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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Mirapexin®/Sifrol®		**EudraCT No.:** 2005 – 003788 – 22	
Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 01 DEC 2008	**Trial No. / U No.:** 248.596 / U08-2208-01	**Date of trial:** 29 Mar 2006 – 20 May 2008	**Date of revision** (if applicable):

Title of trial:	A randomized, double-blind, placebo-controlled, parallel group, efficacy study of pramipexole and placebo, administered orally over a 12-week treatment phase in Parkinson's disease patients with stable motor function and depressive symptoms
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study (76 sites in 13 countries)
Publication (reference):	Data of this study has not yet been published
Clinical phase:	IV
Objectives:	The primary objective of this study was to investigate the efficacy of pramipexole in daily doses from 0.375 mg to 3.0 mg (0.125 mg to 1.0 mg t.i.d.), compared with placebo, over a 12-week treatment period in Parkinson's disease (PD) patients with stable motor function and depressive symptoms. The secondary objectives included assessment and monitoring of the safety and tolerability of pramipexole versus placebo in patients with PD, and assessment of the impact of pramipexole on PD symptomatology during the study period.
Methodology:	This was a randomized, double-blind, placebo-controlled, parallel-group efficacy study, with a 12-week active treatment phase; maximum 5 weeks of titration-to-response followed by at least 7 weeks of maintenance, a week of down-titration, and a follow-up visit.
No. of subjects:	
planned:	entered: 280
actual:	enrolled: 323 entered: 296
	Placebo: entered: 152 treated: 152 analysed (for primary endpoint): 148
	Pramipexole: entered: 144 treated: 144 analysed (for primary endpoint): 139

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Diagnosis and main criteria for inclusion:	Male and female patients aged 30 years or older at the time of the screening visit, with idiopathic Parkinson's disease diagnosed according to UK Brain Bank criteria, with a modified Hoehn and Yahr scale stage of I to III and a Mini-Mental State Examination (MMSE) score ≥24, with the ability to provide written informed consent in accordance with Good Clinical Practice and local legislation. At baseline visit, patients had to have depressive symptoms expressed by a Geriatric Depression Scale (GDS) score ≥5, and Unified PD Rating Scale (UPDRS) Part I Score ≥2 on Question No. 3. Patients had to have stable motor function and/or treatment with levodopa / DOPA decarboxylase inhibitors (either carbidopa or benserazide) or with a combination of levodopa and catechol-*o*-methyltransferase inhibitors at an optimized dose, according the investigator's judgment, this dose being stable for at least 4 weeks prior to baseline and during the treatment phase. Patients must not have received dopamine agonists during the 30 days before baseline visit. Patients with severe depression or suicidal ideation were excluded from the study.	
Test product:	Pramipexole dihydrochloride (Sifrol® / Mirapexin®)	
dose:	A daily dose of 0.125 mg t.i.d.; titration -to-response up to 1.0 mg t.i.d.	
mode of admin.:	Oral	
batch no.:	Pramipexole 0.125 mg Pramipexole 0.25 mg Pramipexole 0.5 mg Pramipexole 1.0 mg	507861 506929 506932 506935
Reference therapy:	Placebo (matching) tablets	
dose:	Not applicable	
mode of admin.:	Oral	
batch no.:	Placebo for pramipexole 0.125 mg Placebo for pramipexole 0.25 mg Placebo for pramipexole 0.5 mg Placebo for pramipexole 1.0 mg	506625 506626 506628 506629

