The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: ROP106066

Title: Clinical Evaluation of Ropinirole PR/XR Tablet for Adjunctive Therapy to L-dopa in Subjects With Advanced Parkinson's Disease

Rationale: Since the prolonged release/extended release (PR/XR) tablets of ropinirole is an extended release version of the immediate release (IR) tablets of ropinirole, the company planned to evaluate the usefulness of ropinirole PR/XR tablets by comparing the pharmacokinetics and clinical study results (clinical efficacy) between ropinirole IR tablets and ropinirole PR/XR tablets. As for the positioning of this study, this was a phase III study to verify the non-inferiority in efficacy and safety of ropinirole PR/XR tablets to ropinirole IR tablets in subjects who were not optimally controlled on concomitant L-dopa therapy.

Phase: III

Study Period: 1 Apr 2009-21 Dec 2010

Study Design: This is a multicenter, randomized, double-blind, double-dummy, parallel group comparison study. This study comprised of 6 phases, screening phase (1 to 4 weeks), non-inferiority verification phase (24 weeks), PR/XR switching phase (8 weeks), long-term phase (22 weeks), down-titration phase (0 to 4 weeks) and follow-up phase (1 to 4 weeks).

Centres: 54 medical institutions in Japan

Indication: Parkinson's disease

Treatment:

For non-inferiority verification phase, at the start of this phase (Week 0), subjects were randomized to the PR-PR group or the IR-PR group in a ratio of 1:1. Subjects in the PR-PR group received ropinirole PR/XR tablets, matching ropinirole PR/XR placebo tablets and matching ropinirole IR placebo tablets, while those in the IR-PR group received matching ropinirole PR/XR placebo tablets and ropinirole IR tablets.

Ropinirole PR/XR tablets (or matching ropinirole PR/XR placebo tablets) were orally administered once daily at the same time each day, preferably in the morning from the viewpoint of usefulness of the PR/XR tablets.

The initial starting dose was dose level 1 with a dose increase every week to dose level 4 at Week 4 (see dose levels below).

Between Week 6 and Week 24, the dose was optionally increased at intervals of 2 weeks or longer from dose level 4 up to dose level 12. The maintenance dose was continuously administered up to Week 24. Provided the current dose level was well tolerated, investigators were to continue to up titrate subjects to the next dose level if they saw incremental clinical benefit on "Off" time or UPDRS motor score at the current dose level or if there was another clinical rationale for continuing up titration. If any onset of an adverse event (AE) required dose reduction, the dose was reduced level by level down to the highest tolerable dose level, which was maintained with the administration continued up to Week 24. However, when the dose of ropinirole PR/XR tablets was reduced from dose level 11 or 12, the dose was reduced to dose level 9, as reduced from level 10. The lowest dose level allowed after dose reduction was dose level 4.

Dose Level	PR/XR tablets	IR tablets	Dose Level	PR/XR tablets	IR tablets
1	Placebo	0.75 mg/day	7	10 mg/day	7.5 mg/day
2	Placebo	1.5 mg/day	8	12 mg/day	9 mg/day
3	2 mg/day	2.25 mg/day	9	14 mg/day	10.5 mg/day
4	4 mg/day	3 mg/day	10	16 mg/day	12 mg/day
5	6 mg/day	4.5 mg/day	11	16 mg/day	13.5 mg/day
6	8 mg/day	6 mg/day	12	16 mg/day	15 mg/day

For PR/XR switching phase, administration of ropinirole PR/XR tablets (or matching ropinirole PR/XR placebo tablets) was continued at the same dose level as that at the end of the non-inferiority verification phase. Ropinirole IR tablets (or matching ropinirole IR placebo tablets) were given until the night of the visit day and were replaced by ropinirole PR/XR tablets (or matching ropinirole PR/XR placebo tablets) on the following morning at the same dose level according to the dose levels below:

Dose Level	IR tablets	PR/XR tablets	Dose Level	IR tablets	PR/XR tablets
4	3 mg/day	4 mg/day	9	10.5 mg/day	10 mg/day
5	4.5 mg/day	4 mg/day	10	12 mg/day	12 mg/day

6	6 mg/day	6 mg/day	11	13.5 mg/day	14 mg/day
7	7.5 mg/day	8 mg/day	12	15 mg/day	16 mg/day
8	9 mg/day	8 mg/day			

If drug efficacy was considered insufficient at Week 26 or 28, the dose could be increased. But the dose was maintained at the level achieved as of Week 28 and the subjects were remained at this dose level for 4 weeks. If dose reduction was necessary due to onset of AEs during upward titration, the subject was down titrated until a tolerated dose was achieved and then was maintained on that dose. However, dose reduction was permitted down to 4 mg/day. The first 200 subjects registered on the non-inferiority verification phase were entered into the long-term phase after completion of the PR/XR switching Phase. The 201st subject or later were entered into the down titration after completion of the PR/XR switching Phase.

