LS = least squares; NA = not applicable; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: SP515,[7] SP650.[8]
[a]Based on safety set.
[b]Patients with a 30% reduction or greater in absolute "off" time from baseline to end of maintenance are "responders."
[c]Response rates analyzed using asymptotic normal approximation methodology.

FIGURE 4: ROTIGOTINE VERSUS PRAMIPEXOLE IN SP515 NON-INFERIORITY ANALYSIS (ADJUSTED MEAN CHANGE IN ABSOLUTE OFF TIME FROM BASELINE TO END OF MAINTENANCE PHASE)

Figure 4 contained confidential data and was removed at the manufacturer's request.

FIGURE 5: ROTIGOTINE VERSUS PRAMIPEXOLE IN SP515 NON-INFERIORITY ANALYSIS (RESPONDER ANALYSIS TEST RESULTS)

Figure 5 contained confidential data and was removed at the manufacturer's request.

TABLE 19: HEALTH-RELATED QUALITY OF LIFE AND COMPLIANCE (BASELINE TO END OF MAINTENANCE PHASE) FOR EARLY PARKINSON DISEASE STUDIES — SAFETY ANALYSIS SET

	SP512 (27 weeks)		SP513 (37 weeks)		
Outcome	**Placebo (n = 96)**	**Rotigotine (n = 180)**	**Placebo (n = 118)**	**Rotigotine (n = 215)**	**Ropinirole (n = 228)**
HRQoL (EQ-5D VAS Health State Score)					
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (SD) from baseline to end of maintenance phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median change (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance					
Compliant (patches) (> = 85% and < 115%), N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-compliant (patches), high (> = 115%), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-compliant (patches), low (< = 85%), n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Compliant (capsules) (> = 85% and < 115%), N (%)		[redacted]	[redacted]	[redacted]	[redacted]
Non-compliant (capsules), high (> = 115%), n/N (%)			[redacted]	[redacted]	[redacted]
Non-compliant (capsules), low (< = 85%), n/N (%)			[redacted]	[redacted]	[redacted]

EQ-5D VAS = EuroQol 5-dimensional scale visual analogue scale; HRQoL = health-related quality of life; SD = standard deviation.
Source: SP512,[5] SP513.[6]

TABLE 20: HEALTH-RELATED QUALITY OF LIFE AND COMPLIANCE (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON DISEASE STUDIES — SAFETY ANALYSIS SET

	SP515 (23 weeks)			SP650 (29 weeks)		
Outcome	**Placebo N = 100**	**Rotigotine N = 201**	**Pramipexole N = 200**	**Placebo N = 119**	**Rotigotine 8 mg/ 24 hours N = 113**	**Rotigotine 12 mg/ 24 hours N = 109**
EQ-5D Health State Score from Baseline to End of Maintenance Phase[a]						
Mean (SD) at baseline						
Mean change (SD) from baseline to end of maintenance phase						
Median change (min, max)						
PDQ-39 Single Index Score Mean Change from Baseline Values						
Mean (SD) at baseline						
Mean change (SD)						
Median change (min, max)						
Compliance						
Compliant (patches) (> = 85% and < 115%), N (%)						
Non-compliant (patches), High (> = 115%), n/N (%)						
Non-compliant (patches), low (< = 85%), n/N (%)						
Compliant (capsules) (> = 85% and < 115%), N (%)						
Non-compliant (capsules), High (> = 115%), n/N (%)						
Non-compliant (capsules), Low (< = 85%), n/N (%)						

EQ-5D = EuroQol 5-dimensional scale; PDQ-39 = Parkinson's Disease Questionnaire-39; SD = standard deviation.
Source: SP515,[7] SP650.[8]
[a]Based on full analysis set for SP650.

TABLE 21: PARKINSON DISEASE SLEEP SCALE SUM SCORE IN SP515 (BASELINE TO END OF MAINTENANCE PHASE) — SAFETY SET

	SP515 (23 weeks)		
PDSS Sum Score	**Placebo N = 99**	**Rotigotine N = 205**	**Pramipexole N = 201**
Mean (SD) at baseline	95.3 (22.48)	93.2 (24.44)	96.2 (22.99)
Mean Change (SD) from baseline to end of maintenance phase	–2.9 (21.78)	4.4 (21.07)	4.8 (19.30)
Median change (min, max)	–2.9 (–86.8, 62.1)	1.8 (–69.6, 69.3)	3.6 (–60.6, 84.6)

PDSS = Parkinson's Disease Sleep Scale; SD = standard deviation.
Source: SP515.[7]
Note: PDSS scores were measured in millimetres (0–100), then converted to centimetres (0–10) for the analysis.

TABLE 22: UNIFIED PARKINSON DISEASE RATING SCALE PART III ONLY AND PART II ONLY (BASELINE TO END OF MAINTENANCE PHASE) FOR EARLY PARKINSON DISEASE — FULL ANALYSIS SET

	SP512 (27 weeks)		SP513 (37 weeks)		
Outcome	**Placebo (n = 96)**	**Rotigotine (n = 177)**	**Placebo (n = 118)**	**Rotigotine (n = 215)**	**Ropinirole (n = 228)**
UPDRS Part III					
Mean (SD) at baseline	21.3 (8.23)	21.6 (8.90)	22.6 (9.90)	23.8 (9.44)	23.2 (9.38)
Mean change (SD) from baseline to end of maintenance phase	0.5 (6.74)	−1.1 (2.98)	−2.1 (7.84)	−5.3 (7.49)	−8.0 (7.82)
Median change (min, max)	−0.8 (−20.0, 15.0)	−4.0 (−25.0, 23.5)	−2.0 (−28.0, 18.0)	−5.0 (−32.0, 14.0)	−7.0 (−46.0, 10.0)
UPDRS Part II					
mean (SD) at baseline	8.7 (4.02)	8.3 (4.62)	8.7 (3.56)	9.3 (4.22)	9.1 (4.17)
Mean change (SD) from baseline to end of maintenance phase	1.0 (3.31)	−0.3 (3.54)	−0.2 (3.52)	−2.0 (3.51)	−3.0 (3.68)
Median change (min, max)	1.0 (−9.0, 13.0)	−1.0 (−9.0, 15.0)	0.0 (−10.0, 13.0)	–2.0 (−11.0, 9.0)	−3.0 (−18.0, 9.0)

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Study SP512,[5] SP513.[6]

TABLE 23: UNIFIED PARKINSON DISEASE RATING SCALE PART III ONLY AND PART II ONLY (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON DISEASE — FULL ANALYSIS SET

	SP515 (23 weeks)			SP650 (29 weeks)		
Outcome	Placebo N = 100	Rotigotine N = 201	Pramipexole N = 200	Placebo N = 119	Rotigotine 8 mg/ 24 hours N = 113	Rotigotine 12 mg/ 24 hours N = 109
UPDRS Part III						
Mean (SD) at baseline	26.8 (11.35)	26.3 (11.43)	26.4 (11.63)	26.3 (13.92)	26.3 (14.71)	27.0 (12.18)
Mean change (SD) from baseline to end of maintenance phase	–4.3 (9.30)	–8.7 (7.99)	–10.3 (8.69)	–3.4 (11.98)	–6.8 (9.94)	–8.7 (10.45)
Median change (min, max)	–3.0 (–29.0, 21.0)	–8.0 (–30.0, 12.0)	–9.0 (–39.0, 14.0)	–3.0 (–67.0, 25.0)	–6.0 (–42.0, 14.0)	–6.0 (–52.0, 9.0)
UPDRS Part II						
Mean (SD) at baseline	12.8 (6.22)	12.3 (5.83)	12.1 (5.95)	12.4 (6.16)	13.2 (6.52)	13.6 (6.70)
Mean change (SD) from baseline to end of maintenance phase	–2.0 (4.28)	–4.2 (4.51)	–4.6 (4.38)	–0.5 (4.78)	–3.1 (5.61)	–3.2 (4.86)
Median change (min, max)	–2.0 (–18.0, 8.0)	–4.0 (–18.0, 7.0)	–4.0 (–21.0, 7.0)	0.0 (–19.0, 9.0)	–2.0 (–26.0 , 7.0)	–3.0 (–17.0, 6.0)

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: SP515,[7] SP650.[8]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse Events

In all studies, the overall frequency of AEs was generally high, though similar between-treatment groups. The most common AEs in both EPD and APD studies were application site reaction, nausea, and somnolence. In the EPD studies, 89% and 90% of patients in the placebo and rotigotine groups, respectively, in SP512, and 77%, 85%, and 82% in the placebo, rotigotine, and ropinirole groups, respectively, in SP513 experienced at least one AE. In the APD studies, 66%, 69%, and 69% of patients in the placebo, rotigotine, and pramipexole groups, respectively, in SP515, and 91%, 93%, and 93% in the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively, in SP650 experienced at least one AE.

3.7.2 Serious Adverse Events

In all studies, the frequency of SAEs was generally low and similar between-treatment groups. In the EPD studies, 4% and 7% of patients in the placebo and rotigotine groups, respectively, in SP512, and 8%, 10%, and 13% in the placebo, rotigotine, and ropinirole groups, respectively, in SP513 experienced at least one SAE. In the APD studies, 9%, 9%, and 7% of patients in the placebo, rotigotine, and pramipexole groups,

respectively, in SP515, and 8%, 7%, and 10% in the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively, in SP650 experienced at least one SAE.

3.7.3 Withdrawals Due to Adverse Events

Overall withdrawals due to adverse events (WDAEs) were relatively high and more prevalent in the active treatment groups. The most common reasons for WDAEs in EPD studies were application site reaction, Parkinsonism aggravated, somnolence, dizziness, and nausea. The most common reasons for WDAEs in APD studies were general disorders and application site reactions, nausea and vomiting, and nervous system disorders. In the EPD studies, 6% and 14% of patients in the placebo and rotigotine groups, respectively, in SP512, and 5%, 17%, and 13% in the placebo, rotigotine, and ropinirole groups, respectively, in SP513 were WDAEs. In the APD studies, 5%, 5%, and 7% of patients in the placebo, rotigotine, and pramipexole groups, respectively, in SP515, and 8%, 16% and 15% in the placebo, 8 mg per 24 hours rotigotine, and 12 mg per 24 hours rotigotine groups, respectively, in SP650 were WDAEs.

3.7.4 Mortality

There were two deaths (< 1%) in the ropinirole group in SP513. In SP515, there was one death (1%) in the placebo group and one death (< 1%) in the rotigotine group. In SP650, there were two deaths (2%) in the placebo group and two deaths (2%) in the 8 mg per 24 hours rotigotine group. Deaths were not considered to be related to the study drug, according to the investigators.

3.7.5 Notable Harms

The CDR reviewers, in discussion with the clinical expert involved in the review, a priori identified several AEs of interest: arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy. In all studies, the incidence of these identified AEs was very low.

TABLE 24: HARMS FOR EARLY PARKINSON DISEASE STUDIES, SAFETY SET

	SP512		SP513		
	Placebo (n = 95)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
AEs					
Patients with > 0 AEs, N (%)	85 (89)	163 (90)	91 (77)	183 (85)	188 (82)
Most common AEs[a]					
Application site reaction	11 (12)	79 (44)	13 (11)	81 (38)	17 (7)
Nausea	16 (17)	75 (41)	19 (16)	63 (29)	82 (36)
Somnolence	19 (20)	60 (33)	24 (20)	50 (23)	64 (28)
SAEs					
Patients with > 0 SAEs, N (%)	4 (4)	13 (7)	10 (8)	22 (10)	29 (13)
WDAEs					
WDAEs, N (%)	6 (6)	25 (14)	6 (5)	37 (17)	29 (13)
Most common reasons					
Application site reaction	0	9 (5)	0	18 (8)	0
Parkinsonism aggravated	2 (2)	1 (< 1)	0	0	0
Somnolence	0	3 (2)	0	0	3 (1)
Dizziness	1 (1)	0	0	0	4 (2)
Nausea	0	2 (1)	0	6 (3)	6 (3)

	SP512		SP513		
	Placebo (n = 95)	Rotigotine (n = 181)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
Deaths					
Number of deaths, N (%)	0	0	0	0	2 (< 1)
Notable Harms, N (%)					
Arrhythmias	1 (1)	1 (< 1)	3 (3)	0	1 (< 1)
Impulsive/asocial behaviour	0	0	0	0	0
Sudden onset of sleep	0	2 (1)	0	6 (3)	4 (2)
Syncope	1 (1)	2 (1)	4(2)	2 (< 1)	7 (3)
Valvulopathy	0	0	0	0	0

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Study SP512,[5] SP513.[6]
[a]Frequency > 1%.

TABLE 25: HARMS FOR ADVANCED PARKINSON DISEASE STUDIES, SAFETY SET

	SP515			SP650		
	Placebo (n = 99)	Rotigotine (n = 205)	Pramipexole (n = 202)	Placebo (n = 120)	Rotigotine 8 mg/ 24 hours (n = 118)	Rotigotine 12 mg/ 24 hours (n = 111)
AEs						
Patients with > 0 AEs, N (%)	65 (66)	141 (69)	140 (69)	109 (91)	110 (93)	103 (93)
Most common AEs[a]						
Application site reaction	10 (10)	42 (21)	17 (8)	16 (13)	43 (36)	51 (46)
Nausea	11 (11)	35 (17)	26 (13)	22 (18)	33 (28)	23 (21)
Somnolence	8 (8)	25 (12)	24 (12)	32 (27)	36 (31)	36 (32)
SAEs						
Patients with > 0 SAEs, N %)	9 (9)	19 (9)	15 (7)	10 (8)	8 (7)	11 (10)
WDAEs						
WDAEs, N (%)	5 (5)	11 (5)	15 (7)	10 (8)	19 (16)	17 (15)
Most common reasons						
General disorders and application site reaction	1 (1)	5 (2)	0	1 (< 1)	2 (2)	4 (4)
Nausea and vomiting	0	3 (1)	1 (< 1)	0	5 (4)	5 (5)
Nervous system disorders	0	2 (1)	4 (2)	3 (3)	10 (8)	4 (4)
Deaths						
Number of deaths, N (%)	1 (1)	1 (< 1)	0	2 (2)	2 (2)	0
Notable Harms, N (%)						
Arrhythmias	3 (3)	4 (2)	6 (3)	1 (< 1)	1 (< 1)	0
Impulsive/asocial behaviour	0	0	1 (0.5)	0	0	1 (< 1)
Sudden onset of sleep	0	0	1 (< 1)	0	0	1 (< 1)
Syncope	1 (1)	3 (2)	2 (1)	1 (< 1)	0	0
Valvulopathy	0	1 (< 1)	0	0	0	0

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: SP515,[7] SP650.[8]
[a]Frequency > 1%.

4. DISCUSSION

4.1 Summary of Available Evidence

Four published, manufacturer-sponsored, double-blind RCTs were included in this systematic review: SP512[5] and SP513[6] in EPD, and SP515[7] and SP650[8] in APD. In SP512 (N = 277), patients received an initial dose of rotigotine 2 mg per 24 hours and were titrated weekly up to 6 mg per 24 hours by transdermal application or matching placebo transdermal patches. In SP513 (N = 561), patients received an initial dose of rotigotine 4 mg per 24 hours and were titrated weekly up to 8 mg per 24 hours by transdermal application, ropinirole capsules taken orally at doses of 0.25 mg titrated weekly up to 5.0 mg, or matching placebo transdermal patches or capsules. In SP515 (N = 506), patients were treated with an initial dose of rotigotine 4 mg per 24 hours titrated weekly up to 16 mg per 24 hours by transdermal application, pramipexole capsules taken orally at doses of 0.375 mg titrated weekly up to 4.5 mg, or matching placebo transdermal patches or capsules. In SP650 (N = 351), patients received either a target dose of rotigotine 8 mg per 24 hours or 12 mg per 24 hours by transdermal application, or matching placebo transdermal patches. No trials comparing rotigotine with levodopa among EPD patients, or trials comparing rotigotine with either entacapone or MAO-B inhibitors among APD patients were found in the scientific literature. All included studies had appropriate randomization and allocation concealment strategies, with generally similar treatment groups at baseline, with the exception of the proportion of males and gastrointestinal disorders. Overall, withdrawal rates were high though similar across treatment groups. Subgroup analyses for patients with severe gastrointestinal disorders or patients who are uncontrolled or intolerant on pramipexole or ropinirole were not performed in the included studies.

