Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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: Pramipexole extended release (ER)		**EudraCT No.:** 2007-000074-23		
Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 1 of 10	**Number:**	**Synopsis No.:**
Ref. to Documentation:	**Module:**	**Volume:**		
Report date: 25 MAR 2009	**Trial No. / U No.:** 248.525 / U09-1270-04	**Date of trial:** 09 MAY 2007 – 19 NOV 2008		**Date of revision:** 09 July 2009

Title of trial:	A double-blind, double-dummy, placebo-controlled, randomized, three parallel groups study comparing the Efficacy, Safety and Tolerability of Pramipexole ER *versus* placebo and *versus* Pramipexole IR administered orally over a 26-week maintenance phase in L-Dopa^{+} treated patients with advanced Parkinson's disease (PD)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multinational and multicentre study (14 countries, 76 active sites), cf. Appendix 16.1.4
Publication (reference):	Data of this study has not been published
Clinical phase:	IIIa
Objectives:	To determine the efficacy, safety and tolerability of pramipexole ER compared with placebo in L-Dopa^{+} treated patients with advanced PD. The final confirmatory analysis of this trial, initially planned at week 33, was finally conducted at week 18, as agreed with Health Authorities and implemented by the amendment N° 5 (dated 8. May 2008) to the protocol. In addition, a numerical comparison of the efficacy of pramipexole ER versus pramipexole IR was done.
Methodology:	A double-blind, double-dummy, placebo-controlled, randomised, parallel group design; prospective comparison of three groups over up to 33 weeks.
No. of subjects:	
planned:	Enrolled: 645 and entered: 516

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actual:	618 enrolled, 518 entered, 517 treated and 507 analysed (for primary endpoint) Pramipexole ER: entered: 165 treated: 164; analysed (for primary endpoint): 161 Pramipexole IR: entered: 175 treated: 175; analysed (for primary endpoint): 172 Placebo: entered: 178 treated: 178; analysed (for primary endpoint): 174
Diagnosis and main criteria for inclusion:	Male or female patients, with idiopathic PD diagnosed for at least 2 years, 30 years of age or older at time of diagnosis, with a modified Hoehn and Yahr scale of 2 to 4 at on-time. Patients should have been treated with L-Dopa$^+$ (i.e. standard and/or controlled release Levodopa/DDC inhibitor), or with a combination of L-Dopa$^+$ and entacapone, at an optimized dose according to the investigator's judgement, this dose being stable for at least 4 weeks prior to baseline. They should have had motor fluctuations (at least 2 cumulative hours of off-time every day during waking hours, documented on a patient diary completed for 2 consecutive days before baseline visit). Patients should not have been treated with dopamine agonists within 4 weeks prior to baseline. A concomitant treatment with one or more of the following drugs was allowed (at a stable dose for at least 4 weeks prior to baseline and the investigator did not intent to change this treatment during the treatment phase): - anti-parkinsonian anticholinergics; - selegiline, rasagiline, or other MAO-B-Inhibitor; - amantadine; - entacapone (or other COMT-Inhibitor); - beta-blockers (e.g. propranolol) when used to treat PD. A previous treatment with pramipexole IR was allowed, provided the treatment had not been discontinued due to a serious/clinically significant drug related adverse event, according to investigator's judgement.
Test product:	Pramipexole ER (tablets of 0.375mg, 0.75mg, 1.5mg, 3.0mg or 4.5mg)
dose:	0.375 mg, 0.75mg, 1.5mg, 2.25mg, 3.0mg, 3.75mg, or 4.5mg
mode of admin.:	Per os, once a day, in the morning