For long-term phase, in both groups, administration of ropinirole PR/XR tablets (or matching ropinirole PR/XR placebo tablets) was continued in the first 200 subjects in the order of registration in the non-inferiority verification phase, at the same dose level as that at the end of PR/XR switching Phase until Week 54. In cases where lack of efficacy was noted or tolerability issues arose due to AEs, the maintenance dose could be changed. However, the lowest dose level allowed after dose reduction was 4 mg/day.

For down-titration phase, subjects who completed Week 54, the 201st subject or later registered in the non-inferiority verification phase who completed Week 32, or withdrawn were down titrated over a 1 to 4 weeks period. Down titration of the final dosage level was not required for ropinirole PR/XR tablets, if administered at Level 4, but was required for ropinirole IR tablets.

Objectives: To investigate the efficacy and the safety of ropinirole PR/XR tablets to ropinirole IR tablets in subjects with advanced Parkinson's disease in conjunction with L-dopa in a double-blind, parallel group comparison study.

Primary Outcome/Efficacy Variable: Change from Baseline (Week 0) in UPDRS Part III total score at Week 24 (last observation carried forward [LOCF]) in the non-inferiority verification phase

Secondary Outcome/Efficacy Variable(s):

Non-Inferiority Verification Phase:

proportion of subjects achieving a 30% and 20% reduction from Baseline in UPDRS Part III total score; change from Baseline in UPDRS Part I, II, and IV total scores; UPDRS Part I, II, III and IV total scores; Clinical Global Impression-Improvement (CGI-I) responders ("very much improved" or "much improved"); proportion of subjects with 20% responder in change from Baseline in awake time spent "Off" (proportion of off time in awake time); proportion of subjects with 20% responder in percent change from Baseline in awake time spent "Off" (proportion of off time in awake time); change from Baseline in awake time spent "Off" (actual hours); change and percent change from Baseline in awake time spent "Off" (proportion of off time in awake time); change from Baseline in awake time spent "On" (actual hours and proportion of on time in awake time); change from Baseline in awake time spent "On" with troublesome dyskinesias (actual hours and proportion of on time in awake time); Modified Hoehn & Yahr staging scale; and proportion of subjects remaining in the study (the time point of Week 24 LOCF was used for the above endpoints except for the proportion of subjects remaining in the study)

PR/XR Switching Phase:

change from switching period Baseline (Week 24) in UPDRS Part I, II, III and IV total scores; UPDRS Part I, II, III and IV total scores; change from switching Period Baseline in awake time spent "Off" (actual hours and proportion of off time in awake time); change from switching Period Baseline in awake time spent "On" with troublesome dyskinesias (actual hours); Modified Hoehn & Yahr staging scale; and proportion of subjects remaining in the study (the time point of Week 32 LOCF was used for the above endpoints except for the proportion of subjects remaining in the study)

Long-term Phase:

proportion of subjects achieving a 30% and 20% reduction from Baseline (Week 0) in UPDRS Part III total score; change from Baseline in UPDRS Part I, II, III and IV total scores; UPDRS Part I, II, III and IV total scores; CGI-I responders ("very much improved" or "much improved"); proportion of subjects with 20% responder in change from Baseline in awake time spent "Off" (proportion of off time in awake time); proportion of subjects with 20% responder in percent change from Baseline in awake time spent "Off" (proportion of off time in awake time); change from Baseline in awake time spent "Off" (actual hours and proportion of off time in awake time); change from Baseline in awake time spent "On" with troublesome dyskinesias (actual hours); Modified Hoehn & Yahr staging scale; and proportion of subjects remaining in the study (the time point of Week 54 was used for the above endpoints except for the proportion of subjects remaining in the study)

Statistical Methods:
Efficacy analyses were based on the Full Analysis Set (FAS) population, which consisted of all randomized subjects who were progressed to the non-inferiority verification phase but excluding those who did not have the target indication, those who did not receive at least one dose of the investigational product and those whose measured data in efficacy were not available after treatment initiation. The primary efficacy endpoint was analyzed based on the Per Protocol Set (PPS) population, consisted of subjects with exclusion from the FAS of those violating the study protocol and assessed to be excluded from the assessment of drug efficacy. All safety endpoints were analyzed using the safety population (SP), consisted of subjects who received at least one dose of the investigational product.