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Duration of treatment:	12 weeks (5 weeks of titration-to-response; 7 weeks of maintenance) + 1 week down-titration
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary efficacy criteria: • Change in depressive symptomatology, defined as the change in total Beck Depression Inventory (BDI) score from baseline (BDI version 1A) Secondary efficacy criteria: • BDI 50% reduction in baseline symptoms • Change from baseline in GDS (15-item version) • Change from baseline in Snaith-Hamilton Pleasure Scale (SHAPS) total score • Change from baseline in UPDRS parts I, II, III and IV • Clinical Global Impression of Improvement (CGI-I) • Change from baseline in Visual Analogue Scale (VAS) for general pain • Change from baseline in Quality of life scales – PDQ-39, and EQ-5D
Safety:	Safety parameters that were assessed included medical examination, vital signs (blood pressure and pulse rate, both supine and standing), clinical laboratory parameters, occurrence and intensity of adverse events.
Statistical methods:	For the analysis of the primary efficacy endpoint analysis of covariance with treatment and country as main effects and baseline as a covariate was used. For the analysis of the secondary efficacy endpoints analysis of covariance, logistic regression, stratified Wilcoxon-Mann-Whitney rank tests and other appropriate statistical methodology were used. A path analysis was employed to disentangle the specific effect of treatment on depressive symptoms from the control of PD motor symptoms.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Of the 296 randomised patients, 13.2% prematurely discontinued the trial during the titration/maintenance treatment phase (placebo: 12.5%, pramipexole: 13.9%). Of the randomised population 99.0% of the patients were white; the proportion of male patients was 47.3% and the mean age was 67.0 years.

Baseline mean total scores for BDI were 19.5 (placebo) and 18.7 (pramipexole); for GDS 9.2 (placebo) and 8.4 (pramipexole); for UPDRS part II 11.6 (placebo), and 11.8 (pramipexole); and for UPDRS part III 24.9 (placebo) and 26.3 (pramipexole). The treatment groups were generally well matched for demographic and baseline parameters. The proportion of patients below 65 years of age was somewhat smaller for the pramipexole group (31.3%) than for the placebo group (40.8%), but mean age was very similar for the 2 groups. The proportion of males was somewhat smaller for the pramipexole group (43.1%) than for the placebo group (51.3%).

The full analysis set (FAS) consisted of 287 patients. The per-protocol set consisted (PPS) consisted of 242 patients.

The primary analysis (performed on the FAS) demonstrated superiority of pramipexole over placebo. Mean changes from baseline in BDI total scores (adjusted for pooled country and baseline BDI score) were −4.0 (placebo) and −5.9 (pramipexole). The treatment difference (95% CI) of −1.9 (−3.4, −0.5) was statistically significant (p = 0.0103). These results were confirmed by the PPS analysis.

Most of the analyses of the key secondary efficacy endpoints supported the primary analysis. BDI clinical response (≥50%) rates were 18.4% (placebo) and 27.3% (pramipexole). The treatment group odds ratio adjusted for pooled country and baseline BDI score was 1.76 (95% CI: 0.99, 3.12), i.e., the odds of a BDI response for pramipexole were 1.76 times as large as the odds of a response for placebo. This was on the borderline of statistical significance (p = 0.0535). Adjusted mean changes in GDS total scores were −1.7 (placebo) and −2.5 (pramipexole). The treatment difference of −0.8 (95% CI: −1.5, −0.1) had a p-value of 0.0346.

Adjusted mean changes in UPDRS Part II (activities of daily living) total scores

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were −1.2 (placebo) and −2.4 (pramipexole). The treatment difference of −1.2 (95% CI: −1.9, −0.4) had a p-value of 0.0030. Adjusted mean changes in UPDRS Part III (motor) total score were −2.2 (placebo) and −4.4 (pramipexole). The treatment difference of −2.2 (95% CI: −3.7, −0.7) had a p-value of 0.0034. Adjusted mean changes in UPDRS Parts II + III total scores were −3.4 (placebo) and −6.8 (pramipexole). The treatment difference of −3.4 (95% CI: −5.4, −1.5) had a p-value of 0.0007.

For the CGI-I scores an adjusted odds ratio of 1.82 (95% CI: 1.19, 2.79) was observed, meaning the odds of having a better CGI-I score on pramipexole were 1.82 times as large as the odds on placebo, with a p-value of 0.0060.