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batch no.:	Please refer to Appendix 16.1.6
Reference therapy:	- Pramipexole IR (tablets of 0.125mg, 0.25mg, 0.5mg, 1.0mg and 1.5mg) - Placebo tablets matching the Pramipexole ER tablets - Placebo tablets matching the Pramipexole IR tablets
dose:	0.375mg, 0.75mg, 1.5mg, 2.25mg, 3.0mg, 3.75mg, or 4.5mg
mode of admin.:	Per os, in equally divided doses 3 times per day (for IR verum and IR placebo) Per os, once a day, in the morning (for PPX ER placebo)
batch no.:	Please refer to Appendix 16.1.6
Duration of treatment:	Seven-week flexible up-titration, followed by an up to 26-week maintenance phase. At the end of the double-blind maintenance treatment phase, patients could be eligible to enter an open-label extension study. Patients not entering the open-label extension study performed an additional 1-week down-titration phase.
Criteria for evaluation:	

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Efficacy / clinical pharmacology:

Primary efficacy criterion:

- UPDRS (Unified Parkinson's Disease Rating Scale) parts II+III score (change from baseline to week 18 (confirmatory analysis) and to week 33 (descriptive analysis)).

Key secondary efficacy criterion (to be assessed at week 18 (confirmatory analysis) and at week 33 (descriptive analysis)):

- Percentage off-time during waking hours – diary based (change from baseline);

Other secondary efficacy criteria (to be assessed at week 18 and at week 33):

- Proportion of patients with at least a 20% improvement relative to baseline in the percentage off-time during waking hours – diary based;
- Percentage on-time: without dyskinesia; with non-troublesome dyskinesia; without dyskinesia or with non-troublesome dyskinesia; with troublesome dyskinesia; during waking hours – diary based (change from baseline);
- Responder rate for Clinical Global Impression of Improvement (CGI-I);
- Responder rate for Patient Global Impression of Improvement (PGI-I);
- Responder rate for Patient Global Impression of Improvement (PGI-I) for early morning off-symptoms (as added in amendment 1, dated 18 April 2007);
- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score;
- UPDRS I, II, III and IV scores separately (change from baseline);
- BDI (Beck's Depression Inventory) version IA (change from baseline);
- PDSS (Parkinson's Disease Sleep Scale) total score (change from baseline);
- 11-point Likert scale for pain related to PD (change from baseline);
- Quality of life scales: PDQ-39 (Parkinson Disease Questionnaire-39 items) and EQ-5D (EuroQoL) (change from baseline);
- L-Dopa daily dose (change from baseline);
- Cost-effectiveness analysis was conducted to compare treatments, the results will be reported separately.

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Safety:	Incidence of Adverse Events, proportion of withdrawals due to Adverse Events, vital signs (blood pressure and pulse rate), weight, Epworth Sleepiness Scale (ESS), Parkinson's Disease Sleep Scale (PDSS) question 15, modified Minnesota Impulsive Disorders Interview (mMIDI), safety laboratory parameters.
Statistical methods:	**Primary analysis:** ANCOVA analysis for change from baseline to week 18 (visit 8) in the UPDRS II+III total score, adjusting for pooled country and baseline (covariate). The primary analysis was based on the Full Analysis Set (FAS) using the LOCF (Last Observation Carried Forward) approach for the comparison of pramipexole ER vs. placebo. The Per Protocol Set (PPS) was used for sensitivity analysis. Furthermore, a mixed model repeated measurement (MMRM) sensitivity analysis was performed with use of all maintenance visits on drug. **Secondary analyses:** The percentage off-time during waking hours (key secondary endpoint) was tested using an ANCOVA model. ANCOVA analysis or non-parametric treatment group comparisons were used as appropriate for the other secondary efficacy endpoints. The secondary analyses were based on the FAS (using LOCF). The study was not powered for an inferential comparison of the active treatment groups, but pramipexole IR was added for sensitivity and orientation (mean maintenance doses, effect on various endpoints, to be presented by 95% confidence intervals). Descriptive statistical methods were used for the analysis of safety endpoints. An unblinded interim safety analysis was done to support a submission to Health Authorities (with a cut-off date end of May 2008). Only descriptive methods were used for the analysis of the safety endpoints. This interim unblinded analysis was performed by an independent Contract Research Organization (CRO), no results were disseminated to persons directly involved in performing the trial.

