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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 6**	© Boehringer Ingelheim International GmbH This Tabulated Study Report is the property of Boehringer Ingelheim International GmbH and may not - in full or in part - be passed on, reproduced, published or otherwise used without the express permission of Boehringer Ingelheim International GmbH
Report date: 27 NOV 07	**Trial-Number:** 248.604	**Study period (dates):** 28 JUL 06 – 23 JUN 07	

Title of study:	A phase IV randomised, double-blind, placebo-controlled, dose titration trial with 0.125-0.75 mg/day pramipexole (Sifrol®, Mirapexin®) orally for 12 weeks to investigate the safety and efficacy in out-patients with idiopathic Restless Legs Syndrome associated with mood disturbances
Investigator:	[redacted]
Study centers:	Multi-centre study with 52 centres in 9 countries (Finland, France, Germany, Ireland, Italy, Republic of Korea, Spain, Sweden, United Kingdom)
Publication (reference):	Montagna, P, Koester, J, Crespi, G. Design of a randomized, placebo-controlled trial of pramipexole in RLS patients with associated mood disturbances. 11th Cong of the European Federation of Neurological Societies (EFNS). Brussels, 25-28 August 2007. Poster. 2007. Abstr. 2166. [P07-09751]. Montagna P, Hornyak M, Ulfberg J, Hong S, Koester J, Crespi G. Pramipexole for the treatment of RLS and associated depressive symptoms. 60th Ann Mtg of the American Academy of Neurology (AAN), Chicago, 12 - 19 Apr 2008 Neurology 2008; 70 (11) (Suppl 1) :A294 [P08-06270] Hornyak M, Montagna P, Ulfberg J, Hong S, Koester J, Crespi G. Treatment of daytime RLS symptoms with pramipexole in patients with mood disturbance. 60th Ann Mtg of the American Academy of Neurology (AAN), Chicago, 12 - 19 Apr 2008 Neurology 2008; 70 (11) (Suppl 1) :A293 [P08-06268] Montagna P, Hornyak M, Ulfberg J, Hong S, Koester J, Crespi G. Rapid onset of action and sustained efficacy of pramipexole in RLS patients with mood disturbance. 60th Ann Mtg of the American Academy of Neurology (AAN), Chicago, 12 - 19 Apr 2008 Neurology 2008; 70 (11) (S uppl 1) :A292 -A293 [P08-06267]
Clinical phase:	IV

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Name of finished product: Sifrol®, Mirapexin®			
Name of active ingredient: Pramipexole		**Page: 2 of 6**	© Boehringer Ingelheim Internationa GmbH This Tabulated Study Report is the property of Boehringer Ingelheim International GmbH and may not - in full or in part - be passed on, reproduced, published or otherwise used without the express permission of Boehringer Ingelheim International GmbH
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Objectives:	The primary objective of this study was to determine the efficacy of pramipexole 0.125 mg to 0.75 mg daily versus placebo on idiopathic Restless Legs Syndrome (RLS) (based on the International Restless Legs Study Group Rating Scale IRLS) and on associated mood disturbances (based on the IRLS item 10) and depressive symptoms (based on the Beck Depression Inventory version II BDI-II). Secondary objectives were the assessment of the effects on the clinical global impressions-global improvement, the IRLS responder rate, depressive symptoms/BDI-II responder rate, pain in limbs, sleep quality and severity of RLS symptoms, anxiety, quality of life, patient global impression, and safety.
Methodology:	Randomised, double-blind, placebo-controlled, multi-centre, parallel-group comparison of patients over an 8-week maintenance period, following a 4-week period of up-titration of pramipexole to a individually optimal dose (0.125 or 0.25 or 0.5 or 0.75 mg/day).
No. of subjects:	
planned:	entered: 360
actual:	enrolled: 498 entered: 404 completed: 336 Pramipexole: entered: 203, treated: 203, analysed (for primary endpoint): 203 Placebo: entered: 201, treated: 200, analysed (for primary endpoint): 199
Diagnosis and main criteria for inclusion:	Out-patients with idiopathic RLS defined by IRLS total score >15, IRLS item-10 score ≥2 and BDI-II total score ≤28 at baseline (exclusion: no intake of dopamine agonists or levodopa within 14 days prior to baseline, no intake of levodopa prior to baseline if augmentation in RLS symptoms was observed, no unsuccessful prior treatment with non-ergot dopamine agonists, no intake of antidepressants within 6 weeks prior to baseline)
Test product:	Pramipexole (Sifrol®, Mirapexin®) 0.25 mg tablets
dose:	0.125 mg/day or 0.25 mg/day or 0.5 mg/day or 0.75 mg/day pramipexole dihydrochloride monohydrate