4.2 Interpretation of Results

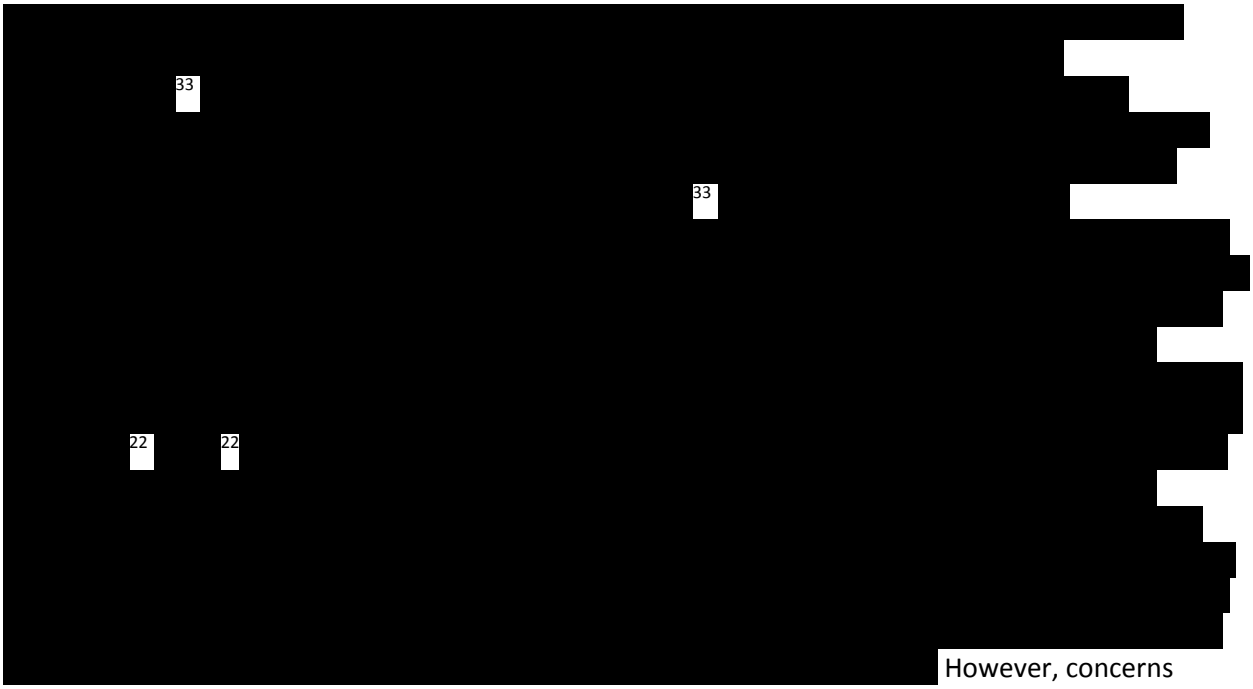
4.2.1 Efficacy

The primary efficacy outcomes in the EPD studies were mean change in UPDRS (parts II and III subscale) score from baseline to the end of the maintenance phase (US primary end point) and mean change in response to therapy (defined as a 20% or greater decrease in UPDRS score) from baseline to the end of the maintenance phase (EU primary end point). In both EPD studies, rotigotine was statistically significantly superior to placebo for both primary efficacy outcomes. Although the MCID for the UPDRS parts II and III subscale total is uncertain (varying ranges, methodologies of derivation, and patient population characteristics), differences between rotigotine and placebo were deemed to be clinically significant by the clinical expert consulted in this review. However, in SP513, the treatment effects were greatest among the ropinirole group for both primary outcomes. Rotigotine did not demonstrate non-inferiority to ropinirole for either the US and EU primary end points in either the FAS or PP analyses. A potential reason for this may be the dose of ropinirole patients received during the maintenance phase, which was higher than would usually be seen in practice for patients with EPD. The clinical expert involved in the review noted that the typical ropinirole dose that is prescribed to patients with EPD ranges between 10 and 15 mg per day; thus, the dose used in SP513 (24 mg per day) was relatively high. Furthermore, there were fewer males in the ropinirole group (40%) than in the rotigotine (55%) and placebo (58%) groups. It is uncertain whether sex differences affected the results, as the clinical expert confirmed that research in this area is limited. Concomitant medication use was generally similar in all treatment groups in the EPD studies, with the exception of more patients taking adamantine derivatives in the placebo group of SP512, potentially favouring the results within this group (Table 28).

The primary efficacy outcomes in the APD studies were mean absolute change in time spent “off” from baseline to the end of the maintenance phase (US primary end point) and mean change in response to therapy (defined as a 30% or greater decrease in time spent “off”) from baseline to the end of the

maintenance phase (EU primary end point). In both APD studies, rotigotine was statistically significantly superior to placebo for both primary efficacy outcomes, with clinically significant differences according to the clinical expert involved in the review. A difference in one hour of "off" time was deemed to be clinically significant, according to the scientific literature[27] and the clinical expert. In SP515, the treatment effects were greatest among the pramipexole group, though comparable to the rotigotine group. Rotigotine was found to be non-inferior to pramipexole for mean absolute change in time spent "off," but not for the response to therapy end point. For 23 weeks or greater, the majority of patients in the rotigotine group were exposed to the 16 mg per 24 hours dose, while the majority of patients in the pramipexole group were exposed to a dose of 4.5 mg (Table 15). The clinical expert noted that the dose of pramipexole was typical of clinical practice. According to the clinical expert, concomitant levodopa use in both APD studies likely had minimal impact on the results, as usage was generally similar among all treatment groups, doses were reflective of clinical practice, and there was minimal variation in dosing over the trial (Table 32). Concomitant medication use was generally similar in all treatment groups in the APD studies, except that almost double the amount of patients were taking entacapone in the rotigotine group of SP512. Increased usage of entacapone may have potentially favoured the treatment effect of rotigotine, although according to the clinical expert, the effect was likely minimal. Catechol-O-methyltransferase (COMT) inhibitors, particularly entacapone, have been used in patients with APD as an adjunct to levodopa to extend its effect.[36]

The selected cut point of a ≥ 20% decrease in UPDRS (parts II and III) subtotal score appears to be reasonable, considering the baseline mean was approximately 30 points; thus, responders were defined as patients who had an approximate decrease of 6 points, which falls within the MCID range (3.5 to 8 points) seen in other studies.[25-27] Similarly, the cut point of a ≥ 30% decrease in absolute "off" time appears reasonable, as the baseline mean was approximately 6.5 hours per day; thus, responders were defined as patients who experienced a reduction of approximately two hours, which is clinically meaningful according to the clinical expert involved in the review.



However, concerns surrounding the selection of the non-inferiority margins may be mitigated somewhat, as the chosen margins were selected a priori, non-inferiority analysis results among the FAS and PPS populations were

consistent, and both non-inferiority studies were adequately powered. The non-inferiority margin of 2.9 points for the change in UPDRS subtotal score in SP513 falls below the range of MCIDs (3.5 to 8 points) seen in other studies[25-27] and, therefore, may be reasonable. The situation is less clear regarding the non-inferiority margin of 1.2 hours of "off" time in SP515 for which the MCID is less certain and may range from one to two hours (as confirmed by the clinical expert involved in the review). Furthermore, given the nature of the results, with the exception of the "off" time end point in SP515, it is unlikely that slight differences in the non-inferiority margins would have affected the overall interpretation of the results.

The overall proportion of patients who discontinued from the study was relatively high, though similar among all treatment groups in the included studies. The majority of discontinuations were due to AEs that were distinct to PD, as confirmed by the clinical expert. There was a large discrepancy between the FAS and PPS populations, as numerous patients encountered protocol deviations due to prohibited concomitant medication use. The proportions of patients encountering protocol deviations were generally similar between-treatment groups. Despite the differences in the FAS and PPS populations, results for both analysis sets were consistent.

In all included studies, improvement in HRQoL, nocturnal sleep (SP515), UPDRS "motor symptoms" (part III only) scores, and UPDRS "activities of daily living" (part II only) scores should be interpreted with caution as they were considered exploratory outcomes, likely not sufficiently powered to detect differences, and were analyzed descriptively.

In the EPD studies, improvement in HRQoL was demonstrated only in SP513 among the active treatment groups. There was no effect on HRQoL measured with the EQ-5D VAS among patients treated with rotigotine in SP512. In SP513, mean change in EQ-5D VAS was greatest in the ropinirole group. The responsiveness of the EQ-5D VAS is questionable, as it is only one component of the generic preference-based HRQoL instrument.

Overall, compliance rates for all treatment methods (patches and capsules in SP513) were high and similar in all treatment groups. Improvements in the UPDRS part III (motor symptoms) scores and UPDRS part II (ADL) scores were greatest in the active treatment groups in each EPD study. In SP513, the greatest improvements in the UPDRS part III (motor symptoms) scores and UPDRS part II (ADL) scores were demonstrated in the ropinirole group.

In APD studies, improvement in HRQoL was demonstrated in all active treatment groups. In SP515, mean change in HRQoL, measured by the PDQ-39 single index score, was greatest among the active treatment groups, with relatively similar results in the rotigotine and pramipexole groups. The PDQ-39 is a disease-specific measure, and likely more responsive to change related to the disease and its treatment. In SP650, improvement in the EQ-5D VAS was greatest in the rotigotine 8 mg per 24 hours group compared with the rotigotine 12 mg per 24 hours group.

Similar to the EPD studies, compliance rates for all treatment methods (patches and capsules in SP515) were high and similar in all treatment groups. In SP515, improvements in nocturnal sleep measured by the PDSS scores from baseline to the end of maintenance phase were greatest in the pramipexole group. According to the clinical expert, baseline PDSS scores indicated that APD patients likely had sleep disturbances. Improvements in the UPDRS part III (motor symptoms) scores and UPDRS part II (ADL) scores were greatest in the active treatment groups in each APD study. In SP515, the greatest improvements in both UPDRS measures were demonstrated in the pramipexole group, while in SP650,

the greatest improvements were demonstrated among patients receiving the higher 12 mg per 24 hours dose of rotigotine.

A total of four extension studies assessed the long-term safety, tolerability, and efficacy of rotigotine in patients with EPD and APD. Two single-arm, open-label extension studies, SP702 (N = 216)[37] and SP716 (N = 380),[38] assessed patients for up to six years from the two included EPD studies. In both studies, UPDRS parts II and III subtotal scores declined, with scores declining to baseline values by the second year in SP702, or declining but remaining improved relative to the baseline values in SP716. The UPDRS scores remained at these levels for four years of the open-label phase. Two single-arm, open-label extension studies, SP516 (N = 395)[39] and SP715 (N = 253),[40] assessed patients for up to six years from the two included APD studies (APPENDIX 6: SUMMARY OF SUPPORTIVE STUDIES). In SP516, performance on ADLs declined to baseline levels after four years of treatment, and above baseline levels after six years in SP715. Furthermore, the number of patients experiencing less "off time" improved from the original studies. Rotigotine as an adjunct to levodopa in APD patients appeared to demonstrate continued efficacy over the follow-up period. Given the limitations of the study designs in the extension studies, and with no statistical analyses performed for the efficacy variables, results should be interpreted with caution (APPENDIX 6: SUMMARY OF SUPPORTIVE STUDIES). Three supportive studies, SP506, SP511, and SP889,[22] which did not meet inclusion criteria of this report due to inappropriate study durations, are summarized in APPENDIX 6: SUMMARY OF SUPPORTIVE STUDIES. Only studies with a treatment duration of 16 weeks or greater were included, because this was considered the minimum amount of time needed to see a clinically meaningful response, based on discussion with the clinical expert involved in the review. In all three supportive studies,[22] rotigotine was safe and well tolerated among patients with idiopathic PD. In SP506, statistically significant and clinical meaningful improvements, as determined by changes from baseline in the combined UPDRS parts II and part III scores, were achieved in the rotigotine group compared with placebo. In SP511, the improvement achieved by rotigotine in absolute time spent "off" from baseline to end of treatment was not significantly different from placebo. Rotigotine led to statistically significant and clinically relevant improvements in sleep and early morning akinesia in patients with idiopathic PD in SP889.

A network meta-analysis (NMA) submitted by the manufacturer suggested that pramipexole, ropinirole, and rotigotine were associated with significantly improving ADLs and motor functioning, both at the 11 to 16 and 24 to 28 week time points (with the exception of ropinirole in EPD which was not associated with significantly improving activities in daily life at 11 to 16 weeks) (Appendix 8: CRITICAL APPRIASAL AND SUMMARY OF RESULTS OF THE MULTIPLE TREATMENT COMPARISON META-ANALYSIS).[41] Similar efficacy was demonstrated when each treatment was compared with each other, suggesting similar benefit in EPD and APD patients. In concordance with this report, the NMA highlighted that the ropinirole dose used in SP513, [redacted] was not typical for Canadian practice.[41] Among patients with EPD, treatment with levodopa was found to be more efficacious than rotigotine and placebo in improving motor function and UPDRS-II and III subtotal scores at the 11 to 16 week time point. Strong evidence from current Canadian clinical practice guidelines[2] suggest the use of levodopa, dopamine agonists, and MAO-B inhibitors for the treatment of EPD, and include entacapone and rasagiline for APD. The guidelines further describe levodopa as the most effective treatment for motor symptoms.[2] The clinical expert identified levodopa as typically being the first-line treatment of choice in both EPD and APD patients.

Results from two systematic reviews[42,43] that examined the effect of ergot (e.g., bromocriptine) and non-ergot (e.g., pramipexole, ropinirole) dopamine agonists (DAs), placebo, and levodopa in patients with EPD revealed greater efficacy with levodopa in providing improved motor symptomatic control than any of the DAs, but was associated with an increase in the risk of developing AEs such as dyskinesias and "wearing-off." When combining non-ergot DAs with lower levodopa doses and when used as monotherapy, patients were less likely to develop motor complications, motor fluctuations, or dystonia. DAs in general were associated with an increase in non-motor AEs and WDAEs. Another systematic review with meta-analyses[44] examined the effects of MAO-B and COMT inhibitors when combined with levodopa in patients with APD. Significant improvements in the control of PD symptoms were associated with the use of both the MAO-B and COMT inhibitors when compared with levodopa alone; however, the risk of developing motor complications, such as dyskinesias, remained. MAO-B inhibitors appeared to be more effective at controlling PD symptoms in combination with levodopa and were not associated with an increased risk in WDAEs like the COMT inhibitors (APPENDIX 7: SUMMARY OF COMPARATORS).

Common themes seen as important in the patient group input were: the need for ease of administration, improved medication adherence, maintaining prolonged drug effectiveness, and reducing or eliminating wearing-off periods (APPENDIX 1: PATIENT INPUT SUMMARY). In all trials, rotigotine appeared to meet each of these needs with high compliance rates with transdermal patches that were applied once daily, though compliance was comparable to other active treatments. Clinically significant reductions in "off" time were demonstrated with use of rotigotine in the APD studies.

4.2.2 Harms

The overall safety results in all the studies revealed that although AEs were high, frequencies were generally similar between all treatment groups. The most common treatment-related AEs were application site reactions, predominantly seen in the rotigotine groups. Application site reactions appear to be an important safety outcome among patients, as a substantial amount of them (38%) noted that they would not tolerate significant skin rash (APPENDIX 1: PATIENT INPUT SUMMARY). With such an extensive difference between application site reactions among patients being treated with rotigotine compared with patients receiving placebo or other active comparators (ropinirole in SP513 and pramipexole in SP515), blinding may have been compromised.

Other common AEs were nausea and somnolence, both of which were greater in the rotigotine group compared with placebo. Frequency of nausea and somnolence were greater among EPD patients receiving ropinirole in SP513 compared with rotigotine. Frequency of nausea was greater among APD patients receiving rotigotine, while frequency of somnolence was comparable with pramipexole in SP515. According to the patient input summary (APPENDIX 1: PATIENT INPUT SUMMARY), nausea is another noteworthy safety outcome among patients, as a substantial amount of patients (49%) would not tolerate this adverse effect.

The frequency of SAEs was low and balanced between-treatment groups. WDAEs were greatest in the rotigotine groups in SP512, SP513, and SP650, and similar in all treatment groups in SP515. In the EPD studies, the most common reason for WDAEs was application site reactions, which was prevalent only in the rotigotine groups. In the SP650, the most common reason for WDAEs was nervous system disorders, which were most prevalent in the rotigotine group. In SP515, WDAEs were low and similar in all treatment groups. Overall, there were two deaths in the EPD studies and six deaths in the APD studies, none of which were treatment related. Rotigotine did not appear to have an effect on arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy. As indicated in the product monograph of rotigotine,[4] ropinirole,[11] and pramipexole,[12] sudden onset of sleep is listed as a

serious warning and precaution. This was not reflected in the included studies, as sudden onset of sleep was uncommon among patients receiving each respective treatment.

