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: ROP109087
Title : An open label, repeat dose, dose escalation study conducted in Parkinson's dis ease patients to characterize the pharmacokinetics and effect of food on ropinirole prolonged release (PR/XL) 12 mg tablets
Rationale: Ropinirole has been developed as a therapeutic agent for the treatment of the signs and symptoms of Parkinson's dis ease (PD). Ropinirole immediate release (IR) is registered in more than 60 countries worldwide for the treatment of PD at dose of up to 24 mg/day (administered as 8 mg three times daily). An extended release tablet of ropinirole has been developed which is registered as ropinirole prolonged release (PR) in Europe and REQUIP XL in the USA. This allows once-daily dosing of ropinirole and provides a simpler dose-titration regimen. Administration of ropinirole PR/XL also results in fewer fluctuations in drug plasma levels throughout the day. Compliance would also be expected to be improved with a once daily regimen versus a three-times daily regimen. Tablet strengths of 2, 3, 4 and 8 mg PR/XL ropinirole were initially registered. A 12 mg tablet has been developed in order to reduce tablet burden for subjects taking higher doses of ropinirole PR/XL. This study was conducted to assess the dose proportionality of ropinirole PR/XL over the tablet strength range 4 to 12 mg, to assess the effect of food (high-fat breakfast) on the pharmacokinetics of ropinirole and to assess the dosage strength equivalence of 3x4 mg tablets vs 1x12 mg tablet
Phase: II
Study Period: 16Apr2007 – 29Aug2007
Study Design: Open, non-randomised sequential design, followed by a 3 period, randomised, cross-over design.
Centres: 2 centres in Germany and South Africa
Indication: Parkinson's disease
Treatment: Subjects received ropinirole PR/XL once daily starting at a dose of 2 mg/day with weekly dose escalation of 2-4 mg (2, 4, 6, 8 and 12 mg dose levels administered). At the 12 mg dose, subjects were randomised to one of three sequential treatments according to six possible treatment sequences.. The three dosing regiments at the 12 mg dose level were: 1 x 12 mg tablet for three days including steady state pharmacokinetic (PK) profile (fasted) on the 3rd day, 1 x 12 mg tablet for three days including steady state PK profile (Food and Drug Administration "hi gh fat" bre akfast) on the 3rd day and 3 x 4 mg for three days including steady state PK profile (fasted) on the 3rd day.
Objectives: **Primary** To demonstrate dose proportionality for ropinirole using an extended release (PR/XL) formulation of ropinirole over the dose range 4-12 mg when administered to subjects with a diagnosis of idiopathic PD. To determine the effect of food administered as a high fat breakfast on the absorption of ropinirole PRXL at 12 mg (highest tablet strength). To determine dosage strength equivalence for ropinirole PR/XL administered as 1 x 12 mg tablet compared with 3 x 4 mg tablets.
Statistical Methods: Dose proportionality of ropinirole was assessed by fitting the $\log_e$-transformed parameters AUC(0-24) and Cmax for ropinirole 1x 4 mg (fasted), 1 x 8 mg (fasted) and 1 x 12 mg (fasted) PR/XL to the Power Model. In addition, Cmin was analysed using similar methods to the primary

endpoints (AUC(0-24) and Cmax).
The effect of food on the highest tablet strength 1 x 12 mg (high fat fed) versus 1 x 12 mg (fasted) was assessed by fitting the $\log_e$-transformed parameters AUC(0-24) and Cmax to a mixed model analysis of variance (ANOVA). In addition, the PK parameter Cmin was analysed using similar methods to the primary endpoints (AUC(0-24) and Cmax). The PK parameter tmax was analysed non-parametrically.
The dosage strength equivalence of 3 x 4 mg PR/XL and 1 x 12 mg PR/XL for ropinirole was assessed by fitting the $\log_e$-transformed parameters AUC(0-24) and Cmax to a mixed effects linear ANOVA model. In addition, the PK parameter Cmin was analysed using similar methods to the primary endpoints. The PK parameter tmax was analysed non-parametrically.

