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.: ROF102100

Title: A randomised, double-blind, placebo-controlled, parallel group study to investigate the safety and efficacy of controlled-release ropinirole (CR) (1-24mg) administered once daily for 12 weeks in subjects with fibromyalgia.

Rationale: This was a proof of concept study, to evaluate the safety and efficacy of ropinirole CR in subjects with fibromyalgia syndrome (FMS).

Phase: II

Study Period: 12 November 2004 - 01 July 2005.

Study Design: Randomised, double-blind, placebo-controlled, parallel group study

Centres: A total of 22 centres screened and recruited at least one subject in the following countries: Belgium, Denmark, Finland, France, Germany, Italy, Sweden, The Netherlands and the United Kingdom.

Indication: Treatment of fibromyalgia syndrome (FMS) in adults.

Treatment: Study medication was provided as: ropinirole CR tablets of 1.0mg, 2.0mg, 4.0mg and 8.0mg, and matching placebo tablets. All tablets were white aqueous film coated capsule shaped tablets, with 'SB' embossed on both sides.

Subjects were randomised (1:1) to receive once daily doses of ropinirole CR or placebo tablets according to the dose titration regimen in the Table below, until an optimal therapeutic dose was achieved based on efficacy and tolerability as judged by the investigator.

Dosage Level	Dosage of Ropinirole CR or Matching Placebo	End of Week Treatment	Minimum Duration (Days)
0	Baseline	Not applicable	7 days
1	1 mg (1 x 1mg)	Day 0	7 days
2	2 mg (1 x 2mg)	Week 1 (Day 7)	7 days
3	4 mg (1 x 4mg)	Week 2 (Day 14)	7 days
4	6 mg (1x 2mg + 1 x 4mg)	Week 3 (Day 21)	7 days
5	8 mg (1 x 8mg)	Week 4 (Day 28)	7 days
6	12 mg (1 x 8mg + 1 x 4mg)	Week 5 (Day 35)	7 days
7	16 mg (2x 8mg)	Week 6 (Day 42)	7 days
8	20mg (2x 8mg + 1 x4mg)	Week 7 (Day 49)	7 days
9	24 mg (3 x 8mg)	Week 8 (Day 56)	7 days

Once an optimal therapeutic dose was achieved, the subject could be maintained on that dose for the remainder of the study. The maximum daily dose was 24mg of ropinirole CR (dose level 9). The last dose increase could only be made by the end of the scheduled Week 8 visit.

Objectives: To evaluate the analgesic efficacy of oral ropinirole controlled release formulation (CR) compared to placebo over a dose range in adult subjects with FMS as measured by the 11-point Pain Intensity Numerical Rating Scale (PI-NRS).

Primary Outcome/Efficacy Variable: Change in pain intensity score from baseline (average of the Baseline Phase pain intensity scores) to the last week of treatment (Week 12), measured by the 11 point Pain Intensity Numerical Rating Scale (PI-NRS)

Secondary Outcome/Efficacy Variable(s):

- Weekly Pain Intensity

Change from baseline in average pain intensity scores measured by the 11 point PI-NRS by each week of treatment

- Pain relief

Proportion of subjects with an average daily pain relief score ≥ 2 (moderate, a lot or complete pain relief) on the Pain Relief Rating Scale (PRS) at each week of treatment

- Brief Pain Inventory

Change in the BPI score between baseline and each scheduled visit

- Patient Global Impression of Change (PGIC)

Proportion of subjects who are 'much improved' or 'very much improved' on the Patient Global Impression of Change scale at each scheduled visit

- Clinician Global Impression of Change (CGIC)

Proportion of subjects who are 'much improved' or 'very much improved' on the Clinician Global Impression of Change scale at each scheduled visit

- Sleep

Change from baseline in each of the 4 domains (sleep disturbance, sleep quantity, sleep adequacy, daytime somnolence) measured by the Medical Outcomes Study Sleep Scale (MOS) at each specified visit

- Responders

Proportion of subjects with a $\geq$ 20%, $\geq$ 30% and/or $\geq$ 50% reduction in pain intensity score from baseline to each week of treatment as measured by the 11 point PI-NRS

- Tender Point Pressure threshold

Change from baseline in the pressure threshold required to produce pain on the thumbnail, mid-trapezius, and lateral epicondyle all in the subject's dominant arm at specified visit(s)

- Rescue Medication Consumption

Average total daily dose of acetaminophen/paracetamol (rescue analgesia medication) consumed during the study.