In the EPD extension studies (SP702 and SP716), rotigotine appeared to be generally well tolerated; more than half of the patients remained on rotigotine at study completion. Common AEs such as somnolence, nausea, and application site reactions were highest in the first year of both open-label extension studies and then decreased in subsequent years. It is unknown whether these AEs were associated with lower rotigotine doses or whether either patients became accustomed to them and did not report them as such, or the AEs subsided with higher rotigotine dosing. In the APD extension studies (SP516 and SP715), treatment continued to be generally well tolerated with approximately 20% of patients discontinuing due to AEs after four years in SP516 and 28% after six years in SP715. The most common of these were somnolence, dyskinesias, applications site reactions, falls, hallucinations, and nausea, with the majority categorized as either mild or moderate in intensity. Nausea and application site reactions were reported to be increased with the lower rotigotine doses used at the beginning of the open-label extension study (APPENDIX 6: SUMMARY OF SUPPORTIVE STUDIES).

5. CONCLUSIONS

Based on two double-blind RCTs in patients with EPD, rotigotine resulted in statistically significant and clinically meaningful improvements in UPDRS subscale scores (parts II and III) and a greater proportion of responders when compared with placebo. The comparison of rotigotine with ropinirole failed to demonstrate non-inferiority and may have been limited by non-equivalence between rotigotine and ropinirole doses. Two double-blind RCTs in patients with APD also demonstrated statistically significant and clinically meaningful improvements in time spent "off" and a greater proportion of responders when patients were treated with rotigotine compared with placebo. The comparison of rotigotine with pramipexole was statistically non-inferior with regard to absolute differences in time spent "off," but not non-inferior for response to therapy. Without between-group comparisons, there is uncertainty regarding differences in HRQoL and nocturnal sleep between rotigotine and placebo or other active comparators (ropinirole and pramipexole). Compliance with study medication was high and similar in all treatment groups. Overall, rotigotine was generally well tolerated, though delivery of rotigotine with a transdermal patch was associated with application site reactions not experienced with oral DAs. The incidence of AEs such as arrhythmias, impulsive or asocial behaviour, sudden onset of sleep, syncope, and valvulopathy with rotigotine did not appear to differ versus placebo, ropinirole, or pramipexole, although studies were not designed to identify between-group differences in these.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient group.

Brief Description of Patient Group(s) Supplying Input

Parkinson Society Canada (PSC) works through regional partners, chapters, and support groups to invest in research and provide education, support, and advocacy on behalf of the more than 100,000 Canadians living with PD. Individual donations account for 97% of annual funding. In 2012, corporate contributors to PSC included AbbVie, Assomption Vie, Bethel Windows and Doors, Business Development Bank of Canada, Canada Life Assurance Company, Charity Intelligence Canada, Clorox Company, Garden Centre Group Co-op Corporation, IBM Canada Ltd, Lombard Canada Ltd, Lubrizol Canada Ltd, McDonald's Corporation, McLean Budden, Nestlé, Nintendo, Oxford Frozen Foods Ltd, Potash Corporation of Saskatchewan Inc., Quali-Grow Garden Products Inc., S&C Electric Canada Ltd, Teva Canada Innovation GP-SENC, TNS Canadian Facts, Trans-Northern Pipelines Inc., Trylon TSF Inc. (TSF CDN), Wawanesa Mutual Insurance Company, Leon's Furniture Ltd, Novartis, and UCB Canada. PSC declared no conflict of interest in the preparation of its submission.

Condition and Current Therapy-Related Information

Information was gathered through a national survey of people living with PD and their care partners in April 2013. More than 600 individuals participated in the bilingual survey (70% patients, 30% caregivers), which comprised a variety of closed- and open-ended questions, including 10-point scale scoring options. Ninety-eight per cent of respondents were residents of Canada and 2% were residents of the United States.

PD is a complex disorder that can be difficult to diagnose, especially in the early stages. Neuropsychiatric symptoms are prevalent even prior to the motor symptoms of PD and become more prominent and challenging to treat with disease progression. The most common symptoms reported by survey respondents included loss of motor control or dexterity, muscle stiffness, nausea, tremors, fatigue, sleep disturbances, mood changes, reduced mobility, memory and cognitive impairment, speech impairment, balance problems, and restless legs. Other symptoms include — but are not limited to — depression, dementia, psychosis, autonomic dysfunction, urinary dysfunction, orthostatic hypotension, constipation, and erectile dysfunction. Respondents indicated the most important symptoms to control were tremors, cognitive issues, dyskinesia, impaired balance and mobility, rigidity of muscles, and sleep problems. Seventy-seven per cent of patient respondents indicated their quality of life has "decreased" or "greatly decreased" since being first diagnosed with PD. Among caregivers, 67% indicated that caring for a loved one with PD has affected their quality of life either "significantly" or "very significantly."

Patients reported experiencing an inability to maintain employment, diminished ability to perform household tasks, reduced participation in family activities, and reduced ability to participate in social or recreational activities. In severe situations, some patients require caregiver support with almost every daily activity, including dressing, hygiene, cutting food to eat, and writing. The impact of PD on caregivers varies with severity of disease. Some caregivers providing support for less severely ill patients report only a few hours a week of care provision, while caregivers of patients with advanced PD need to provide care around the clock. Thus, caregivers have less time for themselves, which may affect their work and social lives. For some, their inability to help alleviate the suffering of those they support causes additional emotional burden.

Current treatment options for patients with PD include non-pharmacological interventions such as physiotherapy, occupational therapy, and other support services, which provide some improvement in quality of life. However, as the disease progresses, patients become more reliant on medication to maintain their ability to function. Medication schedules become more complex and the timing of medication administration becomes crucial because “off periods” (time without medication effect) can strike quickly and at any time, leaving patients immobilized. Seventy-five per cent of respondents experienced “off periods” or “wearing-off” periods with durations varying from less than one hour to between two and five hours. Forty-two per cent of patients found it difficult to adhere to their medication schedules. Caregivers also noted challenges with proper and timely medication administration.

Patients and caregivers reported that common side effects to current medications include nausea, vomiting, dizziness, sleep disruption, mood changes, visual hallucinations, and obsessive compulsive behaviour.

Related Information About the Drug Being Reviewed

Most (78%) respondents deemed it “very important” to have choice and access to PD treatments. Patient and caregiver respondents were unaccepting of significant side effects in new treatments; 59% would not tolerate changes in behaviour, 49% would not tolerate significant nausea, and 38% would not tolerate significant skin rash. To overcome the difficulties associated with keeping up with dosing requirement of current therapies, 78% of survey respondents deemed it “very important” to have access to treatment with a once-a-day dosing schedule. In this regard, patients and caregivers expect rotigotine to meet the need for ease of administration, improved medication adherence, maintaining prolonged drug effectiveness, and reducing or eliminating wearing-off periods.

Three US citizens currently using rotigotine to control PD symptoms were consulted due to difficulties identifying Canadian patients with rotigotine experience. Their experiences suggest an improvement over existing therapy. According to clinicians who led the three Canadian trials, rotigotine has a similar motor benefit and side effect profile to oral dopamine agonists. It has the additional benefit of once-a-day administration, which improves compliance and provides continuous infusion of medication to reduce off periods, improves sleep, confers better morning periods, and decreases overnight freezing. The transdermal patch is also an advantage for PD patients with difficulty swallowing. During the clinical trial, the most commonly seen negative effect was minor skin rash at the site of patch application, which was generally tolerable and manageable by patients. Patients strongly believe Canadians affected by PD would be best served by having access to rotigotine as a treatment option to help manage the disease.

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:	September 6, 2013
Alerts:	Weekly search updates until January 15, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used 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
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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
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

#	Searches	Results
1	(rotigotine* or Neupro* or leganto* or N0437* or N0923* or N0924*).ti,ot,ab,sh,rn,hw,nm.	1559
2	92206-54-7.rn,nm.	1317
3	1 or 2	1663
4	3 use pmez	338
5	*rotigotine/	366
6	(neupro* or rotigotine* or leganto* or N0347* or N0923* or N0924*).ti,ab.	642
7	5 or 6	758
8	conference abstract.pt.	1126937
9	7 not 8	637
10	9 use oemezd	411
11	4 or 10	749
12	remove duplicates from 11	465

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:	September 2013
Keywords:	Neupro; rotigotine; Parkinson's disease
Limits:	No date or language limits used

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Parkinson Study Group (2003)[32]	Inappropriate study duration
Clinical Trial Report [protocol no. sp889][45]	Inappropriate study duration
Watts et al. (2007)[46]	Erratum (to Watts 2007)
Trenkwalder et al. (2011)[47]	Inappropriate study duration
Giladi et al. (2013)[38]	Inappropriate study design (open-label)
Mizuno et al. (2013)[48]	Inappropriate study duration

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 26: KEY EFFICACY OUTCOMES (BASELINE TO END OF MAINTENANCE PHASE) FOR EARLY PARKINSON DISEASE STUDIES — PER-PROTOCOL SET

	SP512 (27 weeks)		SP513 (37 weeks)		
Outcome	**Placebo (n = 80)**	**Rotigotine (n = 148)**	**Placebo (n = 77)**	**Rotigotine (n = 145)**	**Ropinirole (n = 157)**
UPDRS (Subtotal Part II and III)					
Baseline mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS Mean change (SE) from baseline to end of maintenance phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rotigotine – placebo difference (95% CI)	[redacted]		[redacted]		
P value[a]	[redacted]		[redacted]		
Ropinirole – placebo difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		
Response to Therapy (%)					
Responders[b,c] N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rotigotine – placebo difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		
Ropinirole – placebo difference (95% CI)	[redacted]		[redacted]		
P value	[redacted]		[redacted]		

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Study SP512,[5] SP513.[6]
[a]Treatment effect results adjusted for geographic region and baseline UPDRS by means of a main effects ANCOVA model.
[b]Patients with a 20% reduction or greater in UPDRS (II and III) subtotal from baseline to end of maintenance are "responders."
[c]Response rates analyzed using asymptotic normal approximation methodology.

TABLE 27: KEY EFFICACY OUTCOMES (BASELINE TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON DISEASE STUDIES — PER-PROTOCOL SET

Outcome	SP515 (23 weeks)			SP650 (29 weeks)		
	Placebo N = 73	Rotigotine N = 177	Pramipexole N = 165	Placebo N = 85	Rotigotine 8 mg/ 24 hours N = 84	Rotigotine 12 mg/ 24 hours N = 78
Absolute "Off" Time (Hours/Day)						
Baseline mean (SD)[a]	[redacted]					
LS mean change (SE) from baseline to end of maintenance phase	[redacted]					
Rotigotine – placebo difference (95% CI) *P* value	[redacted]					
Pramipexole – placebo difference (95% CI) *P* value	[redacted]					
Response to Therapy (%)						
Responders[b, c] N (%)	[redacted]					
Rotigotine – placebo difference (95% CI) *P* value	[redacted]					
Pramipexole – placebo difference (95% CI) *P* value	[redacted]					

ANCOVA = analysis of covariance; CI = confidence interval; LS= least squares; SD = standard deviation; SE = standard error.Source: SP515,[7] SP650.[8]

[a]Treatment effect results adjusted for geographic region and baseline UPDRS by means of a main effects ANCOVA model.

[b]Patients with a 20% reduction or greater in UPDRS (II and III) subtotal from baseline to end of maintenance are "responders."

[c]Response rates analyzed using asymptotic normal approximation methodology.

TABLE 28: MEDICATIONS TAKEN DURING TREATMENT PERIOD IN EARLY PARKINSON STUDIES — SAFETY SET

	SP512		SP513		
Medication, n (%)	Placebo (n = 96)	Rotigotine (n = 180)	Placebo (n = 77)	Rotigotine (n = 145)	Ropinirole (n = 157)
Adamantane derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dopa and dopa derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dopamine agonists	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethers chemically close to antihistamines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethers of tropine or tropine derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monoamine oxidase type B inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary amines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Study SP512,[5] SP513.[6]

TABLE 29: MEDICATIONS TAKEN DURING TREATMENT PERIOD IN ADVANCED PARKINSON STUDIES — FULL ANALYSIS SET

	SP515 (23 weeks)			SP650 (29 weeks)		
Medication, n (%)	Placebo N = 100	Rotigotine N = 201	Pramipexole N = 200	Placebo N = 119	Rotigotine 8 mg/ 24 hours N = 113	Rotigotine 12 mg/ 24 hours N = 109
Adamantane derivatives	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monoamine oxidase type B Inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Entacapone	[redacted]	[redacted]	[redacted]	[redacted]		

Source: SP515,[7] SP650.[8]

TABLE 30: CHANGE IN HOEHN AND YAHR STAGE SCORES (PRE-TREATMENT TO END OF MAINTENANCE PHASE) FOR EARLY PARKINSON DISEASE — SAFETY SET

	SP512 (27 weeks)		SP513 (37 weeks)		
Outcome	Placebo (n = 96)	Rotigotine (n = 180)	Placebo (n = 118)	Rotigotine (n = 215)	Ropinirole (n = 228)
Hoehn and Yahr Stage Score					
Mean (SD) at pre-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (SD) from pre-treatment to end of maintenance phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median change (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: Study SP512,[5] SP513.[6]

TABLE 31: CHANGE IN HOEHN AND YAHR STAGE SCORES (PRE-TREATMENT TO END OF MAINTENANCE PHASE) FOR ADVANCED PARKINSON DISEASE — SAFETY SET

	SP515 (23 weeks)			SP650 (29 weeks)		
Outcome	**Placebo N = 100**	**Rotigotine N = 201**	**Pramipexole N = 200**	**Placebo N = 119**	**Rotigotine 8 mg/ 24 hours N = 113**	**Rotigotine 12 mg/ 24 hours N = 109**
Hoehn and Yahr Stage Score						
Mean (SD) at pre-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean CHANGE (SD) from pre-treatment to end of maintenance phase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median change (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: SP515,[7] SP650.[8]

TABLE 32: LEVODOPA USAGE IN ADVANCED PARKINSON STUDIES — SAFETY SET

Levodopa Usage (mg/day)	SP515			SP650		
	Placebo (n = 99)	**Rotigotine (n = 205)**	**Pramipexole (n = 202)**	**Placebo (n = 119)**	**Rotigotine 8 mg/ 24 hours (n = 113)**	**Rotigotine 12 mg/ 24 hours (n = 109)**
Baseline						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Maintenance Phase						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Change from Baseline						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: SP515,[7] SP650.[8]

TABLE 33: ROTIGOTINE VERSUS ROPINIROLE IN SP513 TEST OF NON-INFERIORITY (BASELINE TO END OF MAINTENANCE PHASE)

	SP513 (37 weeks)		
Outcome	**Placebo (n = 117)**	**Rotigotine (n = 213)**	**Ropinirole (n = 227)**
UPDRS (Subtotal Parts II and III) LS Mean Change — Full Analysis Set			
Rotigotine – Ropinirole difference[a] (95% CI)	3.96 (2.18 to 5.73)		
UPDRS (Subtotal Parts II and III) LS Mean Change — Per-Protocol Set			
Rotigotine – Ropinirole difference[a] (95% CI)	5.54 (3.37 to 7.71)		
Response to Therapy (%)[b, c] — Full Analysis Set			
Rotigotine – Ropinirole difference[a] (95% CI)	−16.6 (−25.7 to −7.6)		
Response to Therapy (%)[b, c] — Per-Protocol Set			
Rotigotine – Ropinirole difference[a] (95% CI)	−20.0 (−30.5 to −9.4)		

CI = confidence interval; LS = least squares; UPDRS = Unified Parkinson's Disease Rating Scale. Source: SP513.[6]
[a]Predefined non-inferiority margin (–15% for EU, 2.9 for US)
[b]Denotes one-sided test against ropinirole reduced by the non-inferiority margin (alpha = 0.025)
[c]Patients with a 20% reduction or greater in UPDRS (II and III) subtotal from baseline to end of maintenance are "responders."

TABLE 34: ROTIGOTINE VERSUS PRAMIPEXOLE IN SP515 TEST OF NON-INFERIORITY (BASELINE TO END OF MAINTENANCE PHASE)

	SP515 (23 weeks)		
Outcome	**Placebo N = 100**	**Rotigotine N = 201**	**Pramipexole N = 200**
Absolute "Off" Time (Hours/Day) — Full Analysis Set			
Rotigotine – Pramipexole difference[a] (95% CI)	0.35 (–0.21 to 0.92)		
Absolute "Off" Time (Hours/Day) — Per-Protocol Set			
Rotigotine – Pramipexole difference[a] (95% CI)	0.44 (–0.15 to 1.03)		
Response to Therapy (%)[b, c] — Full Analysis Set			
Rotigotine – Pramipexole difference[a] (95% CI)	–7.3 (–16.7 to 2.1)		
Response to Therapy (%)[b, c] — Per-Protocol Set			
Rotigotine – Pramipexole difference[a] (95% CI)	–6.4 (–16.4 to 3.6)		

CI = confidence interval.
Source: SP515.[7]
[a]Predefined non-inferiority margin (–15% for EU, 1.2 for US).
[b]*P* values are two-sided.
[c]Patients with a 30% reduction or greater in absolute "off" time from Baseline to end of Maintenance are "responders."

