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.: SK&F101468/204
Title: A 12-Week, Randomized, Double-Blind, Parallel Group, Multicenter Study to Assess the Tolerability and Clinical Benefits of Ropinirole Extended Release (CR-RLS) Tablets Compared with Ropinirole Immediate Release (IR) Tablets in Subjects with Restless Legs Syndrome (RLS)
Rationale: Ropinirole IR has been approved for treatment of moderate-to-severe primary RLS in over 20 countries worldwide, including the United States. Ropinirole IR is administered 1 to 3 hours before bedtime per label. However, many subjects experience both evening and nighttime symptoms (including periodic leg movements of sleep [PLMS]). Since ropinirole has an elimination half-life of about 5 to 6 hours with C_{max} observed between 1 to 2 hours following oral intake an extended-release formulation (14-hour) of ropinirole for treatment of RLS (ropinirole CR-RLS) had the potential to provide improved tolerability, and longer duration of action and exposure (12 to 14 hours) relative to ropinirole IR. The current study evaluated the safety, tolerability and clinical benefits of ropinirole CR-RLS formulation compared to ropinirole IR in subjects requiring evening and nighttime coverage of RLS symptoms.
Phase: 3b
Study Period: 28Aug2005 – 15Dec2006
Study Design: This was a 12-week, randomized, double-blind, parallel-group, multicenter study to assess the tolerability and clinical benefits of ropinirole CR-RLS tablets compared with ropinirole IR tablets in adult subjects with RLS requiring evening (defined as 17:00 to 19:59 hours) and nighttime (defined as 20:00 to 06:59 hours) coverage of RLS symptoms. Study duration was up to 14 weeks including a minimum 7 day Washout/Screening Phase, 12-week Treatment Phase, and 1-week Follow up Phase. Clinic visits were scheduled at screening, baseline, Weeks 1 to 6, 8, 10 and 12 or early withdrawal, and follow-up (7 ± 3 days after the last study drug dose). During the Washout/Screening Phase, subjects discontinued any medications known to induce drowsiness or affect RLS or sleep for a minimum of 7 consecutive evenings/nights or 5 half-lives of the medication whichever was longer. Medications that could interfere with the assessment of ropinirole for RLS were prohibited during the study.
Centers: This multicenter study was conducted at study centers in Australia, Europe and the United States (US). Subjects were enrolled at 83 study centers and 80 of these study centers randomized subjects
Indication: Moderate to severe primary RLS requiring evening and nighttime coverage of RLS symptoms.
Treatment: Eligible subjects were randomized in a 1:1 ratio to 12 weeks of double blind treatment with ropinirole CR-RLS tablets (with doses of 0.5 to 6mg/day) or ropinirole IR tablets (with doses of 0.25 to 4mg/day). Subjects were instructed to take the study drug at approximately the same times each day, i.e., 1 to 2 hours prior to the usual onset of RLS symptoms for the ropinirole CR-RLS (or matching placebo) dose and 1 to 3 hours before bedtime for the ropinirole IR (or matching placebo) dose. The evening ropinirole CR-RLS dose was taken no earlier than 16:00 hours. Both doses for the day were taken in-clinic during the Baseline Visit (Day 0). On Day 2, the ropinirole IR dosage was increased to 0.5mg. All subjects were then up-titrated during the first 3 weeks of treatment using a fixed-dose escalation to a target of 2mg for ropinirole CR-RLS and 1.5mg for ropinirole IR. A subject who could not tolerate this fixed dose up titration was withdrawn from the study. Doses were adjusted using a flexible dose titration from Weeks 3 to 10 to optimize therapeutic benefit and tolerability. Dose reduction due to an adverse event (AE) was allowed between Weeks 3 and 10. If the AE resolved, the dose could be returned to the original higher level at the next scheduled clinic visit. No further dose adjustments were allowed after the Week 10 visit.
Objective: The primary objective was to demonstrate the superior tolerability of ropinirole CR-RLS compared to ropinirole IR in adult subjects with moderate to severe primary RLS requiring evening and nighttime coverage of RLS symptoms.
Primary Outcome/Safety Variable: The primary endpoint was incidence of nausea during the first 3 weeks of fixed-dose escalation.
Secondary Outcome/Safety Variables: Secondary safety variables included 1) incidence of the most common AE during the first 3 weeks fixed dose titration and during the 12 week treatment phase of the study, 2) incidence of dose reductions during the flexible dose titration phase, 3) incidence of premature withdrawals due to lack of tolerability during the first 3 weeks and during the 12 week treatment phase, and 4) incidence of premature withdrawals due to insufficient therapeutic effect during the 12 week treatment phase. Other safety and tolerability assessments included AEs, weight, vital signs (blood pressure [BP] and heart rate [HR]), electrocardiograms (ECGs), and clinical laboratory tests. AEs were monitored throughout the study. Vital signs were collected at screening, baseline, each on-treatment visit, and follow-up; orthostatic BP was taken pre-dose and 2 and 4 hours post dose at baseline, and ambulatory BP (ABP) was taken on the first evening following each dose increase. Weight, ECGs and laboratory tests were assessed at screening and/or baseline, and Week 12 (or early withdrawal) and/or follow-up. Conduction intervals (including QTc analysis) were manually read from the ECGs.
Secondary Outcome/Efficacy Variables: Secondary efficacy endpoints were: 1) change from baseline at Week 12 last