Differences between the treatment groups for the SHAPS total score and the UPDRS Part I depression score were small, but in favour of pramipexole.

Some of the analyses of the other secondary endpoints supported the primary analysis. The PDQ-39 activities of daily living domain difference in the median changes of −4.2 (95% CI: −8.3, 0.0) had a p-value of 0.0078. Similarly, for the mobility domain difference of −2.5 (95% CI: −5.0, 0.0) a p-value of 0.0804 was observed. An improvement in the EQ-5D overall index score of 0% (placebo) and 7% (pramipexole) was observed, with a difference in the median changes of 4% (95% CI: 0%, 9%) and a p-value of 0.0337.

Differences between the treatment groups for the other secondary endpoints were small but in favour of pramipexole (except the cognitive impairment domain of the PDQ-39).

The analyses performed on the primary efficacy endpoint to investigate whether effects observed on depressive symptoms were related in anyway to the simultaneous control of PD motor symptoms on the whole suggested only a small relationship between the two. The path analysis showed that the total effect of treatment on depressive symptoms was 80% due to the direct effect of treatment on changes in the BDI total score (p = 0.0433) and 20% due to the indirect effect of treatment on changes in the UPDRS Part III total score.

Safety results:

The analysis of safety included all 296 patients who received at least one dose of study medication (placebo or pramipexole. A total of 144 patients received at least 1 dose of pramipexole during the titration and maintenance phase. A total of 152 patients received at least 1 dose of placebo. The mean exposure at the end

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of the maintenance phase was 74.5 days for pramipexole and 76.2 days for placebo.

During the course of the trial, 206 patients (69.6% of the treated set) experienced at least 1 adverse event (AE). Of the 144 patients on treatment with pramipexole, 105 patients (72.9%) experienced an AE, versus 101 patients (66.4% of 152 patients) in the placebo group. Most of the AEs were considered of mild or moderate intensity. AEs of severe intensity were observed in 12 patients (8.3%) in the pramipexole treatment group, and in 6 patients (3.9%) in the placebo treatment group. Drug-related AEs as defined by the investigator, occurred in 73 patients (50.7%) in the pramipexole treatment group, and in the 63 patients (41.4%) in the placebo treatment group. The number of patients who experienced AEs leading to discontinuation of the trial drug was lower in the pramipexole group (6.9%) than in the placebo group (10.5%).

The most frequently reported AE in this trial was nausea (16.7% of patients on pramipexole treatment; 17.1% of patients on placebo treatment), followed by headache (11.1% pramipexole; 7.9% placebo), dizziness (11.1% pramipexole; 5.9% placebo) and somnolence (10.4% pramipexole; 7.9% placebo). Overall, the main system organ classes affected were those classified as nervous system disorders (38.9% pramipexole; 28.9% placebo), gastrointestinal disorders (28.5% pramipexole; 30.9% placebo), and psychiatric disorders (18.8% pramipexole; 13.8% placebo).

There was no trend in the incidence of treatment-emergent adverse events during the maintenance phase within the pramipexole group with regard to the dose of pramipexole at the time of AE onset.

There were no deaths during the course of the trial. However, 1 patient died due to a myocardial infarction 6 months after having completed the study. During this patient's participation in this study, he had been assigned to treatment with pramipexole. The incidence of SAEs was similar in both treatment groups: 6 patients (4.2%) in the pramipexole group and 6 patients (3.9%) in the placebo group. Other significant adverse events (according to ICH E3) were reported in 29 patients (20.1%) treated with pramipexole and 27 patients (17.8%) treated with placebo.

The majority of the patients had stable vital signs throughout the study.

