The prolonged release/extended release tablet formulation of ropinirole used in this study is referred to as ropinirole prolonged release (ropinirole PR) tablets in Europe and International regions and will be known as ropinirole extended release tablets when approved in the US.

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.:ROP105323
Title: A Randomized, Double-Blind, Parallel Group Comparison of 24 Weeks of Treatment with Ropinirole Immediate Release (IR) Tablets or Ropinirole Prolonged Release / Extended Release (PR/XR) Tablets in Advanced Stage Parkinson's Diseas e Subjects who are not Adequately Controlled on L-dopa.
Rationale: Dopamine agonists have been demonstrated to provide relief of the symptoms of Parkinson's dise ase in both early and late stages of the disease. Ropinirole is a dopamine agonist developed for the treatment of early and advanced disease that improves the clinical manifestations of Parkinson's dis ease when used as monotherapy or as an adjunct to l-dopa in advanced cases of the disease. The use of immediate-release (IR) ropinirole, both as monotherapy and as adjunctive therapy to l-dopa, has been approved in some countries. A prolonged release/extended release formulation (PR/XR) of ropinirole has been developed. This study was designed to assess the superiority of ropinirole PR/XR to the currently marketed ropinirole IR formulation in subjects with advanced stage Parkinson's dis ease who were not adequately controlled on L-dopa.
Phase: IIIB
Study Period: 20 June 2006 –2 3 August 2007
Study Design: Multicentre, Randomized, Double-Blind, Double-dummy, Parallel Group, Active-controlled study.
Centres: 65 centres in 14 countries (Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Russian Federation, South Africa, Spain, United Kingdom, and Ukraine).
Indication: Parkinson's d isease
Treatment: Following a 14-day baseline period subjects who continued to meet study eligibility requirements were randomised (1:1) to 24 weeks of double-blind treatment with either ropinirole PR od (2-24mg/day) or ropinirole IR tid (0.75-24mg/day). All subjects underwent a forced titration through the first 4 dose levels during the first 4 weeks of the study to a minimum dose of 3mg daily for ropinirole IR (0.75mg, 1.5mg, 2.25mg and 3.0mg) and 8mg daily for ropinirole PR/XR (2.0mg, 4.0mg, 6.0mg and 8.0mg). Beyond the 4 week forced titration period, the dosing of study medication was left to the investigator's clinical ju dgment to achieve the optimal clinical response. The dose of L-dopa was kept constant from at least 4 weeks prior to the baseline period, during the baseline period, throughout the initial 4-week forced titration and until the subject achieved a 1.5 hour reduction from baseline in "off" time. F ollowing the initial 4-week forced titration and once the change from baseline in "off" time (assessed using patient diaries) was greater than or equal to 1.5 hours, the L-dopa dose was to be reduced and complemented by an increase in study medication to the next dose level. If, at the next assessment, symptom control had been maintained following the first reduction in L-dopa dose, the total dose of L-dopa could be reduced further. Again, the dose of the study medication was also increased to the next level when the dose of L-dopa was reduced. Further reductions in L-dopa, accompanied by dose increases in study medication, could continue until the penultimate assessment at Week 20. If loss of symptom control occurred with the reduction in the L-dopa dose, the dose of study

medication was to be increased to the next dose level with no adjustment in the dose of L-dopa. Subjects who did not experience an improvement in symptoms following upward titration by 2 dose levels of study medication, were "rescue d" with L-dopa. The dose of L-dopa could be increased up to baseline levels but not above them. If it was clinically necessary to increase the dose of L-dopa above baseline levels, the subject was to be withdrawn from the study. For subjects who completed the study or were withdrawn from the study prematurely, study medication was to be down titrated over a 7-day period (except for any subjects who experienced an SAE considered related or potentially related to study medication for whom study medication could be stopped abruptly).
Objectives: To assess the superiority of ropinirole prolonged release / extended release (PR/XR) tablets over ropinirole immediate release (IR) tablets when used as adjunctive therapy to L-dopa in subjects with advanced stage Parkinson's dis ease (PD) who were not adequately controlled on L-dopa (e.g. end of dose akinesia, simple "on"/ "o ff" fluctuations)
Primary Outcome/Efficacy Variable: The percentage of subjects with at least a 20% maintained reduction in time "off" a t endpoint, defined as the percentage of subjects with at least a 20% reduction from baseline in time "off" at e ndpoint (Week 24 last observation carried forward [LOCF]) and the timepoint immediately preceding this endpoint. (The general definition of time "off" inclu des a lack of mobility (bradykinesia) with or without additional features, such as tremor or rigidity.)