observation carried forward (LOCF) in the International Restless Legs Syndrome (IRLS) Rating Scale total score, 2) change from baseline at Weeks 1, 2, 3, 4, 8 and 12 OC in the IRLS Rating Scale total score, 3) change from baseline at Week 12 in the number of hours of RLS symptoms during the evening, and evening and nighttime, 4) the proportion of subjects with no symptoms or symptoms with a maximum intensity of mild severity during the evening and during the evening and nighttime, 5) proportion of RLS symptom free days, 6) time to onset of the first 4 consecutive, RLS symptom-free days within the first 4 weeks of treatment, 7) proportion of responders (subjects with a score of much improved [2] or very much improved [1] on the Clinical Global Impression – Improvement (CGI-I) scale) and time to a response on the CGI-I scale, 8) change from baseline at Week 12 in all domains and indices of the Medical Outcomes Sleep 12-item (MOS-12) Sleep Scale, and 9) change from baseline at Week 12 in the Overall Life Impact Score of the RLS Quality of Life (QoL) Questionnaire.

Statistical Methods: The study was powered to detect a difference of 15 percentage points between nausea incidences on ropinirole CR-RLS compared with ropinirole IR with a total of 480 treated subjects (240 per treatment group) assuming an underlying incidence rate of 45% on ropinirole IR. The primary analysis population for all safety data was the Safety Population which included subjects who took at least one dose of study drug. The primary endpoint was analyzed using a logistic regression model, fitting terms for region and treatment group. The primary analysis was repeated for any on-treatment AE occurring in at least 10% of either treatment group for the Safety Population (1) during the first 3 weeks of fixed-dose titration and (2) during the 12-week Treatment Phase. Secondary and other safety analyses were summarized using descriptive statistics.

Continuous variables were analyzed using a repeated measures model which derived a point estimate and 95% CI for treatment differences. Estimated treatment differences were derived from a single repeated measures model fitting terms for treatment group, visit, treatment group by visit interaction, and region.

The proportion of subjects with a score of 1 ('much improved') or 2 ('very much improved') on the CGI-I was analyzed using a logistic regression model, including terms for treatment group and region.

Changes over time were analyzed using a hierarchical testing approach. First, the treatment difference between ropinirole CR-RLS and ropinirole IR was estimated at Week 12 for each of the efficacy endpoints. If there was a statistically significant treatment difference at the 5% level at a given time point, starting with Week 12, the process continued with estimation of the treatment differences at the previous time point. If a statistically significant treatment difference was not observed at this time-point, analyses from prior time-points were not to be interpreted. Time to event data were analyzed based on a Cox Proportional Hazards regression model including terms for region and treatment group. Subjects who did not experience the event were censored on the day at which they finished the study, either due to early withdrawal or study completion. Kaplan-Meier survival curves and survival estimates of the time-to-event data were produced for all time-to-event endpoints.

Missing data were imputed using the last observation carried forward (LOCF) imputation to estimate subsequent missing assessments for a subject. Safety data were summarized using only the observed cases (OC) dataset with the exception of the primary safety analysis. All secondary efficacy variables were summarized using the OC dataset at each visit and at Week 12 using the LOCF dataset, where appropriate.

The Safety Population included all subjects who received at least one dose of study drug. The primary inferences concerning ropinirole CR-RLS compared to ropinirole IR were made using the Safety Population. The Intent-to-Treat (ITT) Population included all subjects who were entered into the study, received at least one dose of double-blind study drug and had at least one valid post-baseline efficacy assessment available. All efficacy endpoints were analyzed using the ITT Population.

Study drug exposure, AE and assessment data were summarized during the treatment phase based upon events reported after the time of the first dose of randomized study drug, up to and including the day after the last dose of study drug (as subjects were instructed to take their study drug in the evening and attend the study visit the following day).

