Synopsis

Identifier: HM2007/00152/00 **Study Number:** ROR106470

Title: An open label, repeat dose, dose escalation study conducted in RLS patients to characterize pharmacokinetics and food effect of ropinirole controlled release for RLS

Investigators:

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Study centres:

1. [redacted] Germany
2. [redacted] South Africa

Publication(s): None as of the date of this report.

Study period:

24 August 2006 – 12 December 2006

Phase of development: II

Objectives:

Primary

- To determine the effect of food on absorption of ropinirole CR-RLS at 6 mg (highest tablet strength)
- To demonstrate the dose proportionality for ropinirole CR-RLS over the dose range 1-6 mg
- To determine the dosage strength equivalence for ropinirole CR-RLS as 1 x 6 mg tablet compared with 2 x 3 mg tablets

Secondary

- To assess safety and tolerability of ropinirole CR-RLS

Other

- To summarise the pharmacokinetic parameters for the two metabolites of ropinirole, SKF-104557 and SKF-89124.

Endpoints:

Primary

- Ropinirole AUC (0-24), the area under the plasma concentration-time curve over the dosing interval
- Ropinirole Cmax, the maximum plasma concentration

Secondary

- Ropinirole Tmax, the time to attain Cmax
- Ropinirole t1/2: apparent terminal phase half-life
- Incidence of adverse events
- Vital signs, ECG and clinical laboratory data

Other

- AUC(0-24), Cmax, Tmax and t1/2 of the ropinirole metabolites, SKF-104557 and SKF-89124

Methodology:

The study was designed to address several important pharmacokinetic objectives to meet regulatory requirements for the new ropinirole CR-RLS tablet strength of 6 mg for the treatment of Restless Leg Syndrome (RLS). The study was a two-centre, open-label design in subjects with RLS, comprising a non-randomised dose escalation period followed by a 3-period, randomised, crossover. Ropinirole CR-RLS tablets containing ropinirole hydrochloride equivalent to 0.5 mg, 1 mg, 2 mg, 3 mg and 6 mg of active drug substance were dosed in this study. The total duration of the study for each subject was 59 to 93 days. Each subject received ropinirole CR-RLS for 51 days.

Number of subjects:

Number of Subjects	All Subjects
Planned, n	30
Randomized, n	32
Completed, n [%]	26 (81)
Total Withdrawn (any reason), n [%]	6 (19)
Withdrawn due to Serious Adverse Event, n [%]	0
Withdrawn due to Adverse Events, n [%]	5 (16)
Withdrawn due to subject's decision, n [%)]	1 (3)

Diagnosis and main criteria for inclusion:

Male and female subjects with RLS, between the age of 18 and 65 years inclusive; with a body mass index of 18 to 32 kg/m^2 and normal systolic (100 – 140 mmHg) and diastolic (<90 mmHg) blood pressure.

Treatment administration:

The treatments administered during the study were:

Drug	Dose/Form/Route	Batch Number
SKF101468	0.5 mg/Tablet/Oral	061121122
SKF101468	1.0 mg/Tablet/oral	061121124
SKF101468	2.0 mg/Tablet/Oral	061121125
SKF101468	3.0 mg/Tablet/Oral	061121126
SKF101468	6.0 mg/Tablet/Oral	061122682

Criteria for evaluation:

- To estimate the effect of food on absorption of ropinirole following administration of 6 mg CR-RLS.

  The point estimates and 90% confidence intervals were derived for the ratio of "fed to fasted" (D:C) for ropinirole AUC(0-24) and Cmax.

- To demonstrate dose proportionality of ropinirole over a CR-RLS dose range of 1 to 6 mg (treatments A (1mg), B (3mg) and C (6mg)).

  The estimated mean slope and 90% confidence interval were based on the power model and were constructed for ropinirole AUC(0-24) and Cmax. Dose proportionality of ropinirole was demonstrated if the 90% confidence interval of the estimated mean slopes of AUC(0-24) and Cmax were completely contained within the range 0.88 to 1.12.

- To demonstrate dose strength equivalence of ropinirole CR-RLS 1 x 6 mg tablet compared to ropinirole CR-RLS 2 x 3 mg tablets.

  Point estimates and 90% confidence intervals were derived for the ratio of ”ropinirole 1x 6 mg CR-RLS : ropinirole 2 x 3 mg CR-RLS” (C:E). Dose strength equivalence was demonstrated if the 90% confidence interval for the ratios of both ropinirole AUC(0-24) and Cmax were completely contained within the range 0.80 to 1.25.