Study Population:
Male and female subjects with a diagnosis of idiopathic PD, between 30 and 85 years of age with a body mass index of 18 to 32 kg/m^2 and a body weight of at least 50 kg. All subjects were required to provide written informed consent prior to participation in the study.

Number of Subjects:	**Total**
Planned N	36
Randomised N	28
Safety population, n (%)	28 (100)
PK population, n (%)	27 (96)
Completed n (%)	25 (89)
Total Number Subjects Withdrawn N (%)	3 (11)
Withdrawn due to Adverse Events n (%)	1 (4)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	2 (7)
Demographics	
N	28
Females: Males	14:14
Mean Age in Years (sd)	64.5 (8.56)
Mean Weight in Kg (sd)	73.4 (13.20)
White n (%)	27 (96)

Pharmacokinetics (PK)
Summaries (geometric mean, coefficient of variation between subjects (CVb%)) of the PK parameters of ropinirole and metabolites SKF-104557 and SFK-89124:

Regimen	**Ropinirole PK Parameter**				
	N	**AUC(0-24) (ng*hr/mL)**	**Cmax (ng/mL)**	**tmax[a] (hr)**	**Cmin (ng/mL)**
1 x 4mg ropinirole PR/XL (fasted)	27	57.1 (59.3)	3.36 (48.9)	6.00 (2.03 – 14.00)	1.64 (71.5)
1 x 8mg ropinirole PR/XL (fasted)	25	118 (46.8)	6.63 (44.6)	4.03 (2.00 – 10.00)	3.58 (58.1)
1 x 12mg ropinirole PR/XL (fasted)	25	164 (52.3)	9.06 (48.5)	4.02 (2.00 – 16.00)	4.74 (64.5)
1 x 12mg ropinirole PR/XL (fed)	25	197 (51.6)	13.1 (49.7)	10.00 (4.00 – 12.00)	4.57 (81.2)
3 x 4mg ropinirole PR/XL (fasted)	25	173 (53.8)	9.57 (52.4)	6.00 (2.00 – 14.00)	5.07 (60.9)

a. Median (range)

Regimen	SKF-104557 PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/XL (fasted)	27	78.8 (32.7)	4.02 (30.0)	9.98 (3.80 – 14.05)	2.66 (36.7)
1 x 8mg ropinirole PR/XL (fasted)	25	155 (32.8)	7.75 (37.2)	8.00 (0.00 – 14.00)	5.38 (35.5)
1 x 12mg ropinirole PR/XL (fasted)	25	219 (34.9)	10.8 (33.7)	8.00 (4.00 – 16.00)	7.60 (36.3)
1 x 12mg ropinirole PR/XL (fed)	25	250 (32.3)	13.7 (35.4)	10.00 (6.00 – 12.00)	7.70 (38.0)
3 x 4mg ropinirole PR/XL (fasted)	25	230 (24.6)	11.2 (25.5)	8.00 (2.00 – 14.00)	7.97 (26.4)
a. Median (range)					

Regimen	SKF-89124 PK Parameter				
	N	AUC(0-24) (ng*hr/mL)	Cmax (ng/mL)	tmax[a] (hr)	Cmin (ng/mL)
1 x 4mg ropinirole PR/XL (fasted)	27	2.78 (49.5)	0.156 (49.6)	8.00 (1.80 – 20.00)	0.092 (47.2)
1 x 8mg ropinirole PR/XL (fasted)	25	5.72 (43.3)	0.305 (49.3)	6.00 (0.00 – 20.00)	0.200 (44.7)
1 x 12mg ropinirole PR/XL (fasted)	25	8.61 (44.7)	0.463 (45.3)	6.00 (2.00 – 20.02)	0.286 (41.5)
1 x 12mg ropinirole PR/XL (fed)	25	10.2 (44.6)	0.584 (48.0)	10.00 (2.00 – 16.00)	0.315 (47.5)
3 x 4mg ropinirole PR/XL (fasted)	25	9.19 (38.5)	0.494 (40.4)	6.00 (2.00 – 20.00)	0.314 (35.0)
a. Median (range)					