Study Population: Males or females aged ≥18 years and <80 years, with all of the following: RLS diagnosed using the RLS Diagnostic Clinical Interview and the International RLS Study Group (IRLSSG) Diagnostic Criteria, a history of ≥20 evenings and nights of RLS episodes during the previous month, RLS symptoms requiring treatment during the evening (17:00 to 19:59 hours) and nighttime (20:00 to 06:59 hours), ≥3 days of both evening and nighttime symptoms and ≥4 days with symptoms during the 7 days immediately before baseline, a baseline IRLS total score of ≥15, and RLS symptoms causing significant sleep impairment. A subject currently receiving medication to treat RLS or sleep at screening was allowed if the medication had been discontinued and washed-out for a minimum of 5 half lives of the medication or 7 consecutive evenings/nights prior to baseline, whichever was longer. A subject was excluded if (s)he required treatment of daytime (07:00 to 16:59 hours) RLS symptoms, showed signs of secondary RLS, or had a serum ferritin level of <10mcg/L (ng/mL) at baseline.

Study Results: Results are presented below only for subjects treated with ropinirole IR since Ropinirole CR-RLS is not currently approved for marketing as of the date of this posting, August 2007.

Number of Subjects:	**Ropinirole IR**
Planned, N	240
Randomized, N	290
Completed, n (%)	219 (76)
Total Number Subjects Withdrawn, N (%)	70 (24)
Withdrawn due to adverse events n (%)	36 (12)
Withdrawn due to lack of efficacy n (%)	6 (2)
Analysis Populations:	**Ropinirole IR**
Randomized, N	290
Safety, n (%)	289 (>99)
ITT, n (%)	288 (>99)
Demographics	**Ropinirole IR**

N (Safety Population)	289
% Females	58
Mean age, years (SD)	55.1 (12.58)
% Not Hispanic/Latino	93
% White	99
RLS Characteristics at Screening	**Ropinirole IR**
N (ITT Population)	288
Mean age at onset of RLS, years (SD)	36.3 (17.02)
Has subject ever had PLMS? Yes, n (%)	129 (45)
Time current symptoms are mainly present: evening/nighttime, n (%)	256 (89)
Mean IRLS Rating Scale total score at baseline (SD)	26.6 (4.68)
Primary Safety Results:	
	Ropinirole IR
N (Safety Population)	289
Any nausea AE during the first 3 weeks of fixed dose-titration, n (%)	110 (38)
Secondary Safety Outcomes:	
Maximum intensity of nausea AEs during first 3 weeks of fixed dose-titration	
Maximum Intensity	**Ropinirole IR**
N (Safety Population)	289
Any nausea AE during the first 3 weeks of fixed dose-titration, n	110
Mild, n (%)	50 (45)
Moderate, n (%)	34 (31)
Severe, n (%)	26 (24)
Most Common AEs (reported for ≥ 10%) during first 3 weeks of fixed-dose titration	
N (Safety Population)	289
Any on-treatment AE, n	188 (65)
Nausea n (%)	110 (38)
Headache n (%)	42 (15)
Most Common AEs (reported for ≥ 10%) during the 12-week Treatment Phase	
N (Safety Population)	289
Any on-treatment AE, n	244 (84)
Nausea n (%)	158 (55)
Headache n (%)	55 (19)
Somnolence n (%)	28 (10)
Fatigue n (%)	38 (13)
Dizziness n (%)	30 (10)
Vomiting n (%)	33 (11)
Subjects with ≥ 1 dose reduction due to lack of tolerability, n (%)	45 (16)
Subjects with premature withdrawal –	
due to intolerability during fixed dose-titration, n (%)	29 (10)
due to intolerability during 12-week Treatment Phase, n (%)	36 (12)
due to insufficient therapeutic effect, n (%)	4 (1)
Secondary Efficacy Outcomes:	

	Ropinirole IR
N (ITT Population)	288
Change from baseline in IRLS Rating Scale Total Score at Week 12 LOCF	
N (ITT Population)	288
Mean (SD)	−14.8 (8.87)
Change from baseline in IRLS Rating Scale Total Score at Week 12 OC	
n Mean (SD)	205 −16.2 (0.52)
Change from baseline in IRLS Rating Scale Total Score at Week 8 OC	
n Mean (SD)	231 −15.6 (0.53)
Change from baseline in IRLS Rating Scale Total Score at Week 4 OC	
n Mean (SD)	238 −15.0 (0.52)
Change from baseline in IRLS Rating Scale Total Score at Week 3 OC	
n Mean (SD)	248 −14.1 (0.52)
Change from baseline in IRLS Rating Scale Total Score at Week 2 OC	
n Mean (SD)	263 −11.4 (0.51)
Change from baseline in IRLS Rating Scale Total Score at Week 1 OC	
n Mean (SD)	268 −8.1 (0.47)
Daily Number of Hours of RLS Symptoms during the Evening and Evening and Nighttime at Week 12 LOCF	