The primary analysis of change from Week 0 (Baseline) in UPDRS Part III total score at Week 24 between the PR-PR group and the IR-PR group was performed using analysis of covariance (ANCOVA) technique including baseline UPDRS Part III total score as a covariate. Summary statistics for change from Baseline in UPDRS Part III total score by treatment group and two-sided 95% confidence interval (CI) were presented. Non-inferiority of the PR-PR group to the IR-PR group was assessed with a non-inferiority margin of 2.5. The evaluation of non-inferiority of the PR-PR group was based on the PPS population. If non-inferiority of PR/XR to IR was demonstrated, superiority of the PR-PR group to the IR-PR group was to be assessed using the FAS population. This assessment was performed in closed procedure to control for multiplicity.
Continuous secondary endpoints were analyzed using the ANCOVA model adjusting for the baseline assessment. Dichotomous secondary endpoints were analyzed using the logistic regression. Proportion of subjects remaining in the study was presented using Kaplan-Meier method.

Study Population:
Eligible subjects at the start of the screening phase were subjects diagnosed with advanced Parkinson's disease (according to Modified Hoehn & Yahr criteria Stage 2-4); who had received a stable dose of L-dopa for at least 4 weeks prior to the Screening Phase; who had QTc <450 milliseconds (msec) or <480 msec for subjects with bundle branch block; who was 20 years or older at the time of informed written consent; who were able to give informed written consent in person; either male or female; and either inpatients or outpatients. Only subjects whose UPDRS Part III total score (at "On") was 10 points or more were enrolled in the non-inferiority verification phase of the study.

The exclusion criteria at the start of the screening included the following that might affect proper evaluation of the efficacy and safety of the investigational product: late stage advanced subjects demonstrating incapacitating peak dose or biphasic dyskinesia on their stable dose of L-dopa; subjects presenting serious physical signs and symptoms other than those of the Parkinson's disease (e.g. cardiac/hepatic/renal disorder and haematopoietic disorder); symptomatic postural hypotension (e.g. dizziness and syncope); a current or past history of drug abuse or alcoholism; and surgical treatment for Parkinson's disease in the past (e.g. pallidectomy, deep brain stimulation).

The exclusion criteria at the start of the non-inferiority verification phase included the following that might affect proper evaluation of the efficacy and safety of the investigational product: severe dementia (e.g. score 3 or 4 of UPDRS Part I item 1 [Intellectual Impairment]); current or past history of major psychosis (e.g. schizophrenia or psychotic depression) (e.g. score 3 or 4 of UPDRS Part I item 2 [thought disorder] or item 3 [depression]); and use of any dopamine agonist within 4 weeks prior to the non-inferiority verification phase.

	PR-PR	**IR-PR**
Number of Subjects:		
Planned, N	150	150
Randomised, N	156	146
Non-Inferiority Verification Phase and PR/XR Switching Phase		
Entered, N	156	146
Completed, n (%)	124 (79)	117 (80)
Total Number Subjects Withdrawn, n (%)	32 (21)	29 (20)
Withdrawn due to Adverse Events, n (%)	22 (14)	21 (14)
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for other reasons, n (%)	10 (6)	8 (5)
Long-term Phase		
Planned, N (to complete the phase)	130	
Entered, N	73	84
Completed, n (%)	68 (93)	79 (94)
Total Number Subjects Withdrawn, n (%)	5 (7)	5 (6)
Withdrawn due to Adverse Events, n (%)	3 (4)	2 (2)

Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for other reasons, n (%)	2 (3)	3 (4)
Demographics	**PR-PR**	**IR-PR**
N (FAS)	156	146
Females: Males	93:63	81:65
Mean Age, years (SD)	69.3 (7.95)	68.3 (8.22)
Asian - Japanese Heritage, n (%)	156 (100)	146 (100)
Primary Efficacy Results:		
Change From Week 0 in UPDRS Part III Total Score at Week 24 (LOCF) in the Non-Inferiority Verification Phase (PPS)		
	PR-PR (N=146)	**IR-PR (N=139)**
Baseline (Week 0), UPDRS Part III Total Score, Mean (SD)	24.1 (9.38)	24.3 (9.87)
Week 24 LOCF		
N	n=141	n=133
UPDRS Part III Total Score, Mean (SD)	13.4 (9.78)	12.8 (9.33)
Analysis of Change in UPDRS Part III Total Score at Week 24 LOCF		
n	n=141	n=133
Adjusted mean Change From Week 0 in UPDRS Part III Total Score at Week 24 LOCF (SE)	-10.8 (0.62)	-11.1 (0.64)
Treatment difference (95% CI)	0.34 (-1.41, 2.09)	
P-value	0.702	
Secondary Outcome Variable(s):		
Non-Inferiority Verification Phase	**PR-PR (N=156)**	**IR-PR (N=146)**
Responder Rate on UPDRS Part III Total Score (Week 24 LOCF, FAS)		
Percent Reduction From Week 0 ≥20%		
Responder Rate	81% (122/151 subjects)	78% (108/139 subjects)
Odds ratio (95% CI)	1.208 (0.684, 2.133)	
Percent Reduction From Week 0 ≥30%		
Responder Rate	66% (99/151 subjects)	69% (96/139 subjects)
Odds ratio (95% CI)	0.853 (0.521, 1.395)	
UPDRS Part I Total Score (Week 24 LOCF, FAS)		
n	n=151	n=142
Week 24 LOCF, Mean (SD)	0.7 (1.34)	0.8 (1.50)
Adjusted Mean Change From Week 0 (SE)	-0.3 (0.09)	-0.2 (0.10)
Treatment difference (95% CI)	-0.02 (-0.28, 0.24)	
UPDRS Part II (On) Total Score (Week 24 LOCF, FAS)		
n	n=151	n=142
Week 24 LOCF, Mean (SD)	5.2 (5.21)	4.6 (5.23)
Adjusted Mean Change From Week 0 (SE)	-2.6 (0.28)	-3.0 (0.29)
Treatment difference (95% CI)	0.35 (-0.45, 1.16)	
UPDRS Part II (Off) Total Score (Week 24 LOCF, FAS)		
n	n=66	n=76
Week 24 LOCF, Mean (SD)	9.6 (7.24)	8.7 (6.39)
Change From Week 0, Mean (SD)	-4.7 (4.49)	-3.8 (5.15)
UPDRS Part III Total Score (Week 24 LOCF, FAS)		
n	n=151	n=139
Week 24 LOCF, Mean (SD)	13.7 (9.91)	12.7 (9.39)
Adjusted Mean Change From Week 0 (SE)	-10.4 (0.61)	-11.1 (0.63)
Treatment difference (95% CI)	0.72 (-1.01, 2.44)	
UPDRS Part IV Total Score (Week 24 LOCF, FAS)		
n	n=151	n=141
Week 24 LOCF, Mean (SD)	2.1 (2.25)	2.6 (2.49)
Adjusted Mean Change From Week 0 (SE)	-0.6 (0.12)	-0.2 (0.12)
Treatment difference (95% CI)	-0.4 (-0.73, -0.06)	
CGI-I (Week 24 LOCF, FAS)		

Proportion of Responders ("very much improved" or "much improved")	63% (95/151 subjects)		61% (87/142 subjects)	
Odds ratio (95% CI)	1.07 (0.67, 1.72)			
Responder Rate on Awake Time Spent "Off" (Week 24 LOCF, FAS)				
Reduction From Week 0 ≥20%				
Responder Rate	44% (34/78 subjects)		40% (31/77 subjects)	
Odds ratio (95% CI)	0.984 (0.566, 1.712)			
Percent Reduction From Week 0 ≥20%				
Responder Rate	76% (59/78 subjects)		69% (53/77 subjects)	
Odds ratio (95% CI)	1.406 (0.693, 2.851)			
Awake Time Spent "Off" (Week 24 LOCF, FAS)				
n	n=78		n=77	
Adjusted Mean Change From Week 0 (SE) (actual hours)	-2.77 (0.422)		-2.71 (0.425)	
Treatment difference (95% CI)	-0.07 (-1.25, 1.12)			
Adjusted Mean Change From Week 0 (SE) (proportion [%] of off time in awake time)	-17.66 (2.493)		-17.55 (2.509)	
Treatment difference (95% CI)	-0.11 (-7.10, 6.89)			
Adjusted Mean Percent Change From Week 0 (SE) (proportion [%] of off time in awake time)	-42.10 (7.870)		-40.74 (7.921)	
Treatment difference (95% CI)	-1.36 (-23.44, 20.72)			
Awake Time Spent "On" (Week 24 LOCF, FAS)				
n	n=149		n=134	
Adjusted Mean Change From Week 0 (SE) (actual hours)	1.66 (0.230)		1.33 (0.243)	
Treatment difference (95% CI)	0.33 (-0.33, 0.99)			
Adjusted Mean Change From Week 0 (SE) (proportion [%] of on time in awake time)	9.17 (1.291)		7.64 (1.362)	
Treatment difference (95% CI)	1.53 (-2.16, 5.23)			
Awake Time Spent "On" With Troublesome Dyskinesias (Week 24 LOCF, FAS)				
n	n=7		n=13	
Adjusted Mean Change From Week 0 (SE) (actual hours)	0.31 (1.147)		1.01 (0.830)	
Treatment difference (95% CI)	-0.70 (-3.75, 2.35)			
Adjusted Mean Change From Week 0 (SE) (proportion [%] of on time in awake time)	0.90 (7.202)		6.31 (5.199)	
Treatment difference (95% CI)	-5.41 (-24.61, 13.79)			
Modified Hoehn & Yahr Severity of Illness (at "On") (Week 24 LOCF, FAS)				
	Week 0 (n=156)	Week 24 (n=151)	Week 0 (n=146)	Week 24 (n=142)
	n (%)	n (%)	n (%)	n (%)
Stage 0	0	2 (1)	0	4 (3)
Stage 1	0	20 (13)	0	18 (13)
Stage 1.5	0	3 (2)	1 (1)	14 (10)
Stage 2	34 (22)	54 (36)	34 (23)	44 (31)
Stage 2.5	47 (30)	31 (21)	43 (29)	29 (20)
Stage 3	64 (41)	34 (23)	57 (39)	27 (19)
Stage 4	11 (7)	7 (5)	10 (7)	6 (4)
Stage 5	0	0	1 (1)	0
Modified Hoehn & Yahr Severity of Illness (at "Off") (Week 24 LOCF, FAS)				
	Week 0 (n=86)	Week 24 (n=66)	Week 0 (n=88)	Week 24 (n=76)
	n (%)	n (%)	n (%)	n (%)
Stage 0	0	0	0	0
Stage 1	0	5 (8)	0	2 (3)