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Sample size calculation:

The sample size required to show superiority of pramipexole ER over placebo was 172, with an expected mean difference of 5 points between pramipexole ER and placebo in the change from baseline in UPDRS II+III total score with a 90% power, assuming a within-group standard deviation of 14 points and testing at the one-sided alpha level of 0.025.

Analogously the comparison of pramipexole IR and placebo required 172 patients, resulting in a total number of 516 patients (added for early drop-outs without post-baseline efficacy assessments: 3.5%).

In addition, with a treatment group size of 172 patients, it was possible to detect an expected mean difference of 1 hour between pramipexole ER and placebo in the change from baseline in the absolute number of off-time during waking hours with 86% power, assuming a within-group standard deviation of 3 hours and testing at the one-sided alpha-level of 0.025.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

<u>Week 18 confirmatory analysis (FAS 1, PPS 1):</u>

Five hundred and seven (507) patients were included in the FAS 1 (LOCF) analysis (18 weeks of treatment).

<u>Primary endpoint</u>

In FAS 1 with the (LOCF) approach, treatment for 18 weeks with both PPX ER and PPX IR was statistically superior to placebo, as measured by the UPDRS Part II+III total score. The placebo-corrected effect was -4.9 points for PPX ER and -6.7 points for PPX IR. The differences in improvement in UPDRS Part II+III total score were statistically significant for the difference between PPX ER and placebo (ANCOVA, $p=0.0001$) and for the difference between PPX IR and placebo (ANCOVA, $p<0.0001$).

The Per Protocol Set (PPS) 1 Observed Case (OC) analysis and the (PPS 1) endpoint analysis confirmed superiority of both PPX ER and PPX IR over placebo.

The results of the 2 PPX formulations were comparable in all analyses.

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Key secondary endpoint

In FAS 1 (LOCF) and PPS 1 analyses, superiority of PPX ER and PPX IR over placebo after 18 weeks of treatment was also established for percentage off-time during waking hours.

Other secondary endpoints

In FAS 1 (LOCF), the differences between the PPX ER group and the placebo group were statistically significant for UPDRS Part II+III responder rate, percent on-time without dyskinesia or with non troublesome dyskinesia (i.e. "good on time"), CGI-I response rate, PGI-I response rate for early morning off-symptoms, UPDRS Part II score at off-period, UPDRS Part II total score (average at on and off-period) and UPDRS Part III score.

Due to the low baseline scores on the scales evaluating these symptoms, no statistically significant treatment effect could be observed on the non-motor symptoms of PD.

Week 33 descriptive analysis (FAS 2)

Three hundred and eighty five (385) patients were included in the FAS 2 analysis. Out of them, 308 patients were not prematurely withdrawn before week 33 (i.e. completer patients). Maintenance of efficacy at week 33 was assessed in the sub-group of 308 completers (FAS 2 (OC) analysis).

Primary endpoint

In FAS 2 (OC), in the PPX ER group, the change from baseline to week 33 in the UPDRS II+III score was -14.2 points, while the change from baseline to week 18 was -15.0 points. In the PPX IR group, the change from baseline to week 33 was -13.4 points, while the change from baseline to week 18 was -14.9 points. Therefore, maintenance of the effect was confirmed on the UPDRS II+III score in both PPX groups, in the FAS 2 (OC) analysis.

Key secondary endpoints

Maintenance of effect was also confirmed on the percentage off-time during waking hours in both PPX groups, in the FAS 2 (OC) analysis.

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Safety results:

The overall safety profile showed that PPX was safe and well tolerated.