	Ropinirole IR
Evening (17:00 to 19:59 hours)	
Baseline, n	275
Median (Min, Max)	0.75 (0.00, 4.00)
Week 12 LOCF, n	279
Median (Min, Max)	0.17 (0.00, 3.13)
Evening and Nighttime (17:00 to 06:59 hours)	
Baseline, n	268
Median (Min, Max)	3.73 (0.32, 16.00)
Week 12 LOCF, n	275
Median (Min, Max)	0.80 (0.00, 14.00)
Proportion of Subjects with No Symptoms or Symptoms with a Maximum Intensity of Mild Severity at Week 12 LOCF	
	Ropinirole IR
Evening (17:00 to 19:59 hours)	
Baseline, n	275
Number (%)	23 (8%)
Week 12 LOCF, n	279
Number (%)	133 (48%)
Evening and Nighttime (17:00 to 06:59 hours)	
Baseline, n	268
Number (%)	0 (0%)
Week 12 LOCF, n	275
Number (%)	67 (24%)
Proportion of RLS symptom-free days during treatment	
	Ropinirole IR
n	281
Adjusted mean (SE)	42.5% (2.12)
Number (%) of subjects and time to achieving 4 consecutive RLS symptom-free days	
	Ropinirole IR
N (ITT Population)	288
Number (%) achieving endpoint	125 (43)
CGI-I Responders (subject with a score of 2 [much improved] or 1 [very much improved] on the CGI-I scale) at Week 12 LOCF	
	Ropinirole IR
N (ITT Population)	288
Number (%) achieving endpoint	203 (73)
Median time to endpoint	14 days
Change from Baseline in MOS-12 Sleep Scale Domains at Week 12 LOCF	
	Ropinirole IR
N (ITT Population)	288
Change from baseline in sleep disturbance at Week 12 LOCF (0 to 100)	216
Mean (SD)	−28.0 (24.73)
Change from baseline in sleep quantity at Week 12 LOCF (hours)	216
Mean (SD)	0.9 (1.56)
Change from baseline in sleep adequacy at Week 12 LOCF (0 to 100)	216
Mean (SD)	24.9 (30.08)
Change from baseline in somnolence at Week 12 LOCF (0 to 100)	216
Mean (SD)	−16.1 (22.33)
Change from baseline in sleep problems Index 1 at Week 12 LOCF	216
Mean (SD)	−21.7 (20.47)
Change from baseline in sleep problems Index 2 at Week 12 LOCF	216
Mean (SD)	−22.9 (20.50)
Change from Baseline in Overall Life-Impact Score from RLS QoL Questionnaire at Week 12 LOCF	
	Ropinirole IR

Change from baseline in Overall Life-Impact score at Week 12 LOCF	211
Mean (SD)	19.5 (17.43)
Other Safety Results	
Non-fatal Serious Adverse Events – On-treatment	
Preferred Term	**Ropinirole IR**
Subjects with non-fatal SAEs, n (%)	8 (3)
Gastroenteritis viral, n (%)	1 (<1)
Angina pectoris, n (%)	1 (<1)
Animal bite, n (%)	1 (<1)
Chest pain, n (%)	1 (<1)
Hand fracture, n (%)	1 (<1)
Malaise, n (%)	1 (<1)
Orthostatic hypotension, n (%)	1 (<1)
Overdose, n (%)	1 (<1)
Sinus bradycardia, n (%)	1 (<1)
Syncope, n (%)	1 (<1)
Tremor, n (%)	1 (<1)
Fatal Serious Adverse Events – On-treatment – none reported	

Other Safety Outcomes:

- The incidence of body weight changes that met pre-specified criteria for PCC was low.
- Mean orthostatic and postural changes in SBP, DBP, and HR were relatively small through Week 12 and follow-up. The proportion of subjects with orthostatic or postural changes or values of PCC was low through Week 12 and follow-up. The most common values within the range of PCC for orthostatic and postural changes were high and significant increases in diastolic BP. Other values within the range of PCC were seen infrequently . No subject with an orthostatic change of PCC had a BP-related AE.
- ABP monitoring was performed each evening of a dosage increase. Most subjects had ambulatory measurements through 4 hours post-dose. During this period, mean pre- to post-dose changes in ambulatory SBP, DBP, and HR were generally small. The proportion of subjects with at least one ambulatory SBP or DBP of PCC was low.
- No safety concerns were suggested by the ECG findings for subjects treated with ropinirole IR. Mean changes in ECG parameters (pre- to post-dose at baseline and changes from pre-dose baseline to subsequent study visits) were generally small with no clinically-relevant trends observed. No AEs of special interest involving ECGs were noted.

Conclusion: In this 12-week study, the most common adverse events reported by subjects receiving ropinirole IR were nausea and headache. No serious adverse event was reported by more than one subject, and there were no fatalities. Ropinirole IR given 1 to 3 hours before bedtime was effective treatment for the symptoms of primary RLS.

Publications:
No publication

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