Secondary Outcome/Efficacy Variable(s): All secondary endpoints measured at a specific time point were assessed at Week 24 LOCF.

- Mean change from baseline in percentage awake time spent "off."
- Proportion of subjects with a score of "much improved" or "very much improved" on the Clinical Global Impression - global improvement (CGI-I) scale.
- Mean change from baseline in the total motor score of the Unified Parkinson's Disease Rating Scale (UPDRS), with subjects in an "on" state.
- Mean change from baseline in the total motor score of the UPDRS, with subjects in an "off" state.
- Mean change from baseline in the total Activities of Daily Living (ADL) score of the UPDRS, with subjects in an "on" state.
- Mean change from baseline in the total ADL score of the UPDRS, with subjects in an "off" state.
- Mean change from baseline in the total score of the UPDRS, with subjects in an "on" state.
- Mean change from baseline in the total score of the UPDRS, with subjects in an "off" state.
- Mean change from baseline in the thermometer score of the EuroQol 5D (EQ-5D).
- Mean change from baseline in the utility score of the EQ-5D.
- Mean change from baseline in the total score of the Parkinson's Disease Sleep Scale (PDSS).
- Mean change from baseline in the total movement severity score of the Abnormal Involuntary Movement Scale (AIMS), with subjects in an "on" state.
- Percentage of subjects requiring reinstatement of L-dopa.
- Mean change from baseline in the dose of L-dopa.

Statistical Methods: Data from Studies 169 and 044 (these were both trials of ropinirole adjunct treatment with L-dopa in advanced stage PD subjects; Study 169 was a pivotal Phase III study in the ropinirole PR/XR programme, Study 044 was a Phase III study in the ropinirole IR programme) indicated that 344 subjects (172 subjects per treatment group) were required to demonstrate a clinically relevant difference of 17 percentage points between ropinirole PR/XR and ropinirole IR in the proportion of subjects with a ≥20% maintained reduction in time "off" at Week 24 LOCF. To account for an estimated 20% attrition rate up to the Week 1 visit, it was estimated that 430 subjects would be required to be enrolled in the 2-week Baseline Period prior to randomization.

The primary comparison of interest was ropinirole PR/XR versus ropinirole IR for the primary endpoint, the percent of subjects with at least a 20% maintained reduction in time "off" at Week 24 LOCF endpoint (defined as the percent of subjects with at least a 20% reduction from baseline in time "off" at endpoint and at the timepoint immediately preceding this endpoint). If the preceding timepoint was missing the next non-missing timepoint was used; unscheduled visits were not used. This dichotomous efficacy variable was analyzed using logistic regression. The statistical model included terms for centre group and treatment group, with no interaction. Adequacy of the model fit was explored by inspecting plots of the deviance residuals against continuous covariates and half normal plots of the standardized residuals with a 95% simulated envelope. If the assumptions of logistic regression were met, the results were to be presented as the odds-ratio of the incidence rate for PR/XR to IR, along with a 95% confidence interval (CI). If

the assumptions underlying the logistic regression model were violated (for example, due to over-dispersion), the dichotomous variable was to be re-analyzed using non-parametric techniques and the results were to be presented in order to assess the robustness of the parametric analysis.

The ITT Population was defined as consisting of all subjects randomized to treatment, who took at least 1 dose of study medication and who had at least 1 post-baseline efficacy assessment; the primary inferences concerning the superiority and efficacy of ropinirole PR/XR versus ropinirole IR were made using this population. The Safety Population was defined as consisting of all subjects who were randomized and took at least 1 dose of study medication; this was the primary population for safety summaries and tabulations.

