Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: Sifrol®, Mirapexin®			
Name of active ingredient: Pramipexole		**Page** 1 of 7	
Report date: 19 Oct 2007	**Trial Number:** 248.615	**Study period (dates)** 02 AUG 06 – 30 MAY 07	**Date of Revision:**

Title of trial:	A phase IV randomised, double-blind, placebo-controlled, dose titration trial with pramipexole (Sifrol®, Mirapexin®) 0.125-0.75 mg/day per os for 12 weeks to investigate the effects on RLS symptoms (IRLS) and sleep disturbance (MOS sleep scale) in out-patients with idiopathic Restless Legs Syndrome
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study
Publication (reference):	Ferini-Strambi L, Aarskog D, Chaudhuri R, Partinen M, Sohr M, Verrri D. Pramipexole for restless legs syndrome and associated sleep disturbance. 60th Ann Mtg of the American Academy of Neurology (AAN), Chicago, 12 - 19 Apr 2008 Neurology 2008; 70 (11) (Suppl 1) :A294 (P08-06269) Partinen M, Ferini-Strambi L, Aarskog D, Chaudhuri R, Sohr M, Verri D. Effects of pramipexole on daytime symptoms of restless legs syndrome. 60th Ann Mtg of the American Academy of Neurology (AAN), Chicago, 12 - 19 Apr 2008 Neurology 2008; 70 (11) (Suppl 1) :A292 (P08-06266) Ferini-Strambi L, Aarskog D, Chaudhuri R, Partinen M, Sohr M, Verri D. Rapid onset and sustained efficacy of pramipexole in restless legs syndrome. 60th Ann Mtg of the American Academy of Neurology (AAN), Chicago, 12 - 19 Apr 2008 Neurology 2008; 70 (11) (Suppl 1) :A292 (P08-06265)
Clinical phase:	IV

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Objectives:	Primary: To investigate the effects on restless legs syndrome (RLS) symptoms (based on the International Restless Legs Syndrome Study Group Rating Scale [IRLS]) and sleep disturbance (based on Medical Outcomes Study [MOS] sleep scale) of pramipexole 0.125 mg/day to 0.75 mg/day per os for 12 weeks, compared to placebo, in the treatment of patients with idiopathic RLS Secondary: To investigate the effects on Clinical Global Impressions – Global Improvement (CGI-I), RLS, other MOS dimensions, daytime symptoms, associated mood disturbance, pain in limbs, cognitive function, quality of life (QoL) in RLS, patient global impression (PGI) and safety of pramipexole in comparison to placebo
Methodology:	Randomised, double-blind, placebo-controlled, parallel, dose titration design; prospective comparison of 2 groups over 12 weeks.
No. of subjects: **planned:** **actual:**	entered: 320 (160 per group) enrolled: 444 entered: 369 Pramipexole: entered: 182 treated: 182 analysed (for primary endpoint): 178 for both the IRLS total score and the MOS sleep disturbance score Placebo: entered: 187 treated: 187 analysed (for primary endpoint): 179 for the IRLS total score and 178 for the MOS sleep disturbance score
Diagnosis and main criteria for inclusion:	Male or female out-patients aged 18-80 years with idiopathic RLS; RLS symptoms present at least 2 to 3 days per week during the last 3 months prior to baseline; IRLS total score >15 at baseline; no intake of dopamine agonists or levodopa within 14 days prior to baseline, or no intake of levodopa prior to baseline visit, if augmentation in RLS symptoms was observed; no unsuccessful prior treatment with non-ergot dopamine agonists (e.g. pramipexole, ropinirole)
Test product:	Pramipexole (Sifrol®, Mirapexin®)