- Safety data were listed by subject and period in the study and summarized by treatment. No formal statistical comparisons were made for safety data.

Statistical methods:

Code	Regimen
A	1 x 1 mg ropinirole CR-RLS (fasted)
B	1 x 3 mg ropinirole CR-RLS (fasted)
C	1 x 6 mg ropinirole CR-RLS (fasted)
D	1 x 6 mg ropinirole CR-RLS (fed)
E	2 x 3 mg ropinirole CR-RLS (fasted)

The effect of food (D-C) was assessed by fitting the loge-transformed parameters AUC(0-24) and Cmax to a mixed model analysis of variance (ANOVA). Back-transformed point estimates and 90% confidence intervals were derived for the ratio of fed:fasted (D:C).

Dose proportionality of ropinirole was assessed by fitting the loge-transformed parameters AUC(0-24) and Cmax for ropinirole 1, 3 and 6 mg ropinirole CR-RLS (A, B, C) to the Power Model. Dose proportionality was demonstrated if the 90% confidence interval of the estimated mean slope of AUC(0-24) and Cmax were completely contained within the range 0.88 to 1.12.

Dosage strength equivalence (C-E) of ropinirole was assessed by fitting the loge-transformed parameters AUC(0-24) and Cmax to a mixed model analysis of variance (ANOVA). Back-transformed point estimates and 90% confidence intervals for the ratio C:E were presented. Dosage strength equivalence was demonstrated if the 90% confidence intervals for the ratios of both AUC(0-24) and Cmax were completely contained within the range 0.80-1.25.

The parameter Tmax was analysed using the Wilcoxon Signed Rank Test, for the comparisons of dosage strength equivalence (C-E) and food effect (D-C). Point estimates and confidence intervals for the median difference between treatment groups were presented.

Summary:

Demographics

		Total
Sex, n [%]	Males Females	8 (25) 24 (75)
Age [years]	Mean SD	45.0 10.66
	Range	26-64
Race, n [%]	White – White/Caucasian/European Heritage	32 (100)
Ethnicity, n [%]	Not Hispanic or Latino	32 (100)
Height [cm]	Mean	169.9
	SD Range	8.77 154-188
Weight [kg]	Mean	75.3
	SD Range	12.58 50-101
BMI [kg/m^2]	Mean	26.1
	SD Range	3.97 19-33

BMI = Body mass index; n = Number of observations; SD = Standard deviation

Pharmacokinetics

Summaries (geometric mean, coefficient of variation between subjects (CVb%)) of the PK parameters of ropinirole are presented below:

Regimen	PK Parameter				
	N	AUC(0-24) [ng.h/mL]	Cmax [ng/mL]	tmax[a] [h]	t½ [h]
A: 1 x 1 mg ropinirole CR-RLS (fasted)	32	12.6 (53.7)	1.16 (43.9)	3.05 (1.00 – 6.03)	5.89 (21.4)
B: 1 x 3 mg ropinirole CR-RLS (fasted)	31	39.4 (51.2)	3.76 (41.1)	4.00 (2.00 – 6.03)	5.72 (20.0)
C: 1 x 6 mg ropinirole CR-RLS (fasted)	28	75.1 (54.5)	7.27 (43.4)	3.50 (1.10 – 6.02)	5.68 (20.6)
D: 1 x 6 mg ropinirole CR-RLS (fed)	26	74.3 (52.9)	6.89 (45.4)	6.00 (2.00 – 12.42)	5.21 (20.0)
E: 2 x 3 mg ropinirole CR-RLS (fasted)	28	73.7 (46.9)	6.80 (36.0)	4.00 (1.03 – 6.00)	5.82 (20.5)

a. Median (range)

Statistical results for the effect of food on the PK of ropinirole CR-RLS are presented below:

Comparison	Parameter	LS Gmean		Ratio	90% CI
		1 x 6 mg CR-RLS (fed)	1 x 6 mg CR-RLS (fasted)		
D:C	AUC(0-24) [ng.h/mL]	74.5	75.5	0.99	(0.92, 1.06)
D:C	Cmax [ng/mL]	6.90	7.23	0.95	(0.89, 1.03)
D - C	Tmax [h]*	6.00	3.50	1.50	(0.99, 2.50)

* median along with median difference between treatments and 90% CI presented

Statistical results of the dose proportionality assessment (power model) are presented below:

Parameter	Slope	Standard error	CVw%	90% CI
AUC(0-24) [ng.h/mL]	0.999	0.0299	20.91%	(0.949,1.049)
Cmax [ng/mL]	1.030	0.0272	18.97%	(0.984,1.075)