Study Population: Male and female subjects, who were at least 30 years of age, diagnosed with idiopathic PD (according to modified Hoehn and Yahr criteria Stages II to IV) and demonstrating a lack of control with L-dopa therapy (e.g. end of dose akinesia, simple "on" / "off" fluctuations) were considered eligible for the study. Eligible subjects had to have a minimum of 3 hours awake time "off" for each diary day recorded during the baseline period.

Excluded were late stage advanced subjects demonstrating incapacitating dyskinesias on their stable dose of L-dopa as well as subjects with the presence, or history within the previous 3 months, of significant and/or uncontrolled psychiatric, hematological, renal, hepatic, endocrine, neurological (other than PD), or cardiovascular disease or active malignancy (other than basal cell cancer). Also excluded were subjects with any abnormality, at screening, that the investigator deemed to be clinically relevant on history, physical examination and in diagnostic laboratory tests including ECG.

	Ropinirole PR/XR	**Ropinirole IR**
Number of Subjects:		
Planned, N	172	172
Randomised, N	177	173
Completed, n (%)	129	122
Total Number Subjects Withdrawn, N (%)	48	51
Withdrawn due to Adverse Events n (%)	22	15
Withdrawn due to Lack of Efficacy n (%)	2	2
Withdrawn for other reasons n (%)	24	34
Demographics	**Ropinirole PR/XR**	**Ropinirole IR**
N (ITT)	174	169
Females: Males	70/104	78/91
Mean Age, years (SD)	64.9 (9.20)	65.6 (9.01)
White -Whit e/Caucasian/European heritage, n (%)	171 (98)	168 (>99)

Summary Statistics for the dose of Ropinirole (ITT Population)			
	Dose (mg/day)	**Ropinirole PR/XR**	**Ropinirole IR**
Week 24 LOCF	Mean (S.D.)	18.61 (6.446)	10.43 (6.387)
	Median (min, max)	20.0 (2.0, 24.0)	9.0 (0.75, 21.0)

Primary Efficacy Results:
The percentage of subjects with at least a 20% maintained reduction in time "off" at endpoint, defined as the percentage of subjects with at least a 20% reduction from baseline in time "off" at endpoint (Week 24 last observation carried forward [LOCF]) and the timepoint immediately preceding this endpoint.

	Ropinirole PR/XR	**Ropinirole IR**
Adjusted Probability of Response	0.657	0.512
Adjusted Odds Ratio	1.82	
95% Confidence Interval	(1.16, 2.86)	
p-value	= 0.009	

Secondary Outcome Variable(s):

Mean change from baseline in percentage awake time spent "off."

	Ropinirole PR/XR	**Ropinirole IR**
Mean Baseline (S.D.)	41.93 (10.870)	42.73 (11.905)
Mean change from baseline to Week 24 LOCF (S.D.)	-16.22 (18.547)	-14.98 (19.161)
Adjusted Treatment Difference	-1.70	
95% Confidence Interval	(-5.49, 2.09)	

Secondary Outcome Variable(s):

Proportion of subjects with a score of "much improved" or "very much improved" on the Clinical Global Impression – global improvement (CGI-I) scale.

	Ropinirole PR/XR	**Ropinirole IR**
Adjusted proportion of responders	0.544	0.417
Adjusted Odds Ratio	1.67	
95% Confidence Interval	(1.06, 2.63)	

Secondary Outcome Variable(s):

Mean change from baseline in the total motor score of the Unified Parkinson's Disease Rating Scale (UPDRS), with subjects in an "on" state.

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	29.0 (12.34)	28.7 (13.01)
Mean change from baseline to Week 24 LOCF (S.D.)	-10.2 (9.44)	-7.6 (9.58)
Adjusted Treatment Difference	-2.30	
95% Confidence Interval	(-4.27, -0.33)	

Secondary Outcome Variable(s):

Mean change from baseline in the total motor score of the UPDRS, with subjects in an "off" state.

	Ropinirole PR/XR	Ropinirole IR
As data on the total motor score of the UPDRS with subjects in an "off" state were available for less than 10% of subjects, this efficacy variable was not formally analysed.		