- Onset of analgesia

Time to first day of sustained improvement in pain intensity ($\geq$ 2 consecutive days) of at least 2 points, relative to the average daily pain intensity score for the Baseline Period.

Statistical Methods:

A total of 112 evaluable subjects (56 per treatment group) were required to allow a difference of 1.3 points between placebo and active treatment in the change from baseline in PI-NRS score to be detected with 90% power and a 0.05 significance level assuming an underlying standard deviation (SD) of 2.1. It was anticipated that in order to achieve 112 evaluable subjects, it would be necessary to randomise 160 subjects (80 subjects per treatment arm); assuming that approximately 30% of subjects would drop out during the course of the study or be unevaluable for the primary analysis.

The primary population for the analyses was the Intent-to-treat population. Repeated measures analyses were conducted on the primary endpoint, including terms for country, treatment, visit, baseline PI-NRS score, treatment by visit interaction and baseline PI-NRS score by visit interaction. An unstructured correlation matrix was chosen for this model. Primary analyses were carried out at Week 12 using the Observed Case (OC) dataset. Number and percentage of subjects in each category of the key secondary efficacy endpoints were presented by treatment group at each visit and at week 12 LOCF for the Intent-to-treat population. Other secondary efficacy endpoints were not reported.

The three subject populations were defined as:

- The ITT population was defined as consisting of all subjects who were entered into the study, who received at least one dose of double-blind medication, and for whom at least one non missing post-baseline efficacy assessment was available.

- The Per Protocol (PP) population consisted of all subjects who were included in the ITT population but who also met the following criteria:
  - No major protocol violation existed with regard to inclusion or exclusion criteria.
  - No major protocol violation between randomisation and completion of the active treatment phase of the study (Weeks 1-12).

• The Safety population was defined as consisting of all subjects who received at least one dose of randomised study medication (placebo or active drug).

Study Population:

A subject was eligible for inclusion in this study only if all of the following criteria applied:

Subject was a male or female outpatient, at least 18 years of age; a female was eligible to enter and participate in the study if she was of: non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was post-menopausal) or if of childbearing potential, had a negative result on all required pregnancy tests prior to randomisation, and agreed to an acceptable contraceptive method as defined in the Protocol; subject had a diagnosis of fibromyalgia as confirmed by the American College of Rheumatology (ACR) criteria; subject had baseline PI-NRS score averaging ≥ 4 during the week prior to randomisation (Baseline Period) and at least four pain intensity observations were recorded during the 7 days of the Baseline Period; subject was considered clinically appropriate for therapy with ropinirole based upon the Investigator's overall clinical evaluation; subject was in good general health apart from fibromyalgia, as determined by the Investigator (based upon the physical and laboratory examinations, ECG and medical history); subject was able to comprehend the study procedures and schedule and was able to comply with study requirements

Number of Subjects:	Placebo	Ropinirole CR
Planned, N	80	80
Randomised, N	92	90
Completed, n (%)	72 (78)	51 (57)
Total Number Subjects Withdrawn, N (%)	20 (22)	39 (43)
Withdrawn due to Adverse Events n (%)	12 (13)	29 (32)
Withdrawn due to Lack of Efficacy n (%)	2 (2)	3 (3)
Withdrawn for other reasons n (%)	6 (7)	7 (8)
Intent to Treat (ITT) population	91 (99)	90 (100)
Per protocol (PP) population	77 (84)	77 (86)
Safety population	91 (99)	90 (100)

Demographics	Placebo	Ropinirole CR
N (ITT)	91	90
Females: Males	84:7	84:6
Mean Age, years (SD)	47.4 (10.28)	47.9 (9.91)
Race, n (%)		
Caucasian	90 (99)	87 (97)
Baseline PI-NRS Score: Mean (SD)	6.8 (1.48)	6.8 (1.41)
Duration of FMS (months): Mean (SD)	87.8 (102.62)	79.3 (85.38)
Average Daily Dose of Study Medication: Mean (SD) (mg/day)	10.8 (4.34)	8.2 (4.28)

Primary Efficacy Results:
Abbreviations: SE = Standard error for the adjusted mean estimates; Difference = Difference in adjusted means are shown (Ropinirole CR – Placebo)

Change from Baseline in PI-NRS Score at Week 12

Treatment	n/N	Adjusted Mean	SE	Treatment Comparisons		
				Difference	95% CI	P-value
Observed Case (OC) results for the ITT population						
Ropinirole CR	50/90	-1.1	0.26	-0.18	(-0.88, 0.52)	0.619
Placebo	66/91	-1.0	0.24			

Secondary Outcome Variable(s):
This study was a proof of concept study looking at the effects of ropinirole CR in treating subjects with FMS. Because the study did not reach the primary endpoint, only the data for key secondary endpoints were fully processed and presented in data source tables and data source figures.