Stage 1.5	0	3 (5)	0	1 (1)
Stage 2	4 (5)	9 (14)	7 (8)	23 (30)
Stage 2.5	13 (15)	13 (20)	14 (16)	11 (14)
Stage 3	39 (45)	19 (29)	37 (42)	22 (29)
Stage 4	24 (28)	15 (23)	26 (30)	14 (18)
Stage 5	6 (7)	2 (3)	4 (5)	3 (4)
Proportion of Subjects Remaining in the Study in the Non-Inferiority Verification Phase (OC, FAS)				
Time-to Withdrawal	n (%)		n (%)	
175 days	128 (82)		122 (84)	
PR/XR Switching Phase	**PR-PR (N=127)**		**IR-PR (N=122)**	
UPDRS Part I Total Score (Week 32 LOCF, Switching-FAS)				
n	n=127		n=120	
Week 32 LOCF, Mean (SD)	0.4 (1.04)		0.7 (1.34)	
Change From Week 24, Mean (SD)	-0.0 (0.40)		0.1 (0.45)	
UPDRS Part II (On) Total Score (Week 32 LOCF, Switching-FAS)				
n	n=126		n=119	
Week 32 LOCF, Mean (SD)	4.4 (4.59)		4.3 (4.88)	
Change From Week 24, Mean (SD)	-0.0 (1.37)		0.3 (1.77)	
UPDRS Part II (Off) Total Score (Week 32 LOCF, Switching-FAS)				
n	n=57		n=61	
Week 32 LOCF, Mean (SD)	8.5 (7.31)		7.5 (5.78)	
Change From Week 24, Mean (SD)	-0.2 (1.89)		-0.4 (2.35)	
UPDRS Part III Total Score (Week 32 LOCF, Switching-FAS)				
n	n=125		n=118	
Week 32 LOCF, Mean (SD)	11.7 (8.23)		11.3 (8.86)	
Change From Week 24, Mean (SD)	-0.2 (2.81)		-0.7 (3.17)	
UPDRS Part IV Total Score (Week 32 LOCF, Switching-FAS)				
n	n=127		n=119	
Week 32 LOCF, Mean (SD)	1.9 (2.17)		2.3 (2.32)	
Change From Week 24, Mean (SD)	-0.1 (0.64)		-0.2 (1.04)	
Awake Time Spent "Off" (Week 32 LOCF, Switching-FAS)				
n	n=51		n=52	
Change From Week 24, Mean (SD) (actual hours)	-0.07 (2.912)		-0.13 (2.005)	
Change From Week 24 ,Mean (SD) (proportion [%] of off time in awake time)	-0.97 (16.470)		-0.14 (12.913)	
Awake Time Spent "On" With Troublesome Dyskinesias (Week 32 LOCF, Switching-FAS)				
n	n=9		n=12	
Change From Week 24, Mean (SD) (actual hours)	0.00 (3.180)		-1.25 (1.831)	
Modified Hoehn & Yahr Severity of Illness (at "On") (Week 32 LOCF, Switching-FAS)				
	Week 24 (n=127)	Week 32 (n=125)	Week 24 (n=122)	Week 32 (n=119)
	n (%)	n (%)	n (%)	n (%)
Stage 0	2 (2)	3 (2)	4 (3)	3 (3)
Stage 1	20 (16)	17 (14)	16 (13)	19 (16)
Stage 1.5	3 (2)	5 (4)	12 (10)	10 (8)
Stage 2	49 (39)	51 (41)	41 (34)	44 (37)
Stage 2.5	25 (20)	23 (18)	24 (20)	20 (17)
Stage 3	22 (17)	20 (16)	23 (19)	20 (17)
Stage 4	6 (5)	6 (5)	2 (2)	2 (2)
Stage 5	0	0	0	1 (1)
Modified Hoehn & Yahr Severity of Illness (at "Off") (Week 32 LOCF, Switching-FAS)				
	Week 24 (n=58)	Week 32 (n=56)	Week 24 (n=63)	Week 32 (n=61)