mode of admin.:	Per os, once daily in the evening (2-3 h before bedtime)
batch no.:	PD-2732
Duration of treatment:	12 weeks
Reference therapy:	Placebo (pramipexole matching tablets)
dose:	Not applicable
mode of admin.:	Oral, once daily in the evening (2-3 h before bedtime)
batch no.:	PD-2733
Criteria for evaluation:	
Efficacy:	Primary endpoint: change from baseline after 12 weeks of treatment in IRLS total score, IRLS item 10 responder rate after 12 weeks of treatment, and change from baseline after 12 weeks of treatment in BDI-II total score. Secondary endpoints: Clinical Global Impressions − Global Improvement (CGI-I) responder rate, IRLS total score responder rate, BDI-II responder rate, Patient Global Impression (PGI) responder rate, IRLS reduced score, RLS-6 item scores, Hospital Anxiety and Depression Scale − Anxiety Subscale (HADS-A) score, Visual Analogue Scale (VAS) score for pain in limbs, RLS-Quality of Life (RLS-QoL) score.
Safety:	Pulse rate, systolic and diastolic blood pressure, adverse event profile.
Statistical methods:	Confirmatory analysis of the mean change from baseline in IRLS total score and BDI-II total score with baseline adjusted analysis of covariance (ANCOVA) and of the IRLS item 10 responder rate with Cochran-Mantel-Haenszel (CMH) test; exploratory analysis of HADS-A score, RLS-6 item scores, VAS score for pain in limbs by stratified Wilcoxon-Mann-Whitney test; CGI-I, PGI, IRLS and BDI-II responder rates by stratified CMH-test, Kaplan-Meier-plots, descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy results:

For this trial, 498 patients were screened, 404 patients (81.1%) were randomised into the study, and 403 patients (80.9%) received at least 1 dose of trial drug, forming the safety population. A total of 67 patients (16.6% of the safety population) discontinued from the study (pramipexole: 12.8%, placebo: 20.5%); the remaining 336 patients (83.4%) completed the study (pramipexole: 177

patients, placebo: 159 patients).

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 (pramipexole: 67.0%, placebo: 73.0%). The mean age (standard deviation, SD) was 55.5 (13.0) years. RLS was diagnosed de-novo in 49.6% of patients (pramipexole: 49.8%, placebo: 49.5%). The mean IRLS total score at baseline was 25.9 (5.2) for pramipexole and 25.9 (5.5) for placebo, the frequency of patients with an IRLS item 10 score of 'moderate' was 57.1% for pramipexole and 53.0% for placebo (severe: 33.0% vs. 37.5%, very severe: 9.4% vs. 8.5%). The mean BDI-II total score at baseline was 14.26 (8.89) for pramipexole patients, and 13.75 (8.14) for placebo patients.

For the primary endpoint, the pramipexole group showed highly significant improvements compared with placebo. After 12 weeks of treatment, the adjusted mean (SE) change in the IRLS total score was −14.2 (0.7) for pramipexole and −8.1 (0.7) for placebo ($p<0.0001$). The IRLS item 10 responder rate was significantly higher in the pramipexole group (75.9%), compared with the placebo group (57.3%) ($p<0.0001$). The adjusted mean (SE) change in the BDI-II total score was −7.3 (0.4) in pramipexole patients and −5.8 (0.5) in placebo patients, the treatment difference in favour of pramipexole was significant ($p=0.0199$).

For the secondary endpoints, the CGI-I responder rate was after 12 weeks of treatment significantly ($p<0.0001$) higher in pramipexole patients (69.3%), compared with placebo patients (36.9%). The IRLS responder rate in pramipexole patients was 59.9% after 12 weeks of treatment, compared with 32.7% in placebo patients ($p<0.0001$). No statistically significant change in the BDI-II responder rate was seen in patients after 12 weeks of treatment. The PGI responder rate after 12 weeks treatment was 62.6% in the pramipexole group, and 33.5% in the placebo group ($p<0.0001$). A significant treatment difference in favour of pramipexole was found for early improvements of patients' condition; after 1 day of treatment, the PGI responder rate was 17.5% in pramipexole patients and 9.7% in placebo patients ($p=0.0163$). A statistically significant treatment effect in favour of pramipexole was found for early effects on the RLS symptoms of patients: after 1 day of treatment, the adjusted mean change in IRLS reduced score change from baseline was −5.7 for pramipexole, and −4.0 for placebo ($p=0.0085$); after 5 days treatment, the change from baseline was −7.0 for pramipexole, and −4.4 for placebo ($p<0.0001$). Significant treatment differences in favour of pramipexole were found for the RLS-6 item scores