Safety analysis at week 18 (TS 1 population)

The proportions of patients experiencing any AE, regardless of relationship to treatment, were slightly higher in the PPX IR group (64.0%) than in the placebo group (55.6%) and in the PPX ER group (54.9%). The System Organ Class (SOC) in which AEs were most frequently reported was nervous system disorders (placebo: 32.0%, PPX ER: 36.6%, PPX IR: 41.7%), followed by gastrointestinal disorders and psychiatric disorders. In the psychiatric disorders and in the nervous system disorders SOC, a higher proportion of PPX patients reported AEs compared to placebo (for psychiatric disorders - PPX ER: 18.9%, PPX IR: 17.7%, placebo: 9.0% and for nervous system disorders - PPX ER: 36.6%, PPX IR: 41.7%, and placebo: 32.0%). In the SOC 'nervous system disorders', AEs were reported more frequently (≥5% difference) with PPX IR compared to PPX ER (41.7% versus 36.6%, respectively). There was no SOC in which the PPX ER group had more reported AE than the PPX IR group (≥5% difference). The most frequent AEs with PPX ER (more than 5% and more frequent than with placebo) were (by decreasing frequency): dyskinesia, nausea, headache, constipation and hallucination.

Overall, the incidence of AEs was slightly lower in the PPX ER than in the IR group. Dizziness and vomiting were more frequently reported in the PPX IR group compared to the PPX ER group, while anorexia was more frequently reported in the PPX ER (≥3% difference).
The proportions of patients with SAEs were low in all treatment groups: 3.4% patients in the placebo group, 3.0% patients in the PPX ER group, and 4.0% patients in the PPX IR group. None of the SAEs had a fatal outcome. Eight patients experienced SAEs considered to be drug-related (4 patients in each PPX group).

A smaller proportion of patients experienced drug related AEs in the placebo group (34.8%) and the PPX ER group (37.8%), compared to the PPX IR group (44.6%). The proportion of patients who experienced AEs leading to premature discontinuation was similar in the 3 treatment groups: the lowest percentage was recorded in the placebo group (3.9%), followed by PPX IR (4.6%) and the PPX ER group (4.9%).

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The proportion of patients with severe AEs was low, without any relevant differences between the pooled PPX groups and the placebo group or between the 2 PPX groups.

No significant changes were observed in the other safety parameters (including the laboratory parameters and the vital signs).

Safety analysis independent of treatment duration (TS 3 population)

As seen in patients treated for up to 18 weeks, a higher proportion of patients in the PPX IR group (70.3%) experienced AEs, compared to PPX ER (61.0%) and placebo (61.2%). Similarly to patients treated for up to 18 weeks, the SOC in which AEs were most frequently reported was nervous system disorders, followed by gastrointestinal disorders and psychiatric disorders.

The most frequent AEs with PPX ER (more than 5% and more frequent than with placebo) were (by decreasing frequency): dyskinesia, nausea, headache, constipation, anorexia, hallucination, insomnia and dizziness.

The proportion of patients reporting SAEs was similar to data in patients treated for up to 18 weeks. Fifteen patients (8.4%) in the placebo group, 8 patients (4.9%) in the PPX ER group, and 11 patients (6.3%) in the PPX IR group experienced at least one SAE. One not drug-related SAE reported in the PPX IR group had a fatal outcome.

As seen in patients treated for up to 18 weeks, a higher proportion of patients in the PPX IR group (48.0%) experienced drug related AEs, compared to PPX ER (40.2%) and placebo (36.0%).

In both PPX groups, the percentage of patients who experienced AEs leading to premature discontinuation was slightly higher (5.5% for PPX ER and 5.1% for PPX IR) than in patients treated for up to 18 weeks.

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Conclusions:

Three PPX ER patients had a positive mMIDI, 2 patients (1.2%) reported compulsive sexual behaviour and one (0.6%) reported compulsive buying. Two PPX IR patients (1.1%) had a positive mMIDI on pathological gambling. One (0.6%) placebo patient had a positive mMIDI for compulsive buying. Other abnormal behaviours or urges, or AE qualifying for an abnormal behaviour, were reported by 6 PPX ER patients (3.7%), 4 PPX IR patients (2.3%) and one placebo patient (0.6%).