	n (%)	n (%)	n (%)	n (%)
Stage 0	0	0	0	0
Stage 1	5 (9)	4 (7)	2 (3)	3 (5)
Stage 1.5	3 (5)	3 (5)	0	0
Stage 2	9 (16)	12 (21)	21 (33)	16 (26)
Stage 2.5	13 (22)	13 (23)	11 (17)	15 (25)
Stage 3	14 (24)	11 (20)	18 (29)	18 (30)
Stage 4	13 (22)	11 (20)	9 (14)	7 (11)
Stage 5	1 (2)	2 (4)	2 (3)	2 (3)
Proportion of Subjects Remaining in the Study in the PR/XR Switching Phase (OC, Switching-FAS)				
Time-to Withdrawal	n (%)		n (%)	
89 days	124 (98)		117 (96)	
Long-term Phase		**PR-PR (N=73)**		
Responder Rate on UPDRS Part III Total Score (Week 54 OC, Long-FAS)				
Percent Reduction from Week 0 ≥20%				
Responder Rate		84% (57/68 subjects)		
95% CI		72.9, 91.6		
Percent Reduction from Week 0 ≥30%				
Responder Rate		76% (52/68 subjects)		
95% CI		64.6, 85.9		
UPDRS Part I Total Score (Week 54 OC, Long-FAS)				
n		n=68		
Week 54 OC, Mean (SD)		0.6 (0.93)		
Change From Week 0, Mean (SD)		-0.4 (0.95)		
UPDRS Part II (On) Total Score (Week 54 OC, Long-FAS)				
n		n=67		
Week 54 OC, Mean (SD)		4.3 (4.38)		
Change From Week 0, Mean (SD)		-2.6 (4.23)		
UPDRS Part II (Off) Total Score (Week 54 OC, Long-FAS)				
n		n=32		
Week 54 OC, Mean (SD)		9.0 (6.74)		
Change From Week 0, Mean (SD)		-4.6 (3.83)		
UPDRS Part III Total Score (Week 54 OC, Long-FAS)				
n		n=68		
Week 54 OC, Mean (SD)		11.9 (8.08)		
Change From Week 0, Mean (SD)		-12.7 (8.23)		
UPDRS Part IV Total Score (Week 54 OC, Long-FAS)				
n		n=68		
Week 54 OC, Mean (SD)		2.1 (2.28)		
Change From Week 0, Mean (SD)		-0.8 (1.52)		
CGI-I (Week 54 OC, Long-FAS)				
Proportion of Responders ("very much improved" or "much improved")		65% (44/68 subjects)		
95% CI		52.2, 75.9		
Responder Rate on Awake Time Spent "Off" (Week 54 OC, Long-FAS)				
Reduction From Week 0 ≥20%				
Responder Rate		46% (18/39 subjects)		
95% CI		30.1, 62.8		
Percent Reduction From Week 0 ≥20%				
Responder Rate		79% (31/39 subjects)		
95% CI		63.5, 90.7		
Awake Time Spent "Off" (Week 54 OC, Long-FAS)				
n		n=39		
Change From Week 0, Mean (SD) (actual hours)		-2.87 (3.642)		