Statistical results of the ropinirole dose proportionality assessment (power model):

Parameter	Slope	Standard error	90% CI
AUC(0-24) (hr*ng/mL)	0.970	0.0455	(0.893,1.046)
Cmax (ng/mL)	0.905	0.0415	(0.835,0.974)
Cmin (ng/mL)	0.986	0.0639	(0.878,1.093)

Statistical results for the effect of food on the PK of ropinirole:

Parameter	Geometric LS Mean		Ratio	90% CI
	Test (1 x 12 mg Fed)	Ref (1 x 12 mg Fasted)		
AUC(0-24) (hr*ng/mL)	196.59	163.85	1.20	(1.12, 1.28)
Cmax (ng/mL)	13.03	9.02	1.44	(1.34, 1.56)
Cmin (ng/mL)	4.54	4.72	0.96	(0.86, 1.08)
tmax[a] (hr)	10.00	4.02	3.01	(2.00, 4.01)
a. median along with estimated median difference between treatments and 90% CI				

Statistical results for ropinirole dosage strength equivalence:

Parameter	Geometric LS Mean		Ratio	90% CI
	Test (1 x 12 mg PR/XL)	Ref (3 x 4 mg PR/XL)		
AUC(0-24) (hr*ng/mL)	163.85	173.18	0.95	(0.89, 1.01)
Cmax (ng/mL)	9.02	9.56	0.94	(0.88, 1.02)
Cmin (ng/mL)	4.72	5.07	0.93	(0.83, 1.04)
tmax[a] (h)	4.02	6.00	0.00	(-1.00, 1.00)

a. median along with estimated median difference between treatments and 90% CI

Safety results:
Adverse event (AE) monitoring was performed once subjects start dosing with study drug. AEs were monitored throughout the study and any AEs were followed up until they resolved.

Adverse Event:	**2 mg PR/XL (N=28)**	**4 mg PR/XL (N=28)**	**6 mg PR/XL (N=26)**	**8 mg PR/XL (N=25)**	**1 x 12 mg PR/XL (fasted) (N=25)**	**1 x 12 mg PR/XL (high fat fed) (N=25)**	**3 x 4 mg PR/XL (fasted) (N=25)**
No. subjects with AEs n	7	11	2	8	11	4 (16%)	9
Adverse Events: (reported in at least 2 subjects in any treatment group)	**2 mg PR/XL (N=28)**	**4 mg PR/XL (N=28)**	**6 mg PR/XL (N=26)**	**8 mg PR/XL (N=25)**	**1 x 12 mg PR/XL (fasted) (N=25)**	**1 x 12 mg PR/XL (high fat fed) (N=25)**	**3 x 4 mg PR/XL (fasted) (N=25)**
Headache	1 (4%)	5 (18%)	-	3 (12	2 (8%)	1 (4%)	3 (12%
Nausea	2 (7%)	2 (7%)	-	1 (4%)	2 (8%)	-	2 (8%)
Dizziness	-	1 (4%)	-	2 (8%)	3 (12%)	2 (8%)	-
Constipation	1 (4%)	2 (7%)	-	-	1 (4%)	-	-
Somnolence	-	-	-	-	1 (4%)	-	2 (8%)
Rhinitis	2 (7%)	-	-	-	-	-	-
Fatigue	-	2 (7%)	-	-	-	-	-

Serious Adverse Events (SAE):
One subject experienced a moderate SAE of gastric atony (verbatim:atonic stomach) which was unrelated to study medication. The subject completed all study periods.

Publications: No Publication

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