Four patients experienced SOOS (0.6% in placebo, 0.6% in PPX ER, and 1.1% in PPX IR). One patient (0.6%) in the placebo group, one patient (0.6%) in the PPX ER group and 3 patients (1.7%) in the pramipexole IR group experienced a symptomatic treatment emergent orthostatic hypotension during a study visit assessment. In addition to the study visit assessments, 2 placebo patients (1.1%), 3 PPX ER patients (1.8%) and 3 PPX IR patients (1.7%) experienced an AE of orthostatic hypotension.

All treatment groups had a slight improvement in PDSS score.

There were no findings for the other safety variables, such as laboratory evaluation and vital signs.

In summary, superiority of PPX ER over placebo in advanced PD patients was demonstrated after 18 weeks of treatment (TS 1), for the primary and the key secondary efficacy endpoints. Maintenance of efficacy was shown descriptively at week 33 in both pramipexole groups. There was no clinically relevant difference in terms of efficacy between the two pramipexole formulations.
The overall safety profile showed that both PPX ER and PPX IR, in the dose range of 0.375 to 4.5mg daily, were safe and well tolerated by patients with advanced PD.
These results were observed at comparable mean daily dose and duration of treatment for both pramipexole formulations.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for primary and 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 II+III, 18 Weeks	Table 15.2.1.2: 1
Percentage Off-time during Waking Hours, 18 Weeks	Table 15.2.2.1.1: 1
Percentage On-time without Dyskinesia during Waking Hours, 18 Weeks	Table 15.2.2.2.1: 1
Percentage On-time with Non-troublesome Dyskinesia during Waking Hours, 18 Weeks	Table 15.2.2.3.1: 1
Percentage On-time with Troublesome Dyskinesia during Waking Hours, 18 Weeks	Table 15.2.2.5.1: 1
UPDRS I Total Score, 18 Weeks	Table 15.2.2.9.1: 1
UPDRS II Total Score (Average of On and Off Periods), 18 Weeks	Table 15.2.2.10.3.1: 1
UPDRS III Total Score, 18 Weeks	Table 15.2.2.11.1: 1
UPDRS IV Total Score, 18 Weeks	Table 15.2.2.12.1: 1
Patient Disposition	Table 15.1.1.3: 1

Table 15.2.1.2: 1 UPDRS II+III , 18 weeks treatment,
PPS1 (OC)

Primary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS II+III total score Number of patients	153	140	157		
Baseline, Mean (SD)	40.1 (17.8)	41.4 (17.5)	40.6 (17.6)		
Week 18, Mean (SD)	32.8 (16.9)	28.2 (16.5)	26.9 (16.7)		
LS Mean Change (SE) - ANCOVA*	-6.7 (1.0)	-12.0 (1.0)	-13.0 (1.0)	<.0001	<.0001
LS Mean Change (SE) - MMRM**	-6.7 (0.8)	-11.9 (0.9)	-12.6 (0.8)	<.0001	<.0001

Negative change implies improvement
* ANCOVA and MMRM with factors treatment and pooled country and covariate baseline
** LS means per treatment group over visits 6 7 8 9 10 and 11 (maintenance)

Table 15.2.2.1.1: 1 Percentage off time during waking hours, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% off time during waking hours					
Number of patients	174	160	171		
Baseline, Mean (SD)	38.7 (15.6)	36.3 (15.8)	37.8 (13.1)		
Week 18, Mean (SD)	29.6 (19.5)	24.1 (17.8)	22.3 (16.4)		
LS Mean Change (SE) - ANCOVA*	-8.8 (1.3)	-13.3 (1.4)	-15.9 (1.3)	0.0122	<.0001
LS Mean Change (SE) - MMRM**	-8.5 (1.1)	-13.9 (1.1)	-15.7 (1.1)	0.0004	<.0001