Secondary Outcome Variable(s):

Mean change from baseline in the total Activities of Daily Living (ADL) score of the UPDRS, with subjects in an "on" state.

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	10.0 (5.64)	10.0 (5.89)
Mean change from baseline to Week 24 LOCF (S.D.)	-3.3 (4.17)	-2.7 (4.06)
Adjusted Treatment Difference	-0.69	
95% Confidence Interval	(-1.51, 0.13)	

Secondary Outcome Variable(s):

Mean change from baseline in the total ADL score of the UPDRS, with subjects in an "off" state.

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	18.7 (6.82)	18.8 (6.74)
Mean change from baseline to Week 24 LOCF (S.D.)	-4.6 (5.97)	-3.8 (6.16)
Adjusted Treatment Difference	-0.77	

95% Confidence Interval	(-2.13, 0-.60)

Secondary Outcome Variable(s):

Mean change from baseline in the total score of the UPDRS, with subjects in an "on" state.

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	41.3 (17.21)	40.2 (18.29)
Mean change from baseline to Week 24 LOCF (S.D.)	-14.0 (12.56)	-10.6 (13.08)
Adjusted Treatment Difference	N/A*	
95% Confidence Interval	N/A*	

*A formal statistical analysis of the mean change from baseline in the total score of the UPDRS with subjects in an "on" state was not planned or conducted.

Secondary Outcome Variable(s):

Mean change from baseline in the total score of the UPDRS, with subjects in an "off" state.

	Ropinirole PR/XR	Ropinirole IR
As data on the total score of the UPDRS with subjects in an "off" state were available for less than 10% of subjects, this efficacy variable was not formally analysed.		

Secondary Outcome Variable(s):

Mean change from baseline in the thermometer score of the EuroQol 5D (EQ-5D).

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	58.4 (17.78)	57.9 (18.11)
Mean change from baseline to Week 24 LOCF (S.D.)	9.8 (19.13)	6.6 (17.94)
Adjusted Treatment Difference	3.68	
95% Confidence Interval	(0.24, 7.12)	

Secondary Outcome Variable(s):

Mean change from baseline in the utility score of the EQ-5D.

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	0.543 (0.2533)	0.569 (0.2218)
Mean change from baseline to Week 24 LOCF (S.D.)	0.098 (0.2565)	0.056 (0.2388)

Adjusted Treatment Difference	0.03
95% Confidence Interval	(-0.01, 0.08)

Secondary Outcome Variable(s):

Mean change from baseline in the total score of the Parkinson's Dise ase Sleep Scale (PDSS).

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	100.03 (24.435)	102.22 (25.062)
Mean change from baseline to Week 24 LOCF (S.D.)	5.79 (23.199)	5.65 (20.326)
Adjusted Treatment Difference	-0.18	
95% Confidence Interval	(-4.61, 4.25)	

Secondary Outcome Variable(s):

Mean change from baseline in the total movement severity score of the Abnormal Involuntary Movement Scale (AIMS), with subjects in an ö n" state.

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	2.24 (3.417)	2.65 (4.217)
Mean change from baseline to Week 24 LOCF (S.D.)	-0.24 (3.207)	-0.50 (2.837)
Adjusted Treatment Difference	0.05	
95% Confidence Interval	(-0.54, 0.65)	

Secondary Outcome Variable(s):

Percentage of subjects requiring reinstatement of L-dopa.

	Ropinirole PR/XR	Ropinirole IR
Formal statistical analysis of this endpoint was deemed not appropriate due to low proportions of subjects requiring L-dopa reinstatements (ropinirole PR/XR 2 subjects; ropinirole IR 3 subjects).		

Secondary Outcome Variable(s):

Mean change from baseline in the dose of L-dopa (mg).

	Ropinirole PR/XR	Ropinirole IR
Mean Baseline (S.D.)	685 (365.8)	657 (330.9)

Mean change from baseline to Week 24 LOCF (S.D.)	-162 (225.6)	-113 (137.7)
Adjusted Treatment Difference	N/A*	
95% Confidence Interval	N/A*	
*A formal statistical analysis of the mean change from baseline in the dose of L-dopa was not planned or conducted.		