Statistical results for dosage strength equivalence are summarized below:

Comparison	Parameter	LS Gmean		Ratio	CVw%	90% CI
		1 x 6 mg CR-RLS	2 x 3 mg CR-RLS			
C:E	AUC(0-24) [ng.h/mL]	75.5	74.8	1.01	16.34%	(0.94, 1.09)
C:E	Cmax [ng/mL]	7.23	6.82	1.06	16.04%	(0.99, 1.14)
C - E	**Tmax [h]***	3.00	4.00	-0.45	-	(-1.00, 0.48)

* median along with median difference between treatments and 90% CI presented

Safety

Across all treatment regimens, 31 of 32 subjects enrolled in this study reported adverse events. The most common AEs over all treatment periods were nervous system disorders such as headache, gastrointestinal disorders such as vomiting and nausea, and general disorders, such as fatigue.

Ropinirole induced a slight reduction in blood pressure and heart rate values derived from the ABPM data, particularly during the up-titration period with the most prominent changes seen at the 5 mg dose level. The maximal effects of about –10 mmHg for both systolic and diastolic blood pressure and –11 bpm for heart rate (mean values) occurred within 4 hours of ropinirole administration. The reduction in ABPM-derived blood pressure was not clinically overt and was not associated with adverse events such as hypotension. The slight changes as described for the ABPM data were also visible from the serial vital signs measurements in supine and standing positions. Although reduction in blood pressure and hypotension occasionally occurred following ropinirole treatment, there appears to be no increased risk of hypotension symptoms after ropinirole dosing in this study. Neither vital signs values derived from the ABPM data nor those derived from serial measurements in supine and standing position raised any serious clinical concern by the investigator, nor did they constitute any AE. However, 7 subjects had a drug-related orthostatic hypotension as assessed by the investigator when considering the changes in BP from supine to standing position. Safety laboratory values did not show any clinically relevant or dose-dependent changes during repeated treatment with ropinirole. One subject was withdrawn by the investigator due to atrial fibrillation. All other abnormal ECG findings were considered to be not clinically relevant and there was no apparent trend for the ECG variables. All AEs that were documented in this study have been previously reported under treatment with ropinirole, thus no unknown and no unexpected AE occurred in this study.

	0.5 mg	1 mg	2 mg	3 mg	4 mg	5 mg	1x6 mg fasted	1x6 mg fed	2x3 mg fasted	Overall
	N=32	N=32	N=31	N=31	N=31	N=30	N=28	N=28	N=28	N=32
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any AE	11 (34)	13 (41)	11 (35)	17 (55)	14 (45)	16 (53)	14 (50)	16 (57)	19 (68)	31 (97)
Total number of AEs	18	25	23	45	43	38	30	32	39	293
Subjects with drug related AEs	10 (31)	11 (34)	8 (26)	16 (52)	12 (39)	14 (47)	11 (39)	10 (36)	15 (54)	28 (88)
Total number of drug-related AEs	15	18	18	42	33	35	22	23	30	236
Subjects with AEs by maximal intensity										
Mild	3 (9)	7 (22)	4 (13)	2 (6)	1 (3)	4 (13)	2 (7)	4 (14)	4 (14)	2 (6)
Moderate	8 (28)	6 (19)	7 (23)	12 (29)	11 (35)	11 (37)	9 (32)	6 (21)	10 (36)	14 (44)
Severe	0	0	0	3 (10)	2 (6)	1 (3)	3 (11)	6 (21)	5 (18)	15 (47)

N = Number of subjects on regimen; n = Number of subjects with AEs; IMP = Investigational medicinal product; AE = Adverse event

Conclusions

- No evidence of any food effect was observed on Cmax and AUC(0-24) of ropinirole when ropinirole 1 x 6 mg CR-RLS was administered with a high fat meal, compared with ropinirole 1 x 6 mg CR-RLS in the fasted state. However tmax was delayed by, on average, 1.5 hours when ropinirole CR-RLS was administered with a high fat meal, compared to the fasted state.
- The pharmacokinetics of ropinirole were dose proportional over the dose range 1 to 6 mg CR-RLS.
- Dose strength equivalence was demonstrated for 1 x 6 mg CR-RLS ropinirole tablet and the 2 x 3 mg CR-RLS ropinirole tablets.
- All treatments regimens with ropinirole, investigated in this study, were generally well tolerated. No unknown or unexpected AE occurred during the study.

Date of Report:

October 2007