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To describe and assess the validity and reliability of functional, mobility, and quality of life measures used in the rotigotine studies:

- Unified Parkinson's Disease Rating Scale (UPDRS)
- Hoehn and Yahr Staging
- The Parkinson's Disease Questionnaire-39 (PDQ-39)
- EuroQol (EQ-5D)
- The Parkinson's Disease Home Diary (PDHD)
- The Parkinson's disease sleep scale (PDSS)

MCIDs are included where available.

Findings

Unified Parkinson's Disease Rating Scale

The UPDRS is a measure of disability and impairment in PD. The scale consists of four parts: part I (mentation, behaviour, and mood: four items), part II (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 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 for both on and off (0 to 52 for the on state and 0 to 52 for the off state); 3) Motor Examination (0 to 56); and 4) Complications of Therapy (0–23).[49] The scale provides a relatively comprehensive assessment of the motor features of PD, but is less comprehensive in its assessment of non-motor symptoms.[50]

The UPDRS has demonstrated high internal consistency, inter-rater reliability, moderate construct validity,[51-53] and patient-investigator reproducibility;[54] however, reliability is reduced when used in mildly impaired individuals.[55] Several estimates of an MCID for the UPDRS have been made, with variation from the method of estimation (anchor or distribution-based), patient population (EPD or APD), intervention, time of evaluation, and study type.[25-27] The estimated MCID on the UPDRS motor component (part III) has ranged from 2.5 to 5 points, and the MCID for the subtotal score (parts I, II, and III) has ranged from 3.5 to 8 points (Table 35). The MCID estimates[25,27] 3.5 and 5 points on the motor component and 8 points on the subtotal score were derived among patients with newly diagnosed and/or EPD and likely cannot be generalized to patients with advanced disease.[25]

TABLE 35: MINIMAL CLINICALLY IMPORTANT DIFFERENCES FOR UPDRS SUBSCALES AND TOTAL SCORES

Study	Methods/Trial Characteristics	Anchor (and Stage)	MCID (Points)	
			UPDRS III (Motor Score)	UPDRS Total Score (Subscales I, II, III)
Schrag et al. 2006	• 2 prospective randomized DB trials • 603 pts with EPD • Active comparators (RP, BC, L-Dopa) • Analysis using 6 months' data	CGI-1	5	8
Shulman et al. 2010	• Assessed during routine office visits • 653 pts with PD (asymmetrical onset of at least 2 or 3 cardinal signs: resting tremor, rigidity, bradykinesia); no atypical signs or exposure to dopamine-blockers • Used anchor- and distribution-based analysis	SF-12 SE Scale HY Scale	2.5	4.5
Hauser et al. 2011	• 2 randomized, PL-controlled, DB trials; comparator RS • Trial 1: 404 pts with EPD (no dopamine therapy) • Trial 2: 472 pts on L-Dopa • Analyzed at 14 weeks of treatment	CGI-1	NA	3.5 (EPD)

BC = bromocriptine; CGI-1 = Clinical Global Impression-Global Improvement; DB = double blind; EPD = early Parkinson disease; HY = Hoehn and Yahr Scale; L-Dopa = levodopa; MCID = minimal clinically important difference; NA = not applicable; PD = Parkinson disease; PL = placebo; pts = patients; RP = ropinirole; RS = rasagiline; SE Scale = Schwab and England Activities of Daily Living Scale; SF-12 = 12-Item Short Form Health Survey, version 2; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Schrag et al.,[25] Shulman et al.,[26] Hauser et al.[27]

Hoehn and Yahr Staging

The Hoehn and Yahr staging scale[56] was introduced in 1967 and was intended to provide an estimate of clinical function in PD.[57] 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.[57] For these reasons, the scale is used in clinical trials to define inclusion and exclusion criteria, but not typically as an outcome measure.

The Parkinson's Disease Questionnaire-39

The PDQ-39 is a disease-specific quality of life scale consisting of 39 items graded on a 5-point scale (0 = never; 4 = always). There are eight domains, consisting of 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).[58] All domains and a summary index may be transformed to have a range of 0 to 100, with higher scores indicating worse quality of life. It takes approximately 10 to 20 minutes to complete the scale, depending on disease severity; patients with APD take longer than those with mild disease.[59]

Marinus et al.[60] reported the PDQ-39 has good test-retest reliability and content validity; the scale has been validated in many languages. The PDQ-39 includes dimensions relevant to PD that may not be included in other measures of HRQoL, such as social stigma, cognition, and communication. Construct validity has been demonstrated through comparisons with generic HRQoL scales, disease-specific scales, and what was referred to by Marinus et al. as "known groups." Responsiveness to a worsening in disease status has also been demonstrated.[60]

The change scores that may be considered clinically important to patients, based on a study of 728 patients with PD reporting their health was "about the same" or "a little worse," differ based on the domain (Table 36).[61] Such differences on a 0 to 100 scale appear small, and larger differences are desirable; however, these smaller changes were meaningful to patients. A recent trial of deep brain stimulation compared with medical treatment reported a between-treatment difference on the summary index of the PDQ-39 scale of approximately 8 points as the MCID.[62]

TABLE 36: MEAN (SD) PDQ-39 CHANGE SCORES OF RESPONDENTS REPORTING THEIR HEALTH WAS "ABOUT THE SAME" OR "A LITTLE WORSE"

	"About the Same"	"A Little Worse"
Summary Index	–0.6 (9.51)	–1.6 (8.9)[c]
Mobility	–1.5 (14.09)	–3.2 (13.3)[a]
ADL	–0.7 (15.9)	–4.4 (16.6)[a]
Emotional Well-being	0.3 (14.2)	–4.2 (17.1)[a]
Stigma	0.8 (18.5)	–5.6 (23.0)[c]
Social Support	–1.2 (15.7)	–11.4 (23.3)[b]
Cognitions	0.4 (15.8)	–1.8 (15.6)
Communications	–0.8 (16.4)	–4.2 (18.7)[b]
Pain	1.3 (17.7)	–2.1 (18.7)

ADL = activities of daily living; PDQ-39 = the Parkinson's Disease Questionnaire-39; SD = standard deviation.
[a] $P \leq 0.001$ (t-tests for difference between times 1 and 2 [6 months]).
[b] ≤ 0.01 (t-tests for difference between times 1 and 2 [6 months]).
[c] ≤ 0.05 (t-tests for difference between times 1 and 2 [6 months]).
Source: Peto et al.[61]
Note: PDQ-39 summary index and domain scores may range from 0 to 100.

EuroQol

The EQ-5D[63,64] is a well-accepted, validated, and reliable generic quality of life instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain

or discomfort, and anxiety or depression. Each dimension has three possible levels (1, 2, or 3), representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[63,64] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions, represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The MCID for the EQ-5D ranges from 0.033 to 0.074.[65]

The Parkinson Disease Home Diary

The PDHD is a home diary that patients being treated for idiopathic PD 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.[28] The PDHD consists of five categories: (1) asleep, (2) "off", (3) "on" without dyskinesia (ONW), (4) "on" with non-troublesome dyskinesia (ONN), and (5) "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).[28]

The PDHD was only validated and found reliable within itself and was not validated through a comparison with other validated external tools;[28] therefore, its external validity and reliability remain uncertain.

Internally, the diary was shown to be both feasible and simple in its use.[28] It was found to be sufficiently internally reliable; 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 VAS measures and corresponding PDHD measures when they were compared (Table 37), thus showing acceptable predictive validity.[28] In addition, a one-hour reduction in "off" time was considered to be an MCID in actively treated patients.[27]

TABLE 37: PDHD 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 (ONT% + ONN%)	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; PDHD = Parkinson disease home diary; VAS = visual analogue scales.
Source: Hauser et al.[28]

The Parkinson's Disease Sleep Scale

The PDSS is a 15-item scale that assesses sleep disturbances typically reported by patients with PD (primarily during nocturnal sleep as opposed to daytime sleep disturbance), using a VAS.[29-31,66-69] It attempts to distinguish between the causes of sleep disturbances in patients with any stage of PD.[30] 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 through 13), sleep refreshment (item 14), and daytime dozing (item 15)."[29] Patients or caregivers (as a proxy) 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); hence, the total score ranges from 0 to 150.[29,30] A total score of 120 points has been suggested as the cut-off point to detect sleep disturbances in patients with PD.[31] However, an MCID has not been formally derived.

This tool has been reported to be easy to use,[29,30,66,68] reliable,[29,30,66,67] and valid in assessing sleep disturbances in patients with PD.[31,66,67,69,70] It has also been demonstrated to discriminate between sleep problems associated with early and advanced PD,[29] and also between those with PD and healthy controls.[29,66] However, PDSS items to total correlations may be considered poor.[30,68,70]

Therefore, the PDSS has been demonstrated as an easy to use, valid, and reliable tool used to assess nocturnal sleep disturbances in patients with PD.

APPENDIX 6: SUMMARY OF SUPPORTIVE STUDIES

Aim

To summarize the safety and efficacy results of the open-label extension studies SP702[37] and SP716,[38] the phase II studies SP506 and SP511,[22] and a phase 3 study, SP889, that included patients with either EPD or APD.[22] None of these studies met the inclusion criteria for the CDR systematic review.

Early Parkinson Disease Extension Studies

Two extension studies — SP702[37] and SP716[38] — assessed the longer-term safety, and efficacy of rotigotine in patients who were classified as having EPD at baseline of their previously completed phase 3 studies, SP512 and SP513, respectively. Only those patients with ongoing serious adverse events considered related to the trial medication by the investigators at the end of the double-blind study were excluded. These studies were not included in the systematic review because they were single-arm, open-label extension studies.

Study Characteristics

Two hundred and sixteen (SP702) and 380 (SP716) EPD patients were evaluable for safety and efficacy; however, patients were not followed according to their original treatment groups and were examined as per their rotigotine treatment in the extension phase. Patients had similar characteristics in both extension studies. Patients were predominantly white males (68% in SP702 and 61% in SP716) with a mean duration of PD of 1.3 years, and a mean age of 63.2 years in SP702 and 61.6 years in SP716. In both studies, de-escalation of the study drugs administered during the double-blind phase (i.e., during studies SP512 and SP513) occurred prior to the commencement of the titration phase of the extension studies. Optimal rotigotine dosing for each patient was achieved by up-titrating weekly at 2 mg per 24 hours up to a maximum of 6 mg per 24 hours (SP702) or 8 mg per 24 hours (SP716). After the first year of the maintenance phase, patients were permitted to up-titrate again in the same increments to a maximum of 16 mg per 24 hours. In addition, patients were also permitted dose adjustments of rotigotine during the maintenance phase to maximize efficacy or deal with tolerability issues. Visits occurred weekly during the titration phase and for the first month of the maintenance phase, then at three-month intervals thereafter. The severity of patient illness at baseline is presented in Table 38.

TABLE 38: BASELINE CHARACTERISTICS FOR OUTCOMES RELATED TO ILLNESS IN THE EXTENSION STUDIES SP702 AND SP716

Characteristic	SP702	SP716
	All Patients (n = 216)	All Patients (n = 380)
UPDRS scores, mean (SD)		
Part II score	8.1 (4.3)	9.0 (4.2)
Part III score	21.1 (8.3)	23.2 (9.5)
Parts II and III subtotal score	29.2 (11.0)	32.1 (12.6)

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Elmer et al.,[37] Giladi et al.[38]

If patients required adjunct therapy, anti-Parkinson medications were permitted after one month of treatment in the maintenance phase. These included levodopa (combined with benserazide or carbidopa), monoamine oxidase B (MAO-B) inhibitors, anticholinergic drugs, NMDA antagonists, entacapone, atypical neuroleptics, and modafinil.

The primary safety and tolerability outcomes of interest included incidence of AEs, WDAEs, seriousness and intensity of AEs, daytime sleepiness (assessed with the Epworth sleepiness scale [ESS]), and extent of rotigotine exposure. Secondary outcomes included time to adjunctive levodopa therapy and dyskinesias. Evaluable patients included those who received at least one dose of rotigotine and returned for at least one visit.
Table 39 outlines the patient disposition and discontinuations during the extension studies.

TABLE 39: PATIENT DISPOSITION AND DISCONTINUATIONS IN STUDIES SP702 AND SP716 (SAFETY SET)

Patient Disposition	SP702 n (%)	SP716 n (%)
Prior to Entering OLE		
Randomized to DB phase, n	277	561
Randomized but not entering OLE	60 (21.7)	180 (32.1)
DB maintenance phase not completed	54 (90.0)	152 (84.4)[a]
Patient elected not to enter OLE	6 (10.0)	28 (15.6)[a]
During OLE		
Included in safety population set	216 (99.5)	380 (99.7)
Withdrawn from OLE	217 (100.0)	381 (100)
Major protocol violation	1 (0.5)	N/A
Lack of efficacy	12 (5.5)	22 (5.8)
AE	52 (24.0)	93 (24.4)
Unsatisfactory compliance	6 (2.8)	3 (0.8)
Withdrew consent	27 (12.4)	43 (11.3)
Study ended per sponsor	102 (47.0)	197 (51.7)
Lost to follow-up	4 (1.8)	17 (4.5)
Other	13 (6.0)	3 (0.8)

AE = adverse event; DB = double blind; N/A = not applicable; OLE = open-label extension.
[a]Percentages were calculated according to the number of randomized patients not entering the OL extension (n = 180).
Source: CSR SP513,[6] CSR SP512OL.[71]

Results

Safety

Rotigotine Exposure and the Use of Other Medications for Parkinson Disease

The median patient exposure to rotigotine during the open-label extension studies was longer in SP702 (1,910 days) than in SP716 (1,564 days); however, the corresponding ranges were quite large (Table 40). At the end of the treatment, mean rotigotine doses were similar between extension studies at 7.2 mg per 24 hours in SP702 and 8.2 mg per 24 hours in SP716.

Rotigotine treatment was supplemented with levodopa in 74% (SP702) and 69% (SP716) of patients. The median time to levodopa initiation was somewhat different between the extension studies (374 days in SP702 and 485 days in SP716), yet the mean levodopa doses were similar (373.5 mg per day in SP702 and 342.9 mg per day in SP716). Anticholinergic drug use was greater in SP702 at 40% when compared with SP716 at 11%. The use of other dopamine receptor agonists was similar between studies, particularly in the last week of the open-label extension maintenance phase prior to stopping rotigotine treatment (Table 40).

TABLE 40: EXPOSURE TO ROTIGOTINE AND OTHER MEDICATIONS FOR PARKINSON DISEASE DURING EXTENSION STUDY MAINTENANCE PHASE (SAFETY SET)

Drug Exposure	SP702 (n = 216)	SP716 (n = 380)
Rotigotine		
Median Exposure Time, Days (Range)	1,910 (1–2,188)	1,545 (5–2,154)
End of Study Dose (mg/24 hours), Mean (SD)	7.2 (3.4)	8.2 (3.8)
Concomitant Levodopa		
Patients Initiating Treatment, n (%)	159 (74)	264 (69)
Median Time to Initiation, Days (Range)	374 (1–2,019)	485 (14–2,076)
Dose over Entire Study, Mean (SD)	373.5 (184.3)	342.9 (263.9)
Other Medications for Parkinson disease, n (%)		
Anticholinergic Drugs	87 (40)	42 (11)
Adamantine	NR	39 (10)
MAO-B Inhibitors	NR	30 (8)
Other DAs Prior to Last Week of OL Study	12 (6)	12 (3)
Other DAs in Last Week of OL Study Participation	26 (12)	16 (4)

DA = dopamine receptor agonists; MAO-B = monoamine oxidase B; NR = not reported; OL = open-label; SD = standard deviation.
Source: CSR SP513,[6] CSR SP512OL.[71]

Adverse Events

The AEs observed in the extension studies were consistent with those associated with transdermal patch use, dopamine receptor stimulation, and PD. Ninety-nine per cent of patients experienced at least one AE in SP702;[37] however, the total number of patients experiencing an AE was not reported for SP716.[71] The most common AEs in both studies were somnolence, falls, peripheral edema, nausea, and application site reactions (Table 41); these were largely reported as mild or moderate in intensity. Peripheral edema occurred more frequently in SP702 (14.2% per patient year) than in SP716 (7.0% per patient year). Discontinuations due to AEs occurred in 24% of patients over the course of both extension studies.