dose:	4 weeks individual dose titration starting with 0.125 mg, next steps: 0.25 mg, 0.5 mg and 0.75 mg; maintenance dose for 8 weeks, once daily
mode of admin.:	Tablets, oral
batch no.:	PD-2732
Reference therapy:	Placebo
dose:	Not applicable (procedure as for investigational product)
mode of admin.:	Pramipexole matching tablets; oral
batch no.:	PD-2733
Duration of treatment:	12 weeks
Criteria for evaluation:	
Efficacy:	Primary: IRLS total score, change from baseline; MOS sleep disturbance score, change from baseline (co-primary endpoint) Secondary: Key secondary efficacy endpoints: IRLS responder rate (at least 50% reduction from baseline of IRLS total score) and CGI-I responder rate (at least 'much improved' compared with baseline). Further secondary endpoints: PGI responder rate (responder comprising 'much better' and 'very much better'), change from baseline in the IRLS reduced score at Visits 3 and 4, the IRLS item 10 score, the scores of other MOS sleep scale dimensions, the RLS-6 items 4-6 scores, the VAS score for pain in limbs, the verbal fluency tests scores, and the RLS-QoL total score.
Safety:	Adverse events (AEs); Vital signs

Statistical methods:

The primary efficacy endpoints, i.e., the changes from baseline to endpoint in the IRLS total score and the MOS sleep disturbance score, were analysed using an analysis of covariance (ANCOVA) with pooled centre and treatment as main effects and baseline scores as a covariate included in the model. The primary objective of the trial was addressed by a system of hierarchically ordered 2-sided statistical tests at the 5% level of significance. The null hypothesis that there is no difference in the change in parameter score between pramipexole and placebo was tested against the alternative hypothesis that there is a difference.

The changes from baseline to the end of treatment in secondary efficacy variables were analysed using the Wilcoxon-Mann-Whitney rank test. Response rates at the end of the treatment phase were analysed using a Cochran-Mantel-Haenszel (CMH) test stratified by pooled centre.

No formal statistical analysis was planned for the assessment of safety. The descriptive summaries of safety data were based on the Safety Set.

SUMMARY – CONCLUSIONS:

Efficacy results:

Patient demography and baseline disease characteristics of the safety population were similar in both treatment groups with the exception of the proportion of female patients (63.6% placebo vs. 72.5% pramipexole). The mean (standard deviation [SD]) age was 56.9 (13.0) years for placebo and 56.3 (12.4) years for pramipexole. The median duration of RLS was also similar between treatments (0.9 years [placebo] vs. 1.3 years [pramipexole]), as was the mean (SD) IRLS total score (24.6 [5.7] vs. 24.2 [5.2]) and the mean (SD) MOS sleep disturbance score (55.7 [22.3] vs. 52.8 [20.5]) at baseline.

For both primary endpoints, the pramipexole group showed highly statistically significant improvements compared to placebo. After 12 weeks of treatment, the adjusted mean (standard error [SE]) change in the IRLS total score was –13.4 (0.7) for pramipexole and –9.6 (0.7) for placebo ($p=0.0001$). For the MOS sleep disturbance score, adjusted mean (SE) changes from baseline of –16.8 (1.5) for placebo and –25.3 (1.5) for pramipexole were observed ($p<0.0001$). Statistically significant differences in favour of pramipexole were also seen in key secondary endpoints after 12 weeks of treatment. In the placebo group, 39.7% of patients were IRLS responders compared with 59.6% of pramipexole patients ($p=0.0003$). Similarly, 40.2% of placebo patients compared with 66.3% of pramipexole patients were CGI-I responders