Change from Baseline in PI-NRS Score During the Study (ITT Population)						
Study Visit	Treatment	n/N	Adjusted Mean	SE	Treatment Comparisons	
					Difference	95% CI
Week 1	Ropinirole CR	86/90	-0.2	0.11	-0.25	(-0.53, 0.03)
	Placebo	87/91	0.0	0.10		
Week 2	Ropinirole CR	86/90	-0.4	0.13	-0.33	(-0.67, 0.02)
	Placebo	85/91	0.0	0.13		
Week 3	Ropinirole CR	81/90	-0.4	0.14	0.06	(-0.33, 0.44)
	Placebo	83/91	-0.5	0.14		
Week 4	Ropinirole CR	77/90	-0.5	0.15	-0.07	(-0.47, 0.33)
	Placebo	81/91	-0.4	0.15		
Week 5	Ropinirole CR	74/90	-0.7	0.16	-0.35	(-0.78, 0.09)
	Placebo	80/91	-0.4	0.16		
Week 6	Ropinirole CR	74/90	-0.8	0.18	-0.16	(-0.65, 0.34)
	Placebo	79/91	-0.7	0.18		
Week 7	Ropinirole CR	65/90	-0.8	0.20	-0.09	(-0.62, 0.45)
	Placebo	70/91	-0.7	0.19		
Week 8	Ropinirole CR	60/90	-1.1	0.20	-0.32	(-0.87, 0.23)
	Placebo	70/91	-0.8	0.19		
Week 9	Ropinirole CR	57/90	-1.0	0.22	-0.05	(-0.66, 0.55)
	Placebo	70/91	-1.0	0.21		
Week 10	Ropinirole CR	54/90	-1.1	0.24	-0.01	(-0.65, 0.63)
	Placebo	70/91	-1.1	0.22		
Week 11	Ropinirole CR	50/90	-1.3	0.25	-0.34	(-1.00, 0.33)
	Placebo	67/91	-0.9	0.23		
Week 12	Ropinirole CR	50/90	-1.1	0.26	-0.18	(-0.88, 0.52)
	Placebo	66/91	-1.0	0.24		
Week 12 LOCF	Ropinirole CR	87/90	-0.8	0.22	-0.12	(-0.70, 0.47)
	Placebo	87/91	-0.7	0.22		

Number (%) of Subjects That Experienced a Greater Than or Equal to 20%, 30% or 50% Reduction in Pain Measured by the PI-NRS score (ITT Population)			
Study Visit; n for PBO and ROP	Percentage Reduction From Baseline in PI-NRS Score	Placebo N=91	Ropinirole CR N=90
Week 1; PBO n = 87; ROP n = 86	≥ 20%	5 (6)	9 (10)
	≥ 30%	2 (2)	6 (7)
	≥ 50%	0	0
Week 2; PBO n = 85; ROP n = 86	≥ 20%	14 (16)	10 (12)
	≥ 30%	3 (4)	6 (7)
	≥ 50%	1 (1)	4 (5)
Week 3; PBO n = 83; ROP n = 81	≥ 20%	15 (18)	13 (16)
	≥ 30%	10 (12)	9 (11)
	≥ 50%	3 (4)	3 (4)
Week 4; PBO n = 81; ROP n = 77	≥ 20%	16 (20)	17 (22)
	≥ 30%	9 (11)	11 (14)
	≥ 50%	1 (1)	5 (6)
Week 5; PBO n = 80; ROP n = 74	≥ 20%	18 (23)	21 (28)
	≥ 30%	10 (13)	15 (20)
	≥ 50%	3 (4)	5 (7)
Week 6; PBO n = 79; ROP n = 74	≥ 20%	24 (30)	25 (34)
	≥ 30%	16 (20)	16 (22)
	≥ 50%	4 (5)	8 (11)
Week 7; PBO n = 70; ROP n = 65	≥ 20%	25 (36)	17 (26)
	≥ 30%	15 (21)	12 (18)
	≥ 50%	4 (6)	5 (8)
Week 8; PBO n = 70; ROP n = 60	≥ 20%	26 (37)	23 (38)
	≥ 30%	15 (21)	17 (28)
	≥ 50%	6 (9)	8 (13)
Week 9; PBO n = 70; ROP n = 57	≥ 20%	27 (39)	21 (37)
	≥ 30%	20 (29)	14 (25)
	≥ 50%	9 (13)	6 (11)
Week 10; PBO n = 70; ROP n = 54	≥ 20%	25 (36)	23 (43)
	≥ 30%	20 (29)	17 (31)
	≥ 50%	11 (16)	7 (13)
Week 11; PBO n = 67; ROP n = 50	≥ 20%	25 (37)	20 (40)
	≥ 30%	16 (24)	17 (34)
	≥ 50%	10 (15)	9 (18)
Week 12; PBO n = 66; ROP n = 50	≥ 20%	24 (36)	20 (40)
	≥ 30%	18 (27)	18 (36)
	≥ 50%	11 (17)	8 (16)
Week 12 LOCF;	≥ 20%	27 (31)	27 (31)
PBO n = 87; ROP n = 87	≥ 30%	19 (22)	21 (24)
	≥ 50%	11 (13)	9 (10)
Percentages are calculated on the number of subjects (n) with a non-missing percentage reduction. The percent values do not add up to 100% as each row represents a separate cut off; PBO = Placebo; ROP = Ropinirole CR			