TABLE 41: TREATMENT-EMERGENT ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS IN SP702 AND SP716 (SAFETY SET)

	SP702		SP716	
	Patients Experiencing AE, n (%) (n = 216)	Incidence, % per Patient Year	Patients Experiencing AE, n (%) (n = 380)	Incidence, % per Patient Year
Total AEs	214 (99)	NR	NR	NR
Somnolence	116 (54)	23.4	146 (38)	17.7
Fall	71 (33)	16.5	47 (12)	7.0
Peripheral edema	80 (37)	14.2	72 (19)	7.0
Nausea	66 (31)	12.4	72 (19)	8.7
Application and Instillation site reactions[a]	70 (32)	11.7	118 (31)	11.8
Arthralgia	51 (24)	9.9	NR[b]	NR[b]
Dizziness	58 (27)	9.4	52 (14)	4.8
Back pain	53 (25)	8.3	57 (15)	5.9
Dopamine Receptor Stimulation AEs				
Hallucination	22 (10)	3.5	23 (6)	2.7
Orthostatic hypertension	14 (6)	NR	20 (5)	1.7
Impulsive-compulsive behaviour	18 (8)	NR	25 (7)	NR
Dyskinesias	53 (25)	NR	65 (17)	NR
Total SAE, n (%)	102 (47)	NR	131 (34)	NR
Osteoarthritis	5 (2.3)	NR	11 (2.9)	NR
Myocardial infarction/ Chest pain	6 (2.8)	NR	10 (2.6)	NR
PD	5 (2.3)	NR	9 (2.4)[c]	NR
Fall	3 (1.4)	NR	9 (2.4)	NR
Pneumonia	5 (2.3)	NR	4 (1.1)	NR
Pulmonary embolism	4 (1.9)	NR	NA[d]	NR
Spinal column stenosis	4 (1.9)	NR	NA[b]	NR
Syncope	4 (1.9)	NR	NA[b]	NR
Deaths, n (%)	9 (4.2)	NR	17 (4.5)	NR

AE = adverse event; NA = not applicable; NR = not reported; PD = Parkinson disease; SAE = serious adverse event.
[a]Medical Dictionary for Regulatory Activities (MedDRA) high-level term.
[b]Did not report, as incidence was not above ≥ 10%.
[c]Patients with PD who required or had prolonged in-patient hospitalization.
[d]Not reported by more than 2% of the population.
Source: CSR SP513,[6] CSR SP512OL.[71]

None of the dyskinesias were classified as "completely disabling" in either extension study, with the majority falling under the classification of either "not disabling" (62% in SP702 and 46% in SP716) or "mildly disabling" (30% in SP702 and 31% in SP716).

Serious adverse events occurred in 47% and 43% of patients in SP702 and SP716, respectively. In addition, there were nine deaths in SP702 and 17 deaths in SP716, the majority of which were thought to be unrelated to rotigotine treatment. A summary of the most common serious adverse events is provided in Table 43.

Efficacy

Mean changes for the efficacy variables were calculated from the baselines of the original double-blind studies (SP512 and SP513 for SP702 and SP716, respectively) to the end of maintenance (or the last available value during maintenance) and all data were descriptive with no statistical analysis. The Unified Parkinson's Disease Rating Scale (UPDRS; parts II and III) subtotal score was analyzed based on duration of rotigotine exposure. The UPDRS parts II and III subtotal score improved by a mean of 5.6 points (no standard deviation [SD] provided) in SP702 and –10.5 points (SD of 10.3 points) in SP716 relative to baseline. In both studies, UPDRS II and III scores improved initially, but scores declined toward baseline values by the second year in SP702, or declined but remained improved relative to the baseline values in SP716. UPDRS II and III subtotal scores remained at these levels for four years of the open-label phase. In SP716, UPDRS II and III subtotal scores were still improved relative to the double-blind baseline after five years in patients (n = 20) who did not use concomitant levodopa (–2.0 points [SD of 9.5 points]). In addition, 30% of patients in SP716 were deemed UPDRS II and III responders. The mean clinical global impression (CGI) Item 1 scores in both extension studies were similar and indicative of an increase in the severity of PD. Scores increased from 3.0 (SD of 0.7) at double-blind baseline to 3.5 (SD of 0.9) at the end of the maintenance period in SP702. Similar results were observed in SP716, where CGI Item 1 scores increased from 3.2 (SD of 0.8) at double-blind baseline to 3.6 (SD of 0.9) at the end of maintenance.

Advanced Parkinson Disease Extension Studies

Two extension studies — SP516[39] and SP715[40] — assessed the longer-term safety, tolerability, and efficacy of rotigotine in APD) patients from the phase 3 studies, SP516 and SP715, respectively. These studies were not included in the systematic review as they were single-arm, open-label extension studies.

Study Characteristics

Three hundred and ninety-five (SP516) and 258 (SP715) APD patients were evaluable for safety and efficacy; however, patients were not followed according to their original treatment groups and were examined as per their rotigotine treatment in the extension phase. Only those patients with ongoing serious adverse events considered related to the trial medication by the investigators at the end of the double-blind study were excluded. Patients had similar characteristics in both extension studies: patients were predominantly white (97% in SP516 and 93% in SP715) and male (64% in SP516 and 67% in SP715), with a mean time since diagnosis of PD of 8.5 years (SD of 4.6 years) in SP516 and 7.8 years (SD of 4.5 years) in SP715, and a mean age of 64.4 years in SP516 and 66.4 years in SP715. In both studies, de-escalation of the study drugs administered during the double-blind phase (studies SP515 and SP650) occurred prior to the commencement of the titration phase of the extension studies. Optimal rotigotine dosing for each patient was achieved by up-titrating weekly at 2 mg per 24 hours up to a maximum dose of 16 mg per 24 hours in both studies, except in the first year of the SP715 study whereby the maximum dose was 12 mg per 24 hours. In addition, patients were also permitted dose adjustments of rotigotine during the maintenance phase to maximize efficacy or deal with tolerability issues. Visits occurred weekly during the titration phase and for the first month of the maintenance phase, then at three-month intervals thereafter. The severity of patient illness at baseline is presented in Table 42.

TABLE 42: BASELINE CHARACTERISTICS FOR OUTCOMES RELATED TO ILLNESS IN THE EXTENSION STUDIES SP516 AND SP715 (SAFETY SET)

Characteristic	SP516	SP715
	All Patients (N = 395)	All Patients (N = 258)
UPDRS, Mean (SD)		
Part II score	12.3 (5.9)	12.6 (6.4)
Part III score	27.0 (11.7)	26.1 (13.8)
Parts II and III subtotal score	39.3 (16.1)	38.68 (18.6)

SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Le Witt et al.,[72] CSR SP516,[39] CSR SP650OL.[40]

Patients requiring adjunct therapy were permitted to take the following anti-Parkinson medications: levodopa (combined with benserazide or carbidopa), MAO-B inhibitors, anticholinergic drugs, tolcapone, entacapone, certain atypical neuroleptics, and modafinil. In addition, antiemetic drugs were permitted.

Outcomes of interest included incidence of AEs, efficacy outcomes (assessed using UPDRS parts II and III), seriousness and intensity of AEs (measured with the Hoehn and Yahr Scale), complications of therapy (assessed using the UPDRS part IV), daytime sleepiness (assessed with the ESS), and changes in levodopa therapy. Patients were assessed with the UPDRS parts II and III and Hoehn and Yahr when the patient was in an "on" state. Table 43 outlines the patient disposition and discontinuations during the extension studies.

TABLE 43: PATIENT DISPOSITION AND DISCONTINUATIONS STUDIES IN SP516 AND SP715 (SAFETY SET)

Patient Disposition	SP516 n (%)	SP715 n (%)
Prior to Entering OLE		
Randomized to DB phase, n	506	351
Randomized but not entering OLE	111 (21.9)	93 (26.5)
DB maintenance phase not completed	78[a] (70.3)	91 (25.9)
Ongoing SAEs related to Rotigotine	1[a] (0.9)	1 (0.3)
Patient elected not to enter OLE	33 (29.7)	1 (0.3)
During OLE		
Included in safety population set	395 (100)	258 (100)
Withdrawn from OLE	206 (52.2)	258 (100)
Major protocol violation	4 (1.9)	2 (0.8)
Lack of efficacy	29 (14.1)	12 (4.7)
AE	76 (36.9)	68 (26.4)
Unsatisfactory compliance	7 (3.4)	11 (4.3)
Withdrew consent	51 (24.8)	35 (13.6)
Study ended per sponsor	0	115 (44.6)
Lost to follow-up	4 (1.9)	6 (2.3)
Other	35 (17.0)	9 (3.5)

AE = adverse event; DB = double blind; OLE = open-label extension; SAE = serious adverse events.
[a]Patient 112105 specified two reasons for not entering the OLE (i.e., did not complete 24 weeks of DB maintenance period and ongoing SAE[s] related to study medication).
Source: CSR SP516,[39] CSR SP650OL.[40]

Results

Safety

Rotigotine Exposure

The most common rotigotine doses observed upon entering the open-label maintenance phase were 16 mg per 24 hours in SP516 and 12 mg per 24 hours in SP715. Mean doses at the end of the trial were 11.6 mg per 24 hours (SD of 3.2 mg per 24 hours) in SP516 and 10.1 mg per 24 hours (SD of 3.4 mg per 24 hours) in SP715. Total rotigotine exposure over the entire course of the open-label extensions study ranged from a mean of 857.8 days (SD of 458 days) to 1,328.8 days (SD of 607.9 days) for SP516 and SP715, respectively.[72] Dopamine and dopamine derivatives were taken by all enrolled patients (Table 44).

TABLE 44: ROTIGOTINE EXPOSURE (ALL PHASES) AND CONCOMITANT ANTI-PARKINSON MEDICATIONS DURING MAINTENANCE (TREATMENT) PERIOD (SAFETY SET)

Drug Exposure	SP516 (N = 395)	SP715 (N = 258)
Rotigotine Exposure (days)		
Titration Period, n, mean (SD)	n = 395 38.3 (13.6)	n = 258 29.9 (9.8)
Maintenance period, n, mean (SD)	n = 378 851.4 (431.4)	n = 254 1314.7 (588.3)
De-escalation period, n, mean (SD)	n = 207 9.0 (3.3)	n = 146 7.9 (3.8)
Total	n = 395 857.8 (458.0)	n = 258 1328.8 (607.9)
Dopaminergic Drugs, n (%)[a]		
Dopa and dopa derivatives	395 (100)	258 (100)
Other dopaminergic drugs	122 (30.9)	65 (25.2)
Adamantane derivatives	104 (26.3)	69 (26.7)
Dopaminergic agonists	73 (18.5)	39 (15.1)
MAO-B Inhibitors	72 (18.2)	73 (28.3)

MAO-B = monoamine oxidase B; SD = standard deviation.
[a]Concomitant anti-Parkinson medications taken by ≥ 15% of patients.
Source: CSR SP516,[39] CSR SP650OL.[40]

Adverse Events

AEs observed throughout the extension studies were consistent with those associated with transdermal patch use, dopamine receptor stimulation, and PD. In SP516 and SP715, 90.4% and 100%, respectively, of the patients experienced AEs. The most common AEs in SP516 and SP715 were somnolence, PD, dyskinesias, application site reactions, falls, and nausea (Table 45). Dyskinesias occurred frequently in each study (69% in SP516 and 80% in SP715) with an across-study incidence of 4% to 8% per patient year.[72] Most AEs were reported as mild or moderate in intensity. Withdrawals due to adverse events occurred in 20% and 28% of patients in SP516 and SP715, respectively.

TABLE 45: COMMON TREATMENT-EMERGENT ADVERSE EVENTS AND DISCONTINUATIONS DUE TO AES (REPORTED BY ≥ 10% OF PATIENTS) IN SP516 AND SP715 (SAFETY SET)

	SP516 N = 395 n (%)	SP715 N = 258 n (%)
Any adverse event	357 (90.4)	258 (100)
Adverse Events[a]		
Somnolence	133 (33.7)	150 (58.1)
Parkinson disease	57 (14.4)	43 (16.7)
Dyskinesia	55 (13.9)	28 (10.9)
Application and instillation site reactions[b]	103 (26.1)	84 (32.6)
Fall	63 (15.9)	104 (40.3)
Nausea	54 (13.7)	61 (23.6)
Hallucination	35 (8.9) 29 (7.3)	60 (23.3) 50 (19.4)
Dizziness	27 (6.8) 20 (5.1)	61 (23.6)
Total SAE, n (%)	148 (37.5)	165 (64.0)
Individual SAE, n (%)		
Parkinson disease	18 (4.6)	25 (9.7)
Pneumonia	7 (1.8)	6 (2.3)
Urinary retention	6 (1.5)	NR
Urinary tract infection	5 (1.3)	8 (3.1)
Parkinsonism	4 (1.0)	NR
Osteoarthritis	4 (1.0)	6 (2.3)
Arthralgia	4 (1.0)	NR
Fall	4 (1.0)	13 (5.0)
Hallucination	4 (1.0)	8 (3.1)
Hallucination, visual	4 (1.0)	NR
Cardiac failure	4 (1.0)	7 (2.7)
Deaths, n (%)	15 (3.8)	30 (11.6)
Discontinuations due to AEs	79 (20.0)	72 (28.0)

AE = adverse event; NR = not reported; SAE = serious adverse event.
[a]Incidence ≥ 5% of patients
[b]Medical Dictionary for Regulatory Activities (MedDRA) high-level term.
Source: Elmer et al.,[37] CSR SP516,[39] CSR SP650OL[40]

Serious adverse events occurred in 37.5% and 64% of patients in SP516 and SP715, respectively. In addition, there were 15 deaths in SP516 and 30 deaths in SP715, the majority of which were thought to be unrelated to rotigotine treatment. A summary of the most common serious adverse events is provided in Table 45.

Efficacy

Mean changes for the primary efficacy outcomes (change in UPDRS and off time) were calculated from the baselines of the original double-blind studies to the end of maintenance (or the last available value during maintenance) and all data were descriptive with no statistical analysis. A treatment responder was defined as an improvement of ≥ 20% when compared with baseline in the UPDRS parts II and III subtotal score.

The UPDRS part II scores (ADL) improved during the dose titration phase relative to double-blind baseline, but returned close to baseline value in SP516 or remained 4.1 points higher in SP715. UPDRS part III scores (motor function) also improved during dose titration, gradually declined, but remained improved relative to baseline in SP516. In SP715, the scores also improved from baseline (by 11.4 points) and then returned to baseline values by the end of treatment. UPDRS parts II and III responder rates decreased in both studies from 71% in SP516 and 74% in SP715 at the end of the titration phase to 36% and 24%, respectively, at the end of treatment. "Off time" was measured by the UPDRS part IV score and remained slightly improved relative to baseline, maintained these scores throughout the extension phase with little variation, and then declined slightly at the end of the study.

Other Supportive Studies

The following provides a brief summary of rotigotine studies in patients with idiopathic PD as presented in SP506, SP511, and SP889.[22] These studies were excluded from the systematic review because they did not meet the inclusion criteria; SP506 and SP511 were 12-week trials instead of a minimum 16-week trial, and SP889 included both early- and advanced-stage PD patients with a maintenance phase of only four weeks.

Study Characteristics

Study SP506 was a phase 2b, multi-centre, randomized, double-blind, and placebo-controlled trial to assess the efficacy and safety of escalating transdermal doses of rotigotine in patients with EPD.[22] It involved 329 patients older than 30 years who were randomized to a placebo arm and one of four other rotigotine doses: 2 mg per 24 hours, 4 mg per 24 hours, 6 mg per 24 hours, and 8 mg per 24 hours (Table 46). After a four-week dose-escalation period to achieve the targeted doses, patients in each treatment arm were maintained on the target dose for seven weeks and dose–de-escalated for one week.