Negative change implies improvement
* ANCOVA with factors treatment and pooled country and covariate baseline
** LS means per treatment group over visits 6 7 and 8 (maintenance)

Table 15.2.2.2.1: 1 Percentage on time without dyskinesia during waking hours, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on without dyskinesia Number of patients	174	160	171		
Baseline, Mean (SD)	50.5 (22.2)	53.0 (19.2)	52.8 (17.3)		
Week 18, Mean (SD)	60.0 (23.8)	64.8 (24.8)	65.2 (23.9)		
LS Mean Change (SE) - ANCOVA*	8.9 (1.6)	11.9 (1.7)	12.6 (1.7)	0.1811	0.0904
LS Mean Change (SE) - MMRM**	8.1 (1.4)	12.5 (1.5)	12.5 (1.4)	0.0217	0.0185

Positive change implies improvement
* ANCOVA with factors treatment and pooled country and covariate baseline
** LS means per treatment group over visits 6 7 and 8 (maintenance)

Table 15.2.2.3.1: 1 Percentage on time with non troublesome dyskinesia during waking hours, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on with non troublesome dyskinesia					
Number of patients	174	160	171		
Baseline, Mean (SD)	8.1 (15.5)	7.6 (13.9)	6.8 (12.5)		
Week 18, Mean (SD)	8.7 (17.1)	9.2 (16.6)	10.6 (18.1)		
LS Mean Change (SE) - ANCOVA*	1.0 (1.2)	1.9 (1.2)	3.9 (1.2)	0.5737	0.0678
LS Mean Change (SE) - MMRM**	1.4 (1.0)	1.9 (1.0)	3.4 (1.0)	0.7398	0.1259

Positive change implies improvement
* ANCOVA with factors treatment and pooled country and covariate baseline
** LS means per treatment group over visits 6 7 and 8 (maintenance)

Table 15.2.2.5.1: 1 Percentage on time with troublesome dyskinesia during waking hours, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on with troublesome dyskinesia					
Number of patients	174	160	171		
Baseline, Mean (SD)	2.7 (9.3)	3.1 (7.1)	2.5 (7.2)		
Week 18, Mean (SD)	1.6 (6.4)	2.0 (7.1)	1.8 (6.6)		
LS Mean Change (SE) - ANCOVA*	-1.0 (0.5)	-0.8 (0.5)	-0.8 (0.5)	0.7490	0.7603
LS Mean Change (SE) - MMRM**	-0.8 (0.5)	-0.7 (0.5)	-0.3 (0.5)	0.8028	0.3549

Negative change implies improvement
* ANCOVA with factors treatment and pooled country and covariate baseline
** LS means per treatment group over visits 6 7 and 8 (maintenance)

Table 15.2.2.9.1: 1 UPDRS I total score, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS I score total				Wilcoxon	Wilcoxon
Number of patients	174	161	172		
Baseline, Median (IQR)	1.0 (3.0)	2.0 (2.0)	1.0 (3.0)		
[Q1 - Q3]	[0.0- 3.0]	[1.0- 3.0]	[0.0- 3.0]		
Week 18, Median (IQR)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)		
[Q1 - Q3]	[0.0- 2.0]	[0.0- 2.0]	[0.0- 2.0]		
Change from Baseline, Median (IQR)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.1492	0.9722
[Q1 - Q3]	[-1.0- 0.0]	[-1.0- 0.0]	[-1.0- 0.0]		

Negative change implies improvement

Table 15.2.2.10.3.1: 1 UPDRS II total score, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS II total score Number of patients	174	161	172		
Baseline, Mean (SD)	11.9 (6.1)	12.8 (6.5)	12.3 (5.6)		
Week 18, Mean (SD)	9.8 (6.0)	9.6 (6.0)	8.4 (5.2)		
LS Mean Change (SE) - ANCOVA*	-1.9 (0.3)	-2.8 (0.3)	-3.6 (0.3)	0.0455	<.0001
LS Mean Change (SE) - MMRM**	-1.9 (0.3)	-2.8 (0.3)	-3.6 (0.3)	0.0125	<.0001