Change From Week 0, Mean (SD) (proportion [%] of off time in awake time)	-18.55 (23.038)	
Awake Time Spent "On" With Troublesome Dyskinesias (Week 54 OC, Long-FAS)		
n	n=3	
Change From Week 0, Mean (SD) (actual hours)	-0.33 (0.629)	
Modified Hoehn & Yahr Severity of Illness (at "On") (Week 54 OC, Long-FAS)		
	Week 0 (n=73)	Week 54 (n=67)
	n (%)	n (%)
Stage 0	0	1 (1)
Stage 1	0	8 (12)
Stage 1.5	0	3 (4)
Stage 2	18 (25)	29 (43)
Stage 2.5	19 (26)	15 (22)
Stage 3	35 (48)	11 (16)
Stage 4	1 (1)	0
Stage 5	0	0
Modified Hoehn & Yahr Severity of Illness (at "Off") (Week 54 OC, Long-FAS)		
	Week 0 (n=44)	Week 54 (n=32)
	n (%)	n (%)
Stage 0	0	0
Stage 1	0	3 (9)
Stage 1.5	0	1 (3)
Stage 2	2 (5)	5 (16)
Stage 2.5	8 (18)	9 (28)
Stage 3	21 (48)	6 (19)
Stage 4	11 (25)	7 (22)
Stage 5	2 (5)	1 (3)
Proportion of Subjects Remaining in the Study in the Long-term Phase (OC, Long-FAS)		
Time-to Withdrawal	n (%)	
385 days	68 (93)	
Safety Results: AEs and serious adverse events (SAEs) were collected from the start of investigational product until follow-up contact.		
Most Frequent Adverse Events – Non-Inferiority Verification Phase (the top 10 most frequent events in each group)		
Preferred Term	**PR-PR (N=156)**	**IR-PR (N=146)**
	n (%)	**n (%)**
Subjects with any AE(s)	124 (79)	112 (77)
Nasopharyngitis	20 (13)	18 (12)
Nausea	18 (12)	17 (12)
Somnolence	16 (10)	15 (10)
Constipation	10 (6)	10 (7)
Hallucination	10 (6)	6 (4)
Orthostatic hypotension	9 (6)	11 (8)
Decreased appetite	9 (6)	5 (3)
Dyskinesia	8 (5)	16 (11)
Vomiting	8 (5)	4 (3)
Contusion	5 (3)	6 (4)
Dizziness	3 (2)	10 (7)
Insomnia	3 (2)	7 (5)
Eczema	2 (1)	6 (4)
Most Frequent Adverse Events – PR/XR Switching Phase (the top 10 most frequent events in each group)		
Preferred Term	**PR-PR (N=128)**	**IR-PR (N=122)**
	n (%)	**n (%)**
Subjects with any AE(s)	40 (31)	38 (31)

Nasopharyngitis	7 (5)	5 (4)
Contusion	4 (3)	0
Fall	4 (3)	0
Constipation	3 (2)	1 (<1)
Hallucination	3 (2)	0
Dyskinesia	2 (2)	3 (2)
Back pain	2 (2)	2 (2)
Compression fracture	2 (2)	1 (<1)
Oedema	2 (2)	1 (<1)
Musculoskeletal stiffness	2 (2)	0
Decreased appetite	1 (<1)	2 (2)
Diarrhoea	1 (<1)	2 (2)
Dizziness	0	2 (2)
Excoriation	0	2 (2)
Skin laceration	0	2 (2)
Most Frequent Adverse Events – Week 0 through Week 54 excluding placebo-Run-in period (the top 10 most frequent events in each group)		
Preferred Term	**PR-PR (N=156)**	**IR-PR (N=146)**
	n (%)	**n (%)**
Subjects with any AE(s)	131 (84)	126 (86)
Nasopharyngitis	30 (19)	29 (20)
Nausea	20 (13)	17 (12)
Somnolence	18 (12)	17 (12)
Constipation	14 (9)	11 (8)
Hallucination	14 (9)	9 (6)
Decreased appetite	12 (8)	7 (5)
Orthostatic hypotension	10 (6)	12 (8)
Dyskinesia	9 (6)	17 (12)
Back pain	9 (6)	8 (5)
Contusion	9 (6)	7 (5)
Fall	9 (6)	6 (4)
Vomiting	9 (6)	5 (3)
Dizziness	3 (2)	12 (8)
Insomnia	4 (3)	8 (5)
Note: Subjects in the IR-PR group received ropinirole PR/XR tablets from Week 24 through Week 54.		
Adverse Events – Down-titration Phase (all events)		
Preferred Term	**PR-PR (N=156)**	**IR-PR (N=146)**
	n (%)	**n (%)**
Subjects with any AE(s)	7 (4)	9 (6)
Nasopharyngitis	2 (1)	1 (<1)
Parkinson's disease	1 (<1)	1 (<1)
Chest discomfort	1 (<1)	0
Chest pain	1 (<1)	0
Hyperkeratosis	1 (<1)	0
Pruritus	1 (<1)	0
Trichophytosis	1 (<1)	0
Abdominal pain upper	0	1 (<1)
Dyskinesia	0	1 (<1)
Fall	0	1 (<1)
Nausea	0	1 (<1)
Oedema peripheral	0	1 (<1)
Rhinitis	0	1 (<1)
Somnolence	0	1 (<1)
Adverse Events – Post-treatment (all events)		
Preferred Term	**PR-PR (N=156)**	**IR-PR (N=146)**