TABLE 46: SUMMARY OF BASELINE CHARACTERISTICS OF ALL THE STUDIES

	SP506 (EPD)					SP511 (APD)	PS889 (EPD plus APD)	
	Placebo N = 62	Rotigotine 2 mg/ 24 hours N = 65	Rotigotine 4 mg/ 24 hours N = 60	Rotigotine 6 mg/ 24 hours N = 61	Rotigotine 8 mg/ 24 hours N = 68	All Groups Average[a] (FAS) N = 310	Placebo N = 96	Rotigotine N = 191
Patients' Demographics								
Age, Years								
Mean (SD)	59.7 (10.7)	61.6 (9.6)	59.0 (9.0)	60.7 (10.4)	60.6 (10.8)	63.7	64.4 (10.6)	64.8 (9.3)
Median	60.0	63.0	59.5	62.0	60.5	NR	65.0	66.0
Range	34 to 79	35 to 78	33 to 77	35 to 80	34 to 83	35 to 85	37 to 86	37 to 85
Sex, n (%)								
Female, n (%)	35 (56)	19 (29)	17 (28)	23 (38)	28 (41)	118 (38)	35 (36.5)	68 (35.6)
Male	24 (44)	46 (71)	43 (72)	38 (62)	40 (59)	192 (62)	61 (63.5)	123 (64.4)

	SP506 (EPD)					SP511 (APD)	PS889 (EPD plus APD)	
	Placebo N = 62	Rotigotine 2 mg/ 24 hours N = 65	Rotigotine 4 mg/ 24 hours N = 60	Rotigotine 6 mg/ 24 hours N = 61	Rotigotine 8 mg/ 24 hours N = 68	All Groups Average[a] (FAS) N = 310	Placebo N = 96	Rotigotine N = 191
Disease Severity								
Years since diagnosis, mean (SD)	1.44 (1.7)	1.45 (1.7)	1.52 (2.2)	1.40 (1.3)	1.32 (1.4)	7.6 (7.3 to 7.9)[b]	4.9	4.6
UPDRS (parts II and III), mean (SD)	28.0 (11.1)	28.5 (12.1)	28.5 (11.2)	27.6 (13.5)	27.1 (13.4)	NR	NR	NR
UPDRS part III, mean (SD)	NR	NR	NR	NR	NR	NR	4.9	4.6
Absolute time spent "off," hours	NR	NR	NR	NR	NR	(5.97 to 6.4)[1]	NR	NR

APD = advanced Parkinson disease; EPD = early Parkinson disease; FAS = full analysis set; NR = not reported; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
[a]Data were assembled from text of Neupro Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials. No group-specific data for placebo and rotigotine were found from this source in this regard for study SP511.
[b]Range.
Source: For SP506 and SP511, data have been gathered from Neupro Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials (Manufacturer CD/Category 1). For SP889, data were taken from Neupro Health Canada Modules 2.7.3 and 2.7.6, as well as CSR_889.

The maximum treatment exposure to rotigotine was three months.[22] There were no important differences among the five groups in baseline demographics and clinical variables.[22] The primary efficacy variable was the mean change in the sum of the UPDRS parts II and III score from baseline visit (Day 0) to week 11 (Day 77).[22] Secondary efficacy outcomes of interest included changes in the UPDRS part I (mentation, behaviour, and mood), part II (ADL) and part III (motor examination) scores from baseline to week 11.[22] Safety outcome measures included frequency and severity of AEs and changes in vital signs, electrocardiogram, and clinical laboratory values recorded over the course of the study.[22]

Study SP511 was a phase 2b, multi-centre, double-blind, randomized, placebo-controlled dose-ranging trial with four arms in which a total of 324 APD patients were randomized to receive placebo, or one of three rotigotine doses: 4 mg per 24 hours, 8 mg per 24 hours, or 12 mg per 24 hours.[22] Data were assembled from text of Neupro Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials. No group-specific data for placebo and rotigotine were found from this source for study SP506 with regard to baseline characteristics. The mentioned sources report that treatment groups were well balanced with respect to baseline characteristics (Table 46). Patients had a mean age of 63.7 years with a range of 35 to 85 years, with a mean time since diagnosis of 7.6 years. Absolute time spent "off" ranged from 5.97 to 6.47 hours at baseline and it was similar across treatment groups.[22] All patients had taken at least one anti-Parkinson medication before the run-in period and all had previously used levodopa or levodopa derivative (e.g., levodopa plus carbidopa). Similar proportions in each treatment arm had used MAO-B inhibitors and amantadine derivatives.[22] The trial spanned

approximately 20 weeks, including up to six weeks of pre-treatment period, a treatment period of 12 weeks, and a safety follow-up period of two weeks.[22] Inclusion and exclusion criteria were similar to those outlined in SP515 and SP650 (Table 6: Details of Included Studies for Advanced Parkinson Disease Studies).

The primary efficacy end point was the absolute change from baseline to end of treatment in the absolute time (hours) spent "off." Secondary efficacy end points included (but were not limited to) relative and absolute changes from baseline to end of the treatment in the absolute time spent "off" or "on," and absolute change from baseline to end of the treatment in total UPDRS.[22]

SP889 was a phase 3b, multi-centre, multinational, double-blind, controlled trial to evaluate the effect of rotigotine on the control of early morning motor function, sleep quality, nocturnal symptoms, and non-motor symptoms compared with placebo in patients with EPD or APD .[22] Patients (N = 287) were randomized in a 2:1 ratio to rotigotine or placebo, respectively. The total duration was approximately 22 weeks, consisting of a four-week screening period, a three-day baseline, an eight-week dose titration period, a four-week maintenance period, and a two-week de-escalation period. Table 47 summarizes the patient disposition of SP506, SP511, and SP889.

Baseline characteristics were similar across the two study arms. Mean patient age was 64.4 years in the placebo group and 64.8 years in the rotigotine group.[45] Other demographic details are given in Table 46. Patients had to have unsatisfactory early morning motor impairment base on UPDRS part III score. Patients receiving other anti-Parkinson drugs at baseline had to be on a stable dose for at least 28 days prior to baseline and had to be maintained on that dose for the duration of the trial. Rotigotine doses were titrated starting at 2 mg per 24 hours until a patient's optimal dose or a maximum dose of 16 mg per 24 hours. The optimal dose was defined as the dose at which both the investigator and the patient felt that early morning motor impairment was adequately controlled.

The co-primary efficacy end points were changes from baseline to the end of maintenance period in the UPDRS part II score (early morning, prior to any medication intake) and in the PDSS.[22] The secondary efficacy variables included (but were not limited to) the change from baseline to the end of maintenance in the Nocturnal Akinesia, Dystonia, and Cramps Score (NADCS) and in the number of nocturias.[45]

TABLE 47: PATIENT DISPOSITION FOR ALL STUDIES

	SP506					SP511		SP889	
	PB	Rotigotine				Placebo	Rotigotine	Placebo	Rotigotine
		2 mg/ 24 hours	4 mg/ 24 hours	6 mg/ 24 hours	8 mg/ 24 hours				
Screened, N	329					324		333 (100)	
Randomized, N (%)	104	225				84	240	97 (100)	190 (100)
FAS, N	62	65	60	61	68	81	229	89 (91.8)	178 (93.7)
Safety, N	104	225				NR	NR	97 (100)[a]	190 (100)[a]
Withdrawals, N (%)	8 (13)	29 (11)				8	19	17 (17.5)[b]	24 (12.6)[b]
Reasons for Withdrawal									
Protocol violation, n (%)	0 (0)	2 (0)				NR	NR	0	0
Lack of efficacy, n (%)	3 (5)	9 (4)				NR	NR	4 (4.1)	0
Adverse events, n (%)	3 (5)	43 (17)				NR	NR	6 (6.2)	11 (5.8)[c]
Unsatisfactory compliance, n (%)	0 (0)	2 (0)				NR	NR	0	0
Withdrawal of Consent, n (%)	0 (0)	8 (3)				NR	NR	7 (7.2)	11 (5.8)
Lost to follow-up, n (%)	--	--				NR	NR	0	0
Other, n (%)	2 (3)	2 (0)				NR	NR	0	2 (1.1)

FAS = full analysis set; PB = placebo; PP = per protocol.

[a]Patient 13707 (randomized to placebo) received one dose of rotigotine and was counted with the rotigotine group for the safety evaluation.

[b]Withdrawals include those during the titration period, the maintenance period, the de-escalation period, and safety follow-up.

[c]The primary reason for discontinuation of rotigotine-treated Patient 12003 was withdrawal of consent, but the patient also reported three adverse events, leading to discontinuation.

Source: For SP506 and SP511, data have been gathered from Neupro Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials (Manufacturer CD/Category 1). For SP889, data were taken from Neupro Health Canada Modules 2.7.3 and 2.7.6, as well as CSR_889.

Efficacy Results

Numerically greater improvements were observed for the entire rotigotine dose groups in study SP506 compared with placebo group. However, statistically significant differences in change from baseline in the combined UPDRS part II and part III scores were observed for the 4 mg per 24 hours, 6 mg per 24 hours, and 8 mg per 24 hours doses, but not the 2 mg per 24 hours dose. Primary analysis using the FAS yielded the following effect estimates: –3.123 for 4 mg per 24 hours (95% CI, –5.57 to –0.675); –4.909 for 6 mg per 24 hours (95% CI, –7.341 to –2.477); and –5.035 for 8.0 mg per 24 hours (95% CI, –7.406 to –2.665).[22] It is reported in the manufacturer-submitted literature[22] that a 5.0-point difference in the combined UPDRS score between rotigotine and placebo was considered to be clinically meaningful. Therefore, both the 6 mg per 24 hours and the 8 mg per 24 hours doses achieved statistically significant and clinically meaningful improvements from baseline compared with placebo.[22]

TABLE 48: CHANGE FROM BASELINE TO END OF TREATMENT IN THE UPDRS (PARTS II AND III) SCORES BY TREATMENT GROUP IN SP506 (FULL ANALYSIS SET RANDOMIZED)

UPDRS (Parts II and III)	Placebo (N = 62)	Daily Rotigotine Dose			
		2 mg/24 hours (N = 65)	4 mg/24 hours (N = 60)	6 mg/24 hours (N = 61)	8 mg/24 hours (N = 68)
Baseline mean (SD)	28.02 (11.11)	28.48 (12.05)	28.52 (11.21)	27.57 (13.46)	27.13 (13.41)
EOT mean (SD)	26.63(13.49)	24.98 (11.79)	24.05 (11.53)	21.33 (13.33)	20.84 (11.51)
Change from baseline mean (SD)	–1.39 (7.90)	–3.49 (7.23)	–4.47 (6.81)	–6.25 (7.78)	–6.29 (7.83)
ANCOVA comparison I effect estimate (95% CI)	NR	–2.148 (–4.544 to 0.248)	–3.123 (–5.571 to –0.675)	–4.909 (–7.341 to –2.477)	–5.035 (–7.406 to –2.665)
P value	--	0.0393[a]	0.0063[a]	< 0.0001[a]	< 0.0001[a]

ANCOVA = analysis of variance; CI = confidence interval; EOT = end of treatment; NR = not reported; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[1a]One-sided *P* value.

Source: For SP506 and SP511, data have been gathered from Neupro Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials (Manufacturer CD/Category 1). For SP889, data were taken from Neupro Health Canada Modules 2.7.3 and 2.7.6, as well as CSR_SP889.

In SP511, rotigotine achieved improvements from baseline to end of treatment in absolute time spent "off" (4 mg per 24 hours, 2.0 hours; 8 mg per 24 hours, 1.8 hours; and 12 mg per 24 hours, 2.4 hours) compared with placebo 1.8 hours; however, these were not statistically significant (Table 49).

The results for the UPDRS part III total score in SP889 showed that doses of rotigotine titrated to an optimal dose or a maximal dose resulted in statistically significant and clinically relevant improvement in a patient's early morning motor function at the end of maintenance (–3.5; P = 0.0002; 95% CI, –5.37 to –1.73) (Table 50: Summary of Efficacy End Point Results in SP889). Total PDSS score also showed statistically significant and clinically relevant improvement in a patient's sleep quality at the end of maintenance (–4.26; P ≤ 0.0001; 95% CI, –6.06 to –2.45).

TABLE 49: SUMMARY OF ABSOLUTE CHANGE FROM BASELINE TO END OF TREATMENT IN ABSOLUTE TIME SPENT "OFF" IN SP511 (FULL ANALYSIS SET)

Absolute Time Spent "Off"	Placebo (N = 81)	Daily Rotigotine Dose		
		4 mg/24 hours (N = 77)	8 mg/24 hours (N = 75)	12 mg/24 hours (N = 77)
Primary Efficacy End Point				
Baseline mean (SD), hours	[redacted]	[redacted]	[redacted]	[redacted]
EOT mean (SD), hours	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD), hours	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted mean (SED)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Comparison				
	NA	**ROT 4 mg/ 24 hours – PB**	**ROT 6 mg/ 24 hours – PB**	**ROT 8 mg/ 24 hours – PB**
Net effect[a] (SED)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
P value[b]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary Efficacy End Point				
> 30% responder rates, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

ANCOVA = analysis of variance; CI = confidence interval; EOT = end of treatment; NA = not applicable; PB = placebo; ROT = rotigotine; SD = standard deviation; SED = standard error of difference.

[a]Treatment-adjusted mean minus placebo-adjusted mean.[22]

[b]*P* value based on ANCOVA; model included treatment group as a factor, country as a stratification factor, and baseline value as a covariate.

Source: For SP506 and SP511, data have been gathered from NEUPRO Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials (Manufacturer CD/Category 1). For SP889, data were taken from NEUPRO Health Canada Modules 2.7.3 and 2.7.6, as well as CSR_SP889.

Safety Results

[redacted] (Table 51: Summary of All Drug-related Treatment-Emergent Adverse Events with an Incidence ≥ 5% in SP506, SP511, and SP889).[22]

[redacted]

[22]

[redacted]

[22]

[redacted]

[redacted]22

22

TABLE 50: SUMMARY OF EFFICACY END POINT RESULTS IN SP889

Outcome	SP889	
	Placebo N = 89	Rotigotine N = 178
Change in UPDRS Part III Total Score (FAS with LOCF)		
Baseline,[a] mean (SD)	31.8 (13.6)	29.7 (12.4)
End of maintenance, mean (SD)	27.9 (13.1)	22.7 (12.2)
Change from baseline, mean (SD)	–3.9 (7.3)	–7.0 (7.6)
Difference between rotigotine and placebo	–3.55	
P value (95% CI)	0.0002 (–5.37 to –1.73)	
Change in PDSS Total Score (FAS with LOCF)		
Baseline,[a] mean (SD)	20.3 (10.2)	19.3 (9.2)
End of maintenance, mean (SD)	18.4 (11.3)	13.5 (8.3)
Change from baseline, mean (SD)	–1.9 (8.2)	–5.9 (7.6)
Difference between rotigotine and placebo	–4.26	
P value (95% CI)	≤ 0.0001 (–6.08 to –2.45)	
Change in NADCS Total Score (FAS)		
Baseline,[a] mean (SD)	2.7 (2.1)	2.9 (2.2)
End of maintenance, mean (SD)	1.8 (1.8)	1.7 (1.6)
Change from baseline, mean (SD)	–0.9 (2.1)	–1.3 (1.8)
Difference between rotigotine and placebo	–0.41	
P value (95% CI)	0.0301 (difference is considered exploratory)	

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; NADCS = Nocturnal Akinesia, Dystonia, and Cramps Score; PDSS = Parkinson's Disease Sleep Scale; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Observed/assessed on Day 1.

Source: For SP506 and SP511, data have been gathered from NEUPRO Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials (Manufacturer CD/Category 1). For SP889, data were taken from NEUPRO Health Canada Modules 2.7.3 and 2.7.6, as well as CSR_SP889.

[redacted]22

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In SP889, the most common AEs reported more frequently in rotigotine-treated patients were nausea (rotigotine; 22%; placebo: 9%), and application site reactions (rotigotine: 15%; placebo: 4%).[45] Other common AEs were dizziness, headache, and dyskinesias, which is consistent with the previously reported AE profile for rotigotine.[45] The majority of AEs were mild or moderate in intensity. Incidence of AEs was lower during the maintenance period than during the titration period. The incidence of SAEs was similar between-treatment groups; no SAE occurred in more than one patient.[45] Two deaths in the placebo group were reported resulting from completed suicide and pneumonia aspiration.[45]

TABLE 51: SUMMARY OF ALL DRUG-RELATED TREATMENT-EMERGENT ADVERSE EVENTS WITH AN INCIDENCE ≥ 5% IN SP506, SP511, AND SP889

	SP506					SP511		SP889[b] (SS)	
	PB N = 64	Daily ROT Dose[a]							
		2 mg/ 24 hours N = 67	4 mg/ 24 hours N = 63	6 mg/ 24 hours N = 65	8 mg/ 24 hours N = 70	PB N = 96	ROT N = 191	PB N = 96	ROT N = 191
Any system organ class, (%)									
Application site reactions[c]									
Nausea									
Vomiting									
Somnolence									
Asthenic conditions[d]									
Oedema peripheral									
Insomnia									
Abnormal dreams									
Nervous system disorders									
Dizziness									
Headache									
Dyskinesia									
SAEs									
Most common SAEs									
Gastrointestinal disorders									
Diarrhea (exc. infection)									
Diarrhea									
Deaths, n (%)									

PB = placebo; ROT = rotigotine; SAEs = serious adverse events; SS = safety set; TEAEs = treatment-emergent adverse events.
Note: Adverse events, which are highly probable, possible, or not assessable and missing responses are categorized as drug-related.[45]
[a]Dose-related TEAEs during the whole study period of SP506.
[b]Drug-related TEAEs with an incidence ≥ 5% in the SP889 study.[45]
[c]High-level term includes erythema, pruritus, irritation, rash, dermatitis, vesicles, pain, eczema, inflammation, swelling, discoloration, papules, excoriation, urticarial, hypersensitivity.
[d]High-level term includes fatigue, asthenia, malaise.[22]
Source: For SP506 and SP511, data have been gathered from NEUPRO Health Canada Modules 2.7.3 and 2.7.6 in manufacturer-submitted materials (Manufacturer CD/Category 1). For SP889, data were taken from NEUPRO Health Canada Modules 2.7.3 and 2.7.6, as well as CSR_SP889.