Negative change implies improvement
* ANCOVA and MMRM with factors treatment and pooled country and covariate baseline

Table 15.2.2.11.1: 1 UPDRS III total score, 18 weeks treatment, FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS III total score Number of patients	174	161	172		
Baseline, Mean (SD)	28.1 (13.4)	29.0 (12.7)	28.5 (13.2)		
Week 18, Mean (SD)	23.4 (12.9)	20.0 (12.4)	18.8 (12.3)		
LS Mean Change (SE) - ANCOVA*	-4.3 (0.7)	-8.3 (0.7)	-9.2 (0.7)	<.0001	<.0001
LS Mean Change (SE) - MMRM**	-4.6 (0.6)	-8.6 (0.7)	-9.0 (0.6)	<.0001	<.0001

Negative change implies improvement
* ANCOVA and MMRM with factors treatment and pooled country and covariate baseline

Table 15.2.2.12.1: 1 UPDRS IV total score, 18 weeks treatment,
FAS1 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS IV total score Number of patients	174	161	172		
Baseline, Mean (SD)	5.1 (2.5)	5.1 (2.5)	5.1 (2.7)		
Week 18, Mean (SD)	4.5 (2.4)	4.2 (2.4)	4.2 (2.7)		
LS Mean Change (SE) - ANCOVA*	-0.6 (0.2)	-0.8 (0.2)	-0.9 (0.2)	0.2768	0.1752
LS Mean Change (SE) - MMRM**	-0.6 (0.1)	-0.9 (0.1)	-0.8 (0.1)	0.0363	0.1704

Negative change implies improvement
* ANCOVA and MMRM with factors treatment and pooled country and covariate baseline

Table 15.1.1.3: 1 Disposition of patients - Termination of trial medication - TS3

	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total N (%)
Enrolled				605
Not entered/randomised				87
Entered/randomised	178	165	175	518
Not treated	0	1	0	1
Treated	178 (100.0)	164 (100.0)	175 (100.0)	517 (100.0)
Treated titration-maintenance	178 (100.0)	164 (100.0)	175 (100.0)	517 (100.0)
Not prematurely discontinued titration-maintenance	147 (82.6)	141 (86.0)	162 (92.6)	450 (87.0)
Prematurely discontinued titration-maintenance	31 (17.4)	23 (14.0)	13 (7.4)	67 (13.0)
Adverse event	10 (5.6)	9 (5.5)	8 (4.6)	27 (5.2)
AE study dis. worse	3 (1.7)	3 (1.8)	2 (1.1)	8 (1.5)
AE other dis. worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE other	7 (3.9)	6 (3.7)	6 (3.4)	19 (3.7)
Lack of efficacy	4 (2.2)	2 (1.2)	0 (0.0)	6 (1.2)
Non compl. protocol	2 (1.1)	2 (1.2)	1 (0.6)	5 (1.0)
Lost to follow-up	4 (2.2)	3 (1.8)	2 (1.1)	9 (1.7)
Refused cont. medic.	10 (5.6)	6 (3.7)	2 (1.1)	18 (3.5)
Other	1 (0.6)	1 (0.6)	0 (0.0)	2 (0.4)
Treated taper-down phase	21 (11.8)	20 (12.2)	23 (13.1)	64 (12.4)
Not prematurely discontinued taper-down phase	21 (11.8)	20 (12.2)	22 (12.6)	63 (12.2)
Prematurely discontinued taper-down phase	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Adverse event	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
AE study dis. worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE other dis. worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE other	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non compl. protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Refused cont. medic.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients treated in titration-maintenance but with no taper down performed: 62
Number of patients treated in titration-maintenance but have switched to open-label trial: 391