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Conclusions:

In summary, pramipexole demonstrated statistically significant superiority ($p = 0.0103$) over placebo in terms of mean treatment difference for improvement from baseline in BDI (1A) total scores of −1.9 (95% CI: −3.4, −0.5). The total effect of treatment on depressive symptoms was 80% due to the direct effect of treatment on changes in the BDI total score ($p = 0.0433$) and 20% due to the indirect effect of treatment on changes in the UPDRS Part III total score. Therefore, the beneficial effect of pramipexole on the non-motor symptoms of depression in PD patients was found to be direct and unrelated to the beneficial effects of pramipexole on motor function. In the analysis of safety, the data obtained were generally consistent with the known safety profile of pramipexole.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for secondary endpoints of the trial. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
UPDRS I change from baseline to end of maintenance phase	Table 15.2.4: 6
UPDRS IV change from baseline to end of maintenance phase	Table 15.2.4: 15
SHAPS change from baseline to end of maintenance phase	Table 15.2.3: 2
VAS change from baseline to end of maintenance phase	Table 15.2.8: 2

Table 15.2.4: 6 Analysis of change from baseline to end of maintenance phase in UPDRS Part I total score - full analysis set

UPDRS part I total score	Placebo (N=148)#	Pramipexole (N=139)#
Baseline		
Mean (SE)	5.2 (0.1)	4.8 (0.1)
End of main		
Adjusted mean* (SE)	3.6 (0.1)	3.4 (0.2)
Change to end of main		
Adjusted mean* (SE)	-1.4 (0.1)	-1.6 (0.2)
Difference to Placebo		
Adjusted mean* (SE)		-0.2 (0.2)
95% confidence interval		(-0.6, 0.2)
p-value		0.2824

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and pooled country effect

Table 15.2.4: 15 Analysis of change from baseline to end of maintenance phase in UPDRS Part IV total score - full analysis set

UPDRS part IV total score	Placebo (N=137)#	Pramipexole (N=131)#
Baseline		
Mean (SE)	2.2 (0.2)	2.2 (0.2)
End of main		
Adjusted mean* (SE)	2.0 (0.1)	1.9 (0.1)
Change to end of main		
Adjusted mean* (SE)	-0.2 (0.1)	-0.3 (0.1)
Difference to Placebo		
Adjusted mean* (SE)		-0.1 (0.2)
95% confidence interval		(-0.5, 0.2)
p-value		0.5231

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and pooled country effect

Table 15.2.3: 2 Analysis of change from baseline to end of maintenance phase in SHAPS total score - full analysis set

SHAPS total score	Placebo (N=148)#	Pramipexole (N=139)#
Baseline		
Median	1.0	2.0
(Q1, Q3)	(0.0, 4.0)	(1.0, 3.0)
End of main		
Median	1.0	1.0
(Q1, Q3)	(0.0, 3.0)	(0.0, 3.0)
Change to end of main		
Median	0.0	0.0
(Q1, Q3)	(-2.0, 0.0)	(-2.0, 0.0)
Comparison to Placebo		
p-value*		0.5244
Shift in location**		0.0
95% confidence interval***		(-1.0, 0.0)

\# - N's exclude patients from the analysis set with incomplete data
* - Stratified for pooled country Wilcoxon rank sum test (Van Elteren's test)
** - Hodges-Lehmann estimate of difference in medians
*** - Distribution-free CI (Moses)

Table 15.2.8: 2 Analysis of change from baseline to end of maintenance phase in VAS pain score - full analysis set

VAS pain score	Placebo (N=148)#	Pramipexole (N=139)#
Baseline		
Mean (SE)	34.9 (1.9)	31.4 (2.1)
End of main		
Adjusted mean* (SE)	30.2 (1.8)	29.7 (1.9)
Change to end of main		
Adjusted mean* (SE)	-3.0 (1.8)	-3.5 (1.9)
Difference to Placebo		
Adjusted mean* (SE)		-0.5 (2.6)
95% confidence interval		(-5.6, 4.6)
p-value		0.8471

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and pooled country effect