	n (%)	n (%)
Subjects with any AE(s)	16 (10)	13 (9)
Blood creatine phosphokinase increased	2 (1)	2 (1)
Parkinson's disease	2 (1)	0
Orthostatic hypotension	2 (1)	0
Blood lactate dehydrogenase increased	1 (<1)	0
Diarrhoea	1 (<1)	0
Dizziness	1 (<1)	0
Headache	1 (<1)	0
Hallucination	1 (<1)	0
Restlessness	1 (<1)	0
Acute myocardial infarction	1 (<1)	0
Fatigue	1 (<1)	0
Oedema peripheral	1 (<1)	0
Nasopharyngitis	1 (<1)	0
Conjunctivitis	1 (<1)	0
Decreased appetite	1 (<1)	0
Acne	1 (<1)	0
Constipation	0	2 (1)
Blood prolactin increased	0	1 (<1)
Nausea	0	1 (<1)
Oral pain	0	1 (<1)
Cerebral infarction	0	1 (<1)
Ankle fracture	0	1 (<1)
Excoriation	0	1 (<1)
Spinal compression fracture	0	1 (<1)
Anxiety disorder	0	1 (<1)
Insomnia	0	1 (<1)
Aortic valve incompetence	0	1 (<1)
Oral herpes	0	1 (<1)
Anaemia	0	1 (<1)
Muscle spasms	0	1 (<1)

Serious Adverse Events – Week 0 through Week 54 excluding placebo-Run-in period
n (%) [n considered by the investigator to be related to study medication]

Preferred Term	**PR-PR (N=156)**	**IR-PR (N=146)**
	n (%) [related]	**n (%) [related]**
Subjects with non-fatal SAEs	14 (9) [2]	15 (10) [2]
Pneumonia	2 (1) [0]	0
Appendicitis	0	1 (<1) [0]
Cellulitis	1 (<1) [0]	0
Pyelonephritis	0	1 (<1) [0]
Colitis ischaemic	1 (<1) [0]	0
Diarrhoea	0	1 (<1) [0]
Enterocolitis	1 (<1) [0]	0
Haemorrhoids	0	1 (<1) [0]
Compression fracture	1 (<1) [0]	2 (1) [0]
Hip fracture	1 (<1) [0]	0
Radius fracture	0	1 (<1) [0]
Ulna fracture	0	1 (<1) [0]
Lip and/or oral cavity cancer	0	1 (<1) [0]
Lung neoplasm malignant	1 (<1) [0]	0
Malignant melanoma	1 (<1) [0]	0
Prostate cancer	1 (<1) [0]	0
Cerebral infarction	2 (1) [0]	0

Neuroleptic malignant syndrome	1 (<1) [1]	0
Post herpetic neuralgia	0	1 (<1) [0]
Decreased appetite	1 (<1) [0]	0
Dehydration	0	1 (<1) [0]
Hypoglycaemia	1 (<1) [0]	0
Angina pectoris	0	1 (<1) [0]
Atrial fibrillation	0	1 (<1) [0]
Blood creatine phosphokinase increased	0	1 (<1) [0]
Blood pressure orthostatic decreased	0	1 (<1) [1]
Agitation	1 (<1) [0]	0
Delusion	0	1 (<1) [1]
Arteriosclerosis obliterans	0	1 (<1) [0]
Orthostatic hypotension	0	1 (<1) [0]
Macular degeneration	0	1 (<1) [0]
Myalgia	1 (<1) [0]	0
Renal failure chronic	1 (<1) [1]	0
Decubitus ulcer	0	1 (<1) [0]
Subjects with fatal SAEs	0	0
Note: Subjects in the IR-PR group received ropinirole PR/XR tablets from Week 24 through Week 54.		
Serious Adverse Events – Down-titration Phase **n [n considered by the investigator to be related to study medication]**		
	PR-PR (N=156)	**IR-PR (N=146)**
	n [related]	**n [related]**
Subjects with non-fatal SAEs	0	0
Subjects with fatal SAEs	0	0
Serious Adverse Events – Post-treatment **n [n considered by the investigator to be related to study medication]**		
Preferred Term	**PR-PR (N=156)**	**IR-PR (N=146)**
	n [related]	**n [related]**
Subjects with non-fatal SAEs	3 [0]	1 [0]
Dizziness	1 [0]	0
Parkinson's disease	1 [0]	0
Fatigue	1 [0]	0
Cerebral infarction	0	1 [0]
Subjects with fatal SAEs	1 [0]	0
Acute myocardial infarction	1 [0]	0

Conclusion:
Ropinirole PR/XR tablets administered twice daily for 24 weeks were demonstrated to show non-inferiority to ropinirole IR tablets administered three times daily for 24 weeks for adjunctive therapy to L-dopa in subjects with advanced Parkinson's disease. The efficacy of ropinirole PR/XR tablets was demonstrated through Week 54.
No major differences in frequencies, types and severities of AEs were found between the group receiving ropinirole PR/XR tablets and the group receiving ropinirole IR tablets. No increase over time in occurrence of AEs was noted.
Overnight-switch from ropinirole IR tablets to ropinirole PR/XR tablets did not result in a difference in the frequency of AEs in the course of switching from ropinirole IR tablets to ropinirole PR/XR tablets compared to continuous treatment with ropinirole PR/XR tablets.