Number (%) of Subjects With a Patient Global Impression of Change Score of Very Much Improved (1) or Much Improved (2) (ITT Population)

Study Visit	PGIC Score of 1 or 2	
	Placebo; N=91 n (%)	Ropinirole CR; N=90 n (%)
Week 1	1 (1)	2 (2)
Week 2	4 (5)	1 (1)
Week 3	10 (12)	5 (6)
Week 4	3 (4)	6 (8)
Week 5	8 (10)	7 (10)
Week 6	7 (9)	9 (14)
Week 7	10 (14)	12 (18)
Week 8	10 (14)	13 (22)
Week 10	14 (20)	12 (22)
Week 12	14 (22)	10 (20)
Week 12 LOCF	14 (16)	14 (16)

Number (%) of Subjects With a Clinician Global Impression of Change Score of Very Much Improved (1) or Much Improved (2) (ITT Population)

Study Visit	CGIC Score of 1 or 2	
	Placebo; N=91 n (%)	Ropinirole CR; N=90 n (%)
Week 1	2 (2)	3 (3)
Week 2	1 (1)	1 (1)
Week 3	11 (13)	7 (9)
Week 4	7 (9)	9 (12)
Week 5	9 (11)	11 (15)
Week 6	14 (18)	11 (16)
Week 7	21 (30)	13 (20)
Week 8	17 (24)	15 (25)
Week 10	21 (29)	16 (29)
Week 12	19 (27)	13 (25)
Week 12 LOCF	20 (22)	17 (19)

Safety Results: An on-therapy adverse event (AE) was defined as an AE with onset on or after start date of study medication but not later than one day after the last date of study medication.

An on-therapy serious adverse event (SAE) was defined as a SAE with onset on or after start date of study medication and up to 2 weeks after the last dose of study medication.

Most Frequent Adverse Events – On-therapy

Preferred term	Placebo; N=91; n (%)	Ropinirole CR; N=90; n (%)
Any AE	73 (80)	82 (91)
Nausea	17 (19)	56 (62)
Dizziness	17 (19)	24 (27)
Headache	17 (19)	23 (26)
Vomiting	4 (4)	22 (24)
Abdominal pain upper	10 (11)	12 (13)
Fatigue	12 (13)	10 (11)
Dry mouth	7 (8)	8 (9)
Nasopharyngitis	8 (9)	6 (7)
Influenza	5 (5)	6 (7)
Constipation	1 (1)	9 (10)

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	Placebo; N=91	Ropinirole CR; N=90
Subjects with non-fatal SAEs, n (%) [related]	1 (1) [0]	2 (2) [0]
Abdominal pain upper	0	1 (1) [0]
Anaemia	1 (1) [0]	0
Angina unstable	0	1 (1) [0]
Subjects with fatal SAEs, n (%) [related]	0	0

Conclusion:

No statistically significant differences between placebo and ropinirole CR were observed for the primary efficacy endpoint or the key secondary efficacy endpoints. In the placebo group 73 subjects (80%) reported non-serious adverse events with the most frequently reported being nausea, dizziness and headache. In the ropinirole CR group 82 subjects (91%) reported non-serious adverse events with the most frequently reported being nausea, dizziness and headache. One subject in the placebo group reported the non-fatal SAE of anaemia. Two subjects in the ropinirole CR group reported a single non-fatal SAE: one subject reported the SAE of unstable angina and one subject reported abdominal pain upper. No fatalities were reported during the study.

Publications: No publication

Date Updated: 21 February 2006