An on therapy adverse experience was defined as an event which occurred after administration of the first dose of study medication up to and including the date of the last dose of study medication (excluding down-titration medication), regardless of whether or not the event was considered drug related.

On therapy serious adverse experiences (SAEs) were defined as events which occurred after administration of the first dose of study medication up to and including the date of the last dose of study medication (excluding down-titration medication), regardless of whether or not the event was considered drug related.

	Ropinirole PR/XR	**Ropinirole IR**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	128 (72)	105 (61)

Nausea	27 (15)	31 (18)
Dyskinesia	20 (11)	10 (6)
Dizziness	17 (10)	11 (6)
Somnolence	13 (7)	11 (6)
Hallucination	13 (7)	4 (2)
Fatigue	12 (7)	12 (7)
Headache	11 (6)	10 (6)
Abdominal pain	10 (6)	10 (6)
Insomnia	10 (6)	11 (6)
Constipation	9 (5)	3 (2)
Hypotension	8 (5)	4 (2)
Dyspepsia	8 (5)	3 (2)
Orthostatic Hypotension	3 (2)	9 (5)
Vomiting	3 (2)	8 (5)
Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**		
	Ropinirole PR/XR	**Ropinirole IR**
Subjects with non-fatal SAEs, n (%)	10 (6)	9 (5)
	n (%) [related]	**n (%) [related]**
Hypotension	2 (1)[1]	0
Abdominal pain	1 (<1)[0]	0
Acute myocardial infarction	1 (<1)[0]	0
Anxiety	1 (<1)[0]	0
Diabetic gangrene	1 (<1)[0]	0
Drop attacks	1 (<1)[1]	0
Inflammation	1 (<1)[0]	0
Intervertebral disc protrusion	1 (<1)[0]	0
Lung infection	1 (<1)[0]	0
Road traffic accident	1 (<1)[0]	0
Pulmonary granuloma	1 (<1)[1]	0
Asthma	0	1 (<1)[0]
Breast cancer	0	1 (<1)[0]
Cardiovascular insufficiency	0	1 (<1)[0]
Diabetes mellitus	0	1 (<1)[0]
Erysipelas	0	1 (<1)[0]
Essential hypertension	0	1 (<1)[0]
Femur fracture	0	1 (<1)[0]
Gastritis	0	1 (<1)[0]
Hypertension	0	1 (<1)[1]
Intestinal obstruction	0	1 (<1)[0]
Urinary tract infection	0	1 (<1)[0]
Transient ischaemic attack	0	1 (<1)[0]
Subjects with fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
No deaths were reported in this study.		

Conclusion:

- A statistically significant benefit of ropinirole PR/XR over ropinirole IR was detected on the primary efficacy variable (20% maintained reduction from baseline in awake time "off" at

Week 24 LOCF).

- Statistically significant benefits of ropinirole PR/XR over ropinirole IR were also detected on key secondary efficacy variables (CGI-global improvement item; UPDRS motor score in an ‘o n” state) and on the thermometer score of the EQ-5D. In addition, the mean change from baseline in the dose of L-dopa at week 24 LOCF was greater for the ropinirole PR/XR group than for ropinirole IR (no statistical analysis of this endpoint was planned).
- Statistically significant benefits of ropinirole PR/XR over ropinirole IR were not demonstrated for the other secondary endpoints (percentage awake time ‘off”, UPDRS A DL score in both an ‘o n” and ‘off”st ate; EQ-5D utility score; PDSS and AIMS scales).
- At Week 24 LOCF the mean dose was 18.6mg/day (median 20mg/day) for ropinirole PR/XR and 10.4mg/day (median 9mg/day) for ropinirole IR.
- In the ropinirole PR/XR tireatment group, 128 subjects (72%) reported adverse events, with the most common events being nausea and dyskinesia. In the ropinirole IR treatment group, 105 subjects (61%) reported adverse events, with the most common events being nausea and fatigue. A total of 10 subjects (6%) in the ropinirole PR/XR group and 9 subjects (5%) in the ropinirole IR group experienced SAEs. No fatalities were reported.

Publications:
No publication

Date Updated: 27-Jun-2008