	(p<0.0001). Results from further secondary endpoints after 12 weeks of treatment were consistent with the above findings. The PGI responder rate was significantly higher with pramipexole than with placebo at all assessed visits, even already 1 day after treatment start. After 12 weeks of treatment, the PGI responder rate was 62.9% with pramipexole compared to 38.0% with placebo (p<0.0001). The difference between treatments in the IRLS reduced score (assessed after 1 day and 5 days of treatment only) was statistically significant after 5 days (p<0.0001) with an adjusted mean (SE) difference between pramipexole and placebo of 2.5 (0.6). The change in MOS sleep adequacy was significant vs. placebo after 12 weeks (p=0.0008); changes in MOS sleep quantity (p=0.0795) and MOS sleep somnolence (p=0.1101) were not statistically significant. Items 4-6 from the RLS-6, which ask about RLS symptoms during daytime, were statistically significantly better with pramipexole compared to placebo after 12 weeks with p-values ranging from 0.0017 to 0.0095. The difference between treatments in the VAS score for pain in limbs was highly significant (p=0.0001) with a median reduction of −11.0 for placebo and −33.5 for pramipexole. Both Verbal Fluency tests were not statistically significant (p=0.4539 for the letter test and p=0.0761 for the category test). Finally, a statistically significant improvement compared to placebo in RLS-Quality of Life was established for pramipexole in comparison to placebo (p=0.0100). In summary, the primary objective of showing the statistical superiority of pramipexole over placebo in the change of the IRLS total and the MOS sleep disturbance scores after 12 weeks of treatment was achieved. Furthermore, pramipexole was shown to be efficacious in the key and most additional secondary variables.
Safety results:	Titration performed during the first 4 weeks based on efficacy (PGI score) and tolerability resulted in final pramipexole doses of 0.125 mg for 28 patients (15.4%), 0.25 mg for 60 patients (33.0%), 0.5 mg for 49 patients (26.9%), and 0.75 mg for 45 patients (24.7%). Placebo patients had a mean (SD) treatment duration of 65.6 (29.3) days vs. 74.9 (22.5) days in the pramipexole group. The mean number of prescribed tablets per day was 1.9 tablets per day in the placebo group and 1.6 tablets per day in the pramipexole group, which corresponds to a mean daily pramipexole dose of 0.4 mg (1 tablet contained 0.25 mg pramipexole; trial medication was to be taken once per day). During the treatment period, 192 patients (52.0%) reported at least 1 AE (86

[46.0%] placebo vs. 106 [58.2%] pramipexole). The corresponding frequencies by pramipexole dose at onset of the AE were 30.9% of patients (0.125 mg pramipexole), 28.5% (0.25 mg), 40.7% (0.5 mg), and 36.0% (0.75 mg). The most frequent AEs were headache (12.8% placebo vs. 14.8% pramipexole), nausea (5.9% vs. 17.6%), nasopharyngitis (4.8% vs. 7.1%), and fatigue (2.1% vs. 8.8%).

The majority of AEs had a worst intensity of either mild (21.9% placebo vs. 25.8% pramipexole) or moderate (18.7% vs. 26.4%). AEs of severe intensity were reported with similar frequencies in either treatment group (5.3% vs. 6.0%). The highest percentage of patients with a severe AE was seen for pramipexole doses of 0.75 mg (6.0% of patients exposed to this dose) and 0.5 mg (3.7%).

Overall, 109 patients (29.5%) suffered from AEs considered to be drug-related as assessed by the investigator (37 patients [19.8%] placebo vs. 72 [39.6%] pramipexole). The most frequent AEs assessed as drug-related were nausea (4.8% placebo vs. 15.4% pramipexole) and headache (6.4% vs. 8.2%).

One patient (placebo group) died during the trial due to a myocardial infarction that was not considered drug related by the investigator.

A total of 6 SAEs were reported during the study in 2 placebo patients (1.1%) and 4 pramipexole patients (2.2%). The events in the placebo group were the aforementioned myocardial infarction and upper abdominal pain (moderate intensity, not considered related). The 4 SAEs in the pramipexole group were atrioventricular block second degree (dose of 0.125 mg at onset, severe in intensity, considered drug related), intervertebral disc protrusion (0.25 mg, severe, not considered related), sciatica (0.5 mg, moderate, not considered related), and syncope (0.75 mg, moderate, considered related).

During the study, 16 placebo patients (8.6%) and 17 pramipexole patients (9.3%) reported an AE leading to premature discontinuation of trial drug intake. The most frequent AEs leading to withdrawal were nausea (1.1% placebo vs. 2.2% pramipexole), dizziness (1.1% vs. 1.6%), headache (0.5% vs. 1.6%), and insomnia (1.1% vs. 0.5%).

No relevant findings were seen in the analysis of vital signs (blood pressure and heart rate).

In summary, 12-week treatment with pramipexole was well tolerated and did

	not raise any concerns in any of the examined safety variables or in any of the 4 dose groups. Findings were consistent with the known safety profile of pramipexole.
Conclusions:	In the examined population of RLS patients, a 12-week treatment with pramipexole was shown to be highly efficacious compared with placebo regarding RLS symptoms as well as RLS-associated sleep disturbances. The primary objective of showing the statistical superiority of pramipexole over placebo in the change of the IRLS total score and the MOS sleep disturbance score after 12 weeks of treatment was achieved. Pramipexole treatment proved to be safe and well tolerated.