Summary

Rotigotine appeared to be generally safe, based on evidence from phase II and III studies of shorter duration (< 16 weeks), as well as from extension studies of randomized controlled trials included in the systematic review for both EPD and APD. The most common adverse events reported with rotigotine were somnolence, falls, peripheral edema, nausea, and application site reactions, vomiting, and fatigue, with the majority categorized as either mild or moderate in intensity.

Rotigotine demonstrated statistically significant improvements in the change from baseline in the UPDRS (parts II and III) subtotal scores versus placebo in study SP506, but the improvement achieved by rotigotine in absolute time spent "off" from baseline to end of treatment was not significantly different from placebo in SP511. Rotigotine showed statistically significant improvement in sleep and early morning akinesia in SP889. Caution should be heeded when interpreting the efficacy results from extension studies, as these were single-arm, open-label studies primarily evaluating safety and tolerability. In addition, no statistical analysis was performed on any efficacy variable in any of the extension studies. UPDRS parts II and III subtotal scores were improved from double-blind baseline at the initiation of the maintenance phase of the extension studies; however, lots of variability was evident (with regard to the standard deviation) and only means, and not medians, were provided for the SP702 and SP716 (EPD). In SP516 and SP715 (APD extension studies), the CGI scores indicated an increase in disease severity in only SP715.

APPENDIX 7: SUMMARY OF COMPARATORS

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Objective

To summarize the comparative information on non-ergot DAsand levodopa in the treatment of patients with EPD and on non-ergot DAs, COMT inhibitors, and MAO-B inhibitors (all in combination with levodopa) in patients with APD.

Findings

A supplemental search (2003-2013) was conducted to identify systematic reviews and meta-analyses of currently used pharmacological options (DAs, levodopa, MAO-B inhibitors, and COMT inhibitors) for the treatment of patients with EPD or APD. Two meta-analyses, from 2008[42] and 2009,[43] were identified that examined the effects of DAs (in the context of either monotherapy or adjunctive therapy) when compared with placebo or levodopa in patients with EPD. One meta-analysis was identified that examined the effects of MAO-B inhibitors and COMT inhibitors as adjuncts to levodopa in patients with APD.[44] No systematic reviews were identified that examined the effects of DAs in APD.

The AMSTAR assessment tool[73] was used to evaluate the quality of the included systematic reviews and meta-analyses.

Dopamine Receptor Agonists

Ergot and non-ergot DAs are drugs that can be administered as alternate first-line treatment in patients with EPD.[72] Non-ergot DAs are generally considered less effective than levodopa (the traditional first-line drug for the treatment of PD); however, they do have the advantage of less complex dosing schedules and fewer incidences of motor adverse effects, such as dyskinesias and "wearing-off."[43]

One systematic review with meta-analysis by Baker et al. consisted of 25 randomized controlled trials (RCTs) with 11 evaluating non-ergot DAs (pramipexole, ropinirole, rotigotine, piribedil; the latter is not available in Canada) in a total of 2,529 patients with EPD; no definition of EPD was stated.[43] Another meta-analysis by Stowe et al. consisted of 29 RCTs in which ergot (bromocriptine, CQA 206-291, lisuride, pergolide, cabergoline) and non-ergot DAs (piribedil, pramipexole, ropinirole) were comparators. The meta-analysis comprised a total of 5,247 patients with EPD, defined as idiopathic in nature, with no history of motor complications (either untreated or treated within the 12 months).[42] These meta-analyses had some similar a priori outcomes of interest, including treatment efficacy (measured using the UPDRS parts II and III subtotal scores), motor complications (specifically dyskinesias and "wearing-off" in that of Baker et al.[43]), WDAEs, and mortality.[42,43] Additionally, Stowe et al. included outcomes such as treatment compliance, other adverse effects, and levodopa use.[42] When compared with placebo, Baker et al. observed that non-ergot DAs were statistically significantly more effective at reducing PD symptoms (weighted mean difference [WMD] –1.67 [95% CI, –2.83 to –0.51] on the UPDRS subtotal score), but were also associated with a statistically significantly higher proportion of WDAEs (odds ratio [OR] 2.57 [95% CI, 1.71 to 3.86]) and increases in the incidence of individual AEs, such as somnolence (OR 3.30 [95% CI, 1.18 to 5.99]), dizziness (OR 1.66 [95% CI, 1.22 to 2.27]), hallucinations (OR 5.28 [95% CI, 2.44 to 11.44]), and nausea (OR 3.44 [95% CI of 2.44 to 4.85]).[43] The non-ergot DAs were observed to be less effective than levodopa in controlling motor symptoms in patients with EPD. Of note, included studies' durations varied widely, ranging from seven to 53 months.[43] Stowe et al.

reported that patients treated with DA monotherapy (ergot and non-ergot DA pooled OR 2.10 [95% CI, 0.71 to 6.20][43] and OR 0.051 [95% CI, 0.43 to 0.60][42]) or in combination with lower doses of levodopa[42] were less likely to develop motor complications (such as dyskinesias and "wearing-off") (OR 0.74 [95% CI, 0.53 to 1.04][42]), motor fluctuations (OR 0.67 [95% CI, 0.25 to 1.81][42]), and dystonia (OR 0.89 [95% CI, 0.61 to 1.28][42]) versus placebo. However, DA treatment was also observed to produce more non-motor adverse effects, such as hallucinations and somnolence, particularly with non-ergot DAs.[42] The Baker et al. meta-analysis reported reductions in levodopa doses when non-ergot DAs were added to existing levodopa therapy.[43] Additionally, delays in the onset of motor complications were observed when non-ergot DAs were initiated prior to levodopa.[43]

The identified systematic reviews and meta-analyses were found to be of high quality,[42,43] as all items on the AMSTAR checklist were satisfied, with the exception that the excluded study list was missing from one.[43] There were, however, notable limitations reported by the authors with regard to the individual studies included in their meta-analyses. The predominant limitation of studies included in the Baker et al. meta-analysis was the potential for publication bias. However, the authors postulated a low risk of publication bias (as shown by funnel plots and Egger's weighted regression statistic).[43] Stowe et al. noted that one source of bias in their meta-analysis could have been the poor quality of data reporting, whereby it was not clear if all randomized patients were included in the intent-to-treat analysis. Additionally, Stowe et al. noted the potential for serious bias if the "dropouts" or non-compliant patients were excluded, as they could have possibly represented atypical patients with worse prognosis or those who had a worse treatment effect.[42] Stowe et al. also noted that only one of the included studies incorporated quality of life as an outcome.[42]

Monoamine Oxidase Type B Inhibitors and Catechol-O-Methyltransferase Inhibitors

MAO-B inhibitors (e.g., selegiline, rasagiline) enhance dopamine's effects in the brain by blocking an enzyme that breaks down dopamine.[74] These drugs can be used as adjunct to levodopa in patients with APD,[44] but have also been used in patients with EPD due to their postulated neuroprotective effects.[74] COMT inhibitors (e.g., entacapone) block peripheral levodopa metabolism, thereby extending the elimination half-life of levodopa and allowing a prolonged effect.[36] COMT inhibitors, particularly entacapone, have been used in patients with APD as an adjunct to levodopa.[36]

One meta-analysis consisting of five trials specific for MAO-B inhibitors, including selegiline and rasagiline (combined with levodopa), with a total of 1,178 patients was identified for patients with APD already on levodopa.[44] The same authors performed another meta-analysis that examined COMT inhibitors, including entacapone and tolcapone (combined with levodopa), and that consisted of nine RCTs with a total of 2,597 patients with APD.[44] The a priori outcomes of interest for both groups of inhibitors included UPDRS scores (part II, part III, and total scores), change in "on" or "off" time, prevalence of dyskinesias, change in levodopa doses, WDAEs, and mortality.[44] As shown by the reduction in UPDRS total score (WMD of –5.03 [95% CI, –7.38 to –2.68]), UPDRS part II (ADL) (WMD of –1.48 [95% CI, –2.13 to –0.8]), UPDRS part III (WMD of –3.19 [95% CI, –4.57 to –1.80]), increased "on" time (not provided for MAO-B inhibitors), and reduction in "off" time (WMD of –0.93 [95% CI,–1.31 to –0.56]), and decreased levodopa dose, statistically significant improvements in PD symptoms were observed with both MAO-B and COMT inhibitors combined with levodopa when compared with levodopa alone.[44] These results, however, did not fall within the range for MCID.[44] In combination with levodopa, MAO-B inhibitors (UPDRS total WMD of –5.03 [95% CI,–7.38 to –2.68]; UPDRS part II WMD of –1.48 [95% CI,–2.13 to –0.83]; UPDRS part III WMD of –3.19 [95% CI,–4.57 to –1.80]) appeared to be more effective in improving PD symptoms than COMT inhibitors (UPDRS total WMD of –2.13 [95% CI,–4.06 to –0.20]; UPDRS part II WMD of –0.99 [95% CI,–1.56 to –0.43]; UPDRS part III WMD of –1.50 [95%

CI,–2.70 to –0.30]).[44] However, caution should be used in the interpretation of the aforementioned results, as the number of studies evaluating MAO-Bs was small.[44] Combination therapy of levodopa with either MAO-B or COMT inhibitors showed superior efficacy to levodopa alone, yet the risk of developing dyskinesias remained even in the presence of the inhibitors as adjunct therapies.[44] The incidence of WDAEs increased with COMT inhibitor use compared with levodopa alone, while no such increases were observed with MAO-B inhibitor use. However, WDAE results from the MAO-B inhibitor group were not statistically significant and the authors noted that some individual studies could have potentially reported adverse events as worsening of the disease.[44] When compared with levodopa alone, the mortality data were not statistically significant (OR of 0.36 [95% CI, 0.07 to 1.81; *P* = 0.214) for either the MAO-B or the COMT inhibitors in combination with levodopa.[44]

The Talati et al. systematic review (and meta-analyses) was considered high quality as it lacked only the excluded studies list from the AMSTAR criteria.[44] The predominant limitations of the meta-analyses included the potential for publication bias (in which the Egger's weighted regression statistic suggested a low likelihood of bias), the lack of indirect comparisons of the two drug classes, and the fact that eight of the 13 total included studies were supported by pharmaceutical companies.[44]

Summary

Two systematic reviews with meta-analyses were identified that examined the effect of ergot and non-ergot DAs, placebo, and levodopa in patients with EPD. Levodopa was observed to provide better motor symptomatic control than any of the DAs, but was associated with an increase in the risk of developing adverse events such as dyskinesias and "wearing-off." Reductions in the dose of levodopa were associated with the addition of non-ergot DAs when they were added to existing levodopa therapy. When combining non-ergot DAs with lower levodopa doses and when used as monotherapy, patients were less likely to develop motor complications, motor fluctuations, or dystonia. Delays in the onset of motor complications were also reported when non-ergot DAs were initiated prior to levodopa. However, DAs in general (but particularly non-ergot DAs) were associated with an increase in non-motor adverse events (such as hallucinations and somnolence) and WDAEs.

One systematic review with meta-analyses was identified that examined the effects of MAO-B and COMT inhibitors when combined with levodopa in patients with APD. Statistically significant improvements in the control of PD symptoms were associated with the use of both the MAO-B and COMT inhibitors when compared with levodopa alone; however, the risk of developing motor complications, such as dyskinesias, remained. MAO-B inhibitors appeared to be more effective at controlling PD symptoms in combination with levodopa and were not associated with an increased risk in WDAEs like the COMT inhibitors. However, the number of studies evaluating MAO-B inhibitors was small, and there was potential ambiguity in how adverse events were reported in some studies, as they may have been reported as symptoms of the disease instead of the treatment.

APPENDIX 8: CRITICAL APPRAISAL AND SUMMARY OF RESULTS OF THE MULTIPLE TREATMENT COMPARISON META-ANALYSIS

Aim

In early (EPD) and advanced Parkinson disease (APD), non-ergot dopamine receptor agonists (DAs) have been evaluated in both placebo-controlled and direct head-to-head comparison randomized controlled trials (RCTs). The manufacturer has submitted a multiple treatment comparison (MTC) network meta-analysis (NMA) consisting of both direct and indirect evidence to examine the comparative efficacy of rotigotine, ropinirole, and pramipexole (DAs) in patients with EPD and APD.[41]

Summary of Multiple Treatment Comparison Network Meta-Analyses

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

Twenty-three trials were included for EPD; [redacted] informing the analysis for the 11 to 16 week post-titration time point and [redacted] informing the analysis for the 24 to28 week post-titration time point. Of these, the following number of trials (in brackets) contained information regarding the following key efficacy outcomes for the 11 to 16 week time point: UPDRS part II ([redacted]), UPDRS part III ([redacted]), and the UPDRS parts II and III subtotal score ([redacted]). The following number of trials (in brackets) contained information regarding the following key efficacy outcomes for the 24 to 28 week time point: UPDRS part II ([redacted]), UPDRS part III ([redacted]), and the UPDRS parts II and III subtotal score ([redacted]).

Twenty-four trials were included for APD; [redacted] informing the analysis for the 11 to 16 week post-titration time point and [redacted] informing the analysis for the 24 to 28 week post-titration time point. Of these, the following number of trials (in brackets) contained information regarding the following key efficacy outcomes for the 11 to 16 week time point: UPDRS part II ([redacted]), UPDRS part III ([redacted]; [redacted]), and the amount of "off time" ([redacted]). The following number of trials (in brackets) contained information regarding the following key efficacy outcomes for the 24 to 28 week time point: UPDRS part II ([redacted]), UPDRS part III ([redacted]; [redacted]), and the amount of "off time" ([redacted]).

Methods

Eligibility Criteria

The MTC included both placebo-controlled trials and those with direct head-to-head comparisons in an attempt to compare non-ergot DAs, increase the patient sample size, and reduce uncertainty. Double-blind and open-label RCTs (exact numbers not provided) were included with the population, intervention, comparators (control interventions), and outcomes considered separately for patients with EPD and APD. Patients were included if they were ≥ 18 years of age and had either EPD or APD. Experimental interventions included rotigotine, ropinirole, and pramipexole with the following control interventions included for both EPD and APD disease (unless otherwise stated): levodopa with and without decarboxylase inhibitors, bromocriptine, cabergoline, piribedil, pergolide, and placebo (for patients with EPD only). Key efficacy outcomes included the UPDRS part II (activities of daily life), UPDRS part III (motor functioning), UPDRS parts II and III subtotal score (EPD only), and "off" time reduction (APD only).

Description of the Bayesian Multiple Treatment Comparison

Bayesian MTC meta-analyses were performed for both "short duration" (defined as including results between 11 and 16 weeks post-titration) and "longer duration" (defined as including results between 24 and 28 weeks post-titration) in EPD and APD.

In the EPD analysis, the MTCs were performed on the change from baseline for the UPDRS part II, UPDRS part III, and UPDRS parts II and III outcomes. [redacted] In APD, the MTCs were performed on the change from baseline for the UPDRS part II, UPDRS part III, and reduction from baseline in "off time."

Mean difference was the effect measure employed as all outcomes were continuous. The "shared parameter" model was used so that originally reported data from the trials could be used for the MTC meta-analyses.

Subgroup analyses were performed by including then excluding the Giladi et al. rotigotine study (SP513) as the reported UPDRS parts II and III subtotal scores were substantially higher than those reported in other trials in patients with EPD at 24 to 28 weeks, when comparing rotigotine to ropinirole. This was only performed for this particular outcome as other outcomes were relatively similar across studies. Another scenario analysis was identified for the UPDRS part III in APD, whereby an abstract was identified but the improvement in the UPDRS part III could not be included as the time point was not reported.