	('Satisfaction with sleep during the last 7 nights': p<0.0001, 'Severity of RLS symptoms at falling asleep': p<0.0001, 'Severity of RLS symptoms during the night': p<0.0001, 'Severity of RLS symptoms during the day when at rest': p=0.0162, 'Tired or sleepy during the day within the last 7 days': p=0.0007), except for the 'severity of symptoms during the day when engaged in activities', which was as expected. Significant treatment differences in favour of pramipexole after 12 weeks of treatment were also found for the HADS-A score (p=0.0110), the VAS score for pain in limbs (p<0.0001), and the John Hopkins RLS-QoL score (p<0.0001). In sum, the primary objective of this trial to establish pramipexole as more effective than placebo in the treatment of idiopathic RLS with associated mood disturbances and depressive symptoms based on the change in the IRLS total score, IRLS item 10 score, and the BDI-II total score after 12 weeks of treatment was achieved.
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 26 patients (12.8%), 0.25 mg for 63 patients (31.0%), 0.5 mg for 75 patients (36.9%), and 0.75 mg for 39 patients (19.2%). Placebo patients had a mean (SD) treatment duration of 73.1 (24.8) days, vs. 78.2 (19.1) days in pramipexole patients, but received 143.4 (75.4) tablets vs. 120.2 (64.8) tablets in pramipexole patients. During the treatment period, 227 patients (56.3%) reported at least 1 AE (pramipexole: 61.1%, placebo: 51.5%). The corresponding incidences by pramipexole dose at onset of AE were 31.0% (0.125 mg pramipexole), 26.5% (0.25 mg), 36.1% (0.5 mg), and 42.2% (0.75 mg). The most frequent AEs by preferred term were nausea (pramipexole: 13.8% vs. placebo: 6.5%), headache (pramipexole: 10.3% vs. placebo: 9.5%), and fatigue (pramipexole: 7.9% vs. placebo: 4.0%). The majority of AEs had a worst intensity of mild (pramipexole: 29.1% vs. placebo: 27.5%) or moderate (pramipexole: 28.1% vs. placebo: 21.0%); AEs of severe intensity were reported with similar incidences in either treatment groups (pramipexole: 3.9% vs. placebo: 3.0%). The incidence of severe AEs was highest in the 0.75 mg dose group (6.7% of patients exposed to this dose). Overall, 119 patients reported AEs considered to be drug-related by the investigator (pramipexole: 33.5% vs. placebo: 25.2%). The most frequent drug-related AEs were nausea (pramipexole: 11.3% vs. placebo: 5.0%), fatigue

	(pramipexole: 7.4% vs. placebo: 3.5%), and headache (pramipexole: 4.4% vs. placebo: 4.5%). There was no death reported in the course of this trial. A total of 2 SAEs was reported, in 1 (0.5%) pramipexole patient (chest pain, mild intensity, 0.5 mg pramipexole, not drug-related), and in 1 (0.5%) placebo patient (cholelithiasis, severe intensity, not drug-related). During the study, 9 pramipexole patients (4.4%) and 11 placebo patients (5.5%) reported an AE leading to premature trial discontinuation. The most frequent AEs leading to discontinuation were psychiatric disorders (pramipexole: 2.0% vs. placebo: 1.0%), gastrointestinal disorders (pramipexole: 1.5% vs. placebo: 0.5%), and nervous system disorders (pramipexole: 1.0% vs. placebo: 3.5%). No relevant findings were seen in the analysis of vital signs. In sum, the 12-week treatment with pramipexole was well tolerated and did not raise 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 with associated mood disturbances and depressive symptoms, a 12-week treatment with pramipexole was shown to be highly efficacious compared with placebo regarding RLS symptoms as well as RLS-associated mood disturbances and depressive symptoms. The primary objective of showing the statistical superiority of pramipexole over placebo in the change of the IRLS total score, the IRLS item 10 responder rate, and the BDI-II total score after 12 weeks of treatment was achieved. Overall, the treatment with pramipexole was shown to be safe and well tolerated by patients.