Patient and Treatment Characteristics

Early Parkinson disease: Several key patient characteristics were similar between the included trials for EPD. In general, patients' average age was approximately 60 to 65 years of age (estimated range of 50 to 75) with an average duration of Parkinson disease between one and two years (estimated range of less than one year to six years). In addition, disease severity was measured at a Hoehn and Yahr staging of I or II, with only a small proportion of patients classified as stage III. 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 the concomitant levodopa plus dopa decarboxylase inhibitors [DDCIs]) and non-ergot DAs:

- Levodopa/DDCI — range of mean dose = 364 mg/day to 753 mg/day
- Pramipexole — range of mean dose = 1.0 mg/day to 4.5 mg/day
- Ropinirole — range of mean dose = 10 mg/day to ≤ 24 mg/day
- Rotigotine — range of median dose = 4.5 mg/day to 18 mg/day.

Advanced Parkinson disease: Several key patient characteristics were similar between the included trials for APD. For the most part, patients were between 60 and 65 years of age (estimated range of 50 to 75 years) with an average duration of Parkinson disease between 4 and 10 years (standard deviation indicated a range of 2 to 20 years). In general, disease severity was measured at a Hoehn and Yahr stage of greater than 2.5, with a large proportion of patients classified as stage III or above. 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 plus DDCI and the following non-ergot DAs:

- Pramipexole — range of mean dose = 2.7 mg/day to 4.59 mg/day
- Ropinirole — range of mean dose = 3.30 mg/day to 18.8 mg/day ; (Leiberman et al., 1998 — stated 0.75 mg/day to 24 mg/day in the same column)

- Rotigotine — range of median dose = 2.00 mg/day to 12.95 mg/day.

Results

Results of the Multiple Treatment Comparison for Early Parkinson Disease

Post-Titration of 11 to 16 Weeks: Statistically significant mean improvements in the UPDRS-III (motor functioning) and UPDRS parts II and III subtotal scores were observed with all interventions (levodopa, pramipexole, ropinirole, and rotigotine) when compared with placebo at 11 to 16 weeks post-titration (Table 52). Statistically significant reductions were observed in UPDRS part II (ADL) scores with levodopa, pramipexole, and rotigotine but not with ropinirole when compared with placebo. No statistically significant improvements were observed with any UPDRS scores when comparing rotigotine with either pramipexole or ropinirole; however, statistically significant improvements in the UPDRS parts III and II and III total scores were reported with the use of levodopa when compared with rotigotine (Table 52).

TABLE 52: EFFICACY COMPARISONS AT 11 TO 16 WEEKS POST-TITRATION IN PATIENTS WITH EARLY PARKINSON DISEASE

Comparison	UPDRS Part II MD[a] (95% CI)	UPDRS Part III MD[a] (95% CI)	UPDRS Part II and III MD[a] (95% CI)
Placebo Comparisons			
L-Dopa vs. placebo	[redacted]	[redacted]	[redacted]
Pramipexole vs. placebo	[redacted]	[redacted]	[redacted]
Ropinirole vs. placebo	[redacted]	[redacted]	[redacted]
Rotigotine vs. placebo	[redacted]	[redacted]	[redacted]
Active Comparisons[b]			
Rotigotine vs. L-Dopa	[redacted]	[redacted]	[redacted]
Rotigotine vs. pramipexole	[redacted]	[redacted]	[redacted]
Rotigotine vs. ropinirole	[redacted]	[redacted]	[redacted]

CI = confidence interval; L-Dopa = levodopa; MD = mean difference; UPDRS = Unified Parkinson Disease Rating Scale; vs. = versus.

[a] Negative MD indicates superiority of the active intervention.

[b] Negative result would favour rotigotine; positive results favours levodopa.

Source: Thorlund (as per Manufacturer's Submission).[41]

Post-Titration of 24 to 28 Weeks: Statistically significant reductions in UPDRS part II (ADL) score and mean improvements in the UPDRS part III (motor functioning) and UPDRS parts II and III subtotal scores were observed with all of the interventions (levodopa, pramipexole, ropinirole, and rotigotine) when compared with placebo at 24 to 28 weeks post-titration (Table 53). No significant reductions in the UPDRS part II or improvements in the UPDRS part III, and UPDRS parts II and III scores were observed when comparing rotigotine with levodopa, pramipexole, or ropinirole (Table 53).

TABLE 53: EFFICACY COMPARISONS AT 24 TO 28 WEEKS POST-TITRATION IN PATIENTS WITH EARLY PARKINSON DISEASE

Comparison	UPDRS part II MD[a] (95% CI)	UPDRS part III MD[a] (95% CI)	UPDRS parts II and III MD[a] (95% CI)
Placebo Comparisons			
L-Dopa vs. placebo	[redacted]	[redacted]	[redacted]
Pramipexole vs. placebo	[redacted]	[redacted]	[redacted]
Ropinirole vs. placebo	[redacted]	[redacted]	[redacted]
Rotigotine vs. placebo	[redacted]	[redacted]	[redacted]
Active Comparisons[b]			
Rotigotine vs. L-Dopa	[redacted]	[redacted]	[redacted]
Rotigotine vs. pramipexole	[redacted]	[redacted]	[redacted]
Rotigotine vs. ropinirole	[redacted]	[redacted]	[redacted]

CI = confidence interval; L-Dopa = levodopa; MD = mean difference; UPDRS = Unified Parkinson Disease Rating Scale; vs. = versus.
[a] Negative MD indicates superiority of the active intervention.
[b] Negative result would favour rotigotine; positive results favours levodopa.
Source: Thorlund (as per Manufacturer's Submission).[41]

Both subgroup analyses (either including or excluding the Giladi study[18]) reported similar results with statistically significant improvements in UPDRS parts II and III subtotal scores observed with all of the interventions when compared with placebo (Table 54). No statistical significance was observed when comparing rotigotine and the other non-ergot DAs; [redacted].[18] study (Table 54).

TABLE 54: EFFICACY COMPARISON SUBGROUP ANALYSES AT 24 TO 28 WEEKS POST-TITRATION FOR THE UPDRS PARTS II AND III SUBTOTAL SCORES IN PATIENTS WITH EARLY PARKINSON DISEASE

Comparison	Scenario Analysis 1[a] UPDRS Part II and III MD[c] (95% CI)	Scenario Analysis 2[b] UPDRS Part II + and III MD[c] (95% CI)
Placebo Comparisons		
L-Dopa vs. placebo	[redacted]	[redacted]
Pramipexole vs. placebo	[redacted]	[redacted]
Ropinirole vs. placebo	[redacted]	[redacted]
Rotigotine vs. placebo	[redacted]	[redacted]
Active Comparisons[d]		
Rotigotine vs. L-Dopa	[redacted]	[redacted]
Rotigotine vs. pramipexole	[redacted]	[redacted]
Rotigotine vs. ropinirole	[redacted]	[redacted]

CI = confidence interval; L-Dopa = levodopa; MD = mean difference; UPDRS = Unified Parkinson Disease Rating Scale; vs. = versus.
[a] Giladi[18] reference excluded.
[b] Giladi[18] reference included.
[c] Negative MD indicates superiority of the active intervention.
[d] Negative result would favour rotigotine; positive results favours the comparator.
Source: Thorlund (as per Manufacturer's Submission).[41]

Results of the Multiple Treatment Comparison for Advanced Parkinson Disease

Post-Titration of 11 to 16 Weeks: Statistically significant reductions in the UPDRS part II and improvements in both the UPDRS part III score and in the amount of "off time" were observed at 11 to 16 weeks post-titration with all interventions when compared with placebo [redacted] (Table 55). Estimated differences in reductions for the UPDRS part II or improvements for either UPDRS part III score or "off time" were not statistically significant between rotigotine and the non-ergot DAs, pramipexole and ropinirole at 11 to 16 weeks (Table 55).

TABLE 55: EFFICACY COMPARISONS AT 11 TO 16 WEEKS POST-TITRATION IN PATIENTS WITH ADVANCED PARKINSON DISEASE

Comparison	UPDRS part II MD[b] (95% CI)	UPDRS part III[a] MD[b] (95% CI)	"Off Time" (hours) MD[b] (95% CI)
Placebo Comparisons			
Pramipexole vs. placebo	–2.03 (–2.69 to –1.37)	[redacted]	[redacted]
Ropinirole vs. placebo	–1.84 (–3.22 to –0.44)	[redacted]	[redacted]
Rotigotine vs. placebo	–1.71 (–2.62 to –0.78)	[redacted]	[redacted]
Active Comparisons[c]			
Rotigotine vs. pramipexole	0.32 [redacted]	[redacted]	[redacted]
Rotigotine vs. ropinirole	0.13 [redacted]	[redacted]	[redacted]

CI = confidence interval; L-Dopa = levodopa; MD = mean difference; UPDRS = Unified Parkinson Disease Rating Scale; vs. = versus.

[a] Results based on scenario #1, [redacted].

[b] Negative MD indicates superiority of the active intervention.

[c] Negative result would favour rotigotine; positive results favours levodopa.

Source: Thorlund (as per Manufacturer's Submission).[41]

Post-Titration of 24 to 28 Weeks: Statistically significant reductions in UPDRS part II scores and improvements in both the UPDRS part III score and the amount of "off time" were associated with all interventions at 24 to 28 weeks post-titration when compared with placebo [redacted] (Table 56). Estimated differences in reductions for the UPDRS part II score or improvements for either UPDRS part III score or "off time" were not statistically significant between rotigotine and the non-ergot DAs, pramipexole and ropinirole at 24 to 28 weeks (Table 56).

TABLE 56: EFFICACY COMPARISONS AT 24 TO 28 WEEKS POST-TITRATION IN PATIENTS WITH ADVANCED PARKINSON DISEASE

Comparison	UPDRS part II MD[b] (95% CI)	UPDRS part III[a] MD[b] (95% CI)	"Off Time" MD[b] (95% CI)
Placebo Comparisons			
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	[redacted] (–3.71 to –0.78)	[redacted] (–7.63 to –1.12)	[redacted] (–2.91 to –0.05)
Active Comparisons[c]			
Rotigotine vs. pramipexole	[redacted]	[redacted]	[redacted]
Rotigotine vs. ropinirole	[redacted]	[redacted]	[redacted]

CI = confidence interval; L-Dopa = levodopa; MD = mean difference; UPDRS = Unified Parkinson Disease Rating Scale; vs. = versus.
[a] Results based on scenario #1, [redacted].
[b] Negative MD indicates superiority of the active intervention.
[c] Negative result would favour rotigotine; positive results favours levodopa.
Source: Thorlund (as per Manufacturer's Submission).[41]

The UPDRS part III scores remained significantly improved at both the 11 to 16 week and 24 to 28 weeks post-titration stage in both subgroup analyses [redacted] (Table 57). [redacted] (Table 57).

TABLE 57: EFFICACY COMPARISON SUBGROUP ANALYSES AT BOTH THE 11 TO 16 AND 24 TO 28 WEEKS POST-TITRATION TIME POINTS IN PATIENTS WITH ADVANCED PARKINSON DISEASE

Comparison	Scenario Analysis 2(a)[a] (UPDRS part III) MD[c] (95% CI)	Scenario Analysis 2(b)[b] (UPDRS part III) MD[c] (95% CI)
Placebo Comparisons		
Pramipexole vs. placebo	[redacted]	[redacted]
Ropinirole vs. placebo	[redacted]	[redacted]
Rotigotine vs. placebo	[redacted]	[redacted]
Active Comparisons[d]		
Rotigotine vs. pramipexole	[redacted]	[redacted]
Rotigotine vs. ropinirole	[redacted]	[redacted]

CI = confidence interval; L-Dopa = levodopa; MD = mean difference; UPDRS = Unified Parkinson Disease Rating Scale; vs. = versus.
[a] UPDRS part III at 11 to 16 weeks [redacted].
[b] UPDRS part III at 24 to 28 weeks [redacted].
[3] Negative MD indicates superiority of the active intervention.
[d] Negative result would favour rotigotine; positive results favour the comparator.
Source: Thorlund (as per Manufacturer's Submission).[41]

Critical Appraisal of Indirect Comparison

TABLE 58: 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.
3.	Are the outcome measures described?	• The outcomes assessed in the indirect comparison analysis were stated.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• The Bayesian Multiple Treatment Comparison was employed and the rationale for using this method was reported. In addition, the handling of potential bias and the analysis framework were provided.
5.	Are sensitivity analyses presented?	• The sensitivity analyses and scenario analyses were 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 the number of patients in the individual trials was omitted. • Trial characteristics were provided. • Figures of the networks were provided.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• Not applicable.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported and complete.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; PICO = population, intervention, comparator, outcome.
Source: Jansen et al.[75]

Strengths

The MTC NMAs were based on a systematic review of the available RCTs. The individual RCTs appeared to contain appropriately representative populations of patients living with EPD and APD; thus, enhancing the generalizability of the results. The MTC included a large number of studies in the analysis, thereby potentially increasing the reliability of the results; however, the number of patients per study was not reported. In terms of the methods used for the statistical analysis, the Bayesian method appeared appropriate for this NMA.

Limitations

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 previously reported, there were some differences between the dosing of the non-ergot DAs and levodopa plus DDCIs between trials; however, upon consultation with the clinical expert engaged with this review, the dose ranges for the non-ergot DAs and levodopa are in line with clinical practice. In addition, the definitions were not provided with regard to EPD and APD. Information regarding the dosing of concomitant medications was varied and, in some cases, not well reported. Hence, there is the possibility that combining such trials may reduce the clinical relevance.

The network of trials included for these analyses was quite large. Although increasing the sample size and number of comparisons generally increases reliability, there is the possibility that the results for the three non-ergot DAs of primary interest (pramipexole, ropinirole, and rotigotine) were diluted, especially with regard to the direct head-to-head comparisons included in the network. In addition, the number of patients within each individual trial was not reported in the NMA. The manufacturer also included medications that were not available in Canada, which could have also unnecessarily further increased the diluting effect. Another important limitation is the lack of EPD and APD descriptions between trials or even a summary describing their similarities and differences.

The NMAs did not assess the comparative efficacy for other outcomes reported in other trials, such as responder rate or sleepiness. By not including analyses for these outcomes, 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-ergot DAs.

The discordance between the results of the NMA and the direct evidence was of concern. One of the key studies by Giladi et al.[18] was reported to be an outlier by the manufacturer due to the 24 to 28 week time point UPDRS parts II and III response results obtained using high doses of ropinirole. Giladi et al.[18] reported a mean decrease from baseline with ropinirole for the UPDRS parts II and III subtotal of –11 (standard deviation [SD] of 10.5) when compared with placebo. The manufacturer noted that this change was substantially larger than changes observed in other trials where results were more homogeneous and ranged from 5.20 to 7.52.[18] For this reason, they performed two subgroup analyses, whereby they examined the mean differences in UPDRS parts II and III against both placebo and active comparators (pramipexole and ropinirole) upon inclusion and exclusion of the Giladi study. The mean differences of ropinirole was within ranges observed in the other included trials versus placebo at [redacted] with the Giladi study excluded and [redacted] with it included. Nonetheless, the design of the Giladi et al. study (i.e., higher ropinirole dose, longer duration) likely contributes to the discordance in the direct and indirect comparison between ropinirole and rotigotine.

[redacted]

Furthermore, it is unclear if the results of the NMAs, which were conducted for time intervals 11 to 16 weeks and 24 to 28 weeks after initiation of treatment, can be extrapolated to beyond 28 weeks. Parkinson disease is a progressive condition and it is possible that the maintenance doses needed over time will increase, especially in cases of advanced disease.

In EPD, monotherapy with levodopa plus carbidopa is considered as the standard of care by many clinicians and, therefore, should be considered as an appropriate comparator. In the NMA submitted by the manufacturer, rotigotine was inferior to levodopa for change from the baseline UPDRS parts II and III subtotal at 11 to 16 weeks. The mean difference compared with levodopa was [redacted] including the Giladi trial, but similar to levodopa when the Giladi et al. trial was excluded (mean difference compared with levodopa was [redacted]).

Summary

In EPD and APD, all three non-ergot DAs of interest (pramipexole, ropinirole, and rotigotine) were associated with significantly improving activities of daily living (part II) and motor functioning (part III), both at the 11 to 16 and 24 to 28 week time points versus placebo (with the exception of ropinirole in EPD, which was not associated with significantly improving activities in daily life at 11 to 16 weeks). When compared with each other, pramipexole, ropinirole, and rotigotine were similar in their effect estimates, suggesting that they will all provide equal benefits to patients with EPD and APD. However, levodopa in EPD was found to be more efficacious in improving motor function and UPDRS parts II and III total scores at the 11 to 16 week time point and the UPDRS parts II and III subtotal scores at the 24 to 28 week time point (in the subgroup analysis, whereby the Giladi et al. trial[18] was included) when compared with rotigotine.

The potential limitations previously described cast some doubt as to the clinical relevance of this NMA. While pramipexole, ropinirole, and rotigotine appeared to be equally efficacious in improving some of the symptoms associated with Parkinson disease, uncertainty remains around the reliability and validity of these results for these specific patient populations.

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