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: Pramipexole extended release (ER)		**EudraCT No.:** 2007-000073-39	
Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAR 2009	**Trial No. / U No.:** 248.524 / U09-1232-03	**Dates of trial:** 23 MAY 2007 – 25 NOV 2008	**Date of revision:** 10 JUL 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 patients with early Parkinson's disease (PD)
Coordinating Investigator:	[redacted]
Trial sites:	Multinational and multicentre study (14 countries, 94 active sites; see Appendix 16.1.4)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of the trial was to determine the efficacy (as measured by the change from baseline in the total score for Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III combined), safety, and tolerability of pramipexole extended release (ER) compared with placebo and pramipexole immediate release (IR) in patients with early PD. The objectives of this final analysis were to evaluate non-inferiority of pramipexole ER to pramipexole IR at 33 weeks on the primary efficacy endpoint (UPDRS II+III) and to evaluate superiority of pramipexole ER over placebo at week 18 on the key secondary endpoints (CGI-I and PGI-I responders rates), (both confirmatory testings). In an interim analysis, superiority of pramipexole ER to placebo at 18 weeks (confirmatory testing) on the primary efficacy endpoint (UPDRS II+III) and maintenance of efficacy in a subset of patients at week 33 were already established, according to the pre-defined hierarchical testing (see interim report [U08-1826-01]).
Methodology:	A double-blind, double-dummy, placebo-controlled, randomised, parallel group design.

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No. of patients:	
planned:	entered: 500 (200 for pramipexole ER, 200 for pramipexole IR, and 100 for placebo)
actual:	enrolled: 599 entered: 539 treated: 539 Pramipexole ER: entered: 223 treated: 223 analysed for primary endpoint: 213 Pramipexole IR: entered: 213 treated: 213 analysed for primary endpoint: 207 Placebo: entered: 103 treated: 103 analysed for primary endpoint: 103
Diagnosis and main criteria for inclusion:	Male or female patients, with idiopathic PD diagnosed within 5 years, 30 years of age or older at time of diagnosis, with a modified Hoehn and Yahr stage of 1 to 3 were eligible for this trial. Total (cumulative) duration of prior exposure to Levodopa should not have exceeded 3 months. Patients must not have been treated with Levodopa within 8 weeks prior to baseline and must 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 intend to change this treatment during the treatment phase): anti-Parkinsonian anticholinergics; selegiline, rasagiline, or other MAOB-I; amantadine; β-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 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg, or 4.5 mg)
dose:	0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg
mode of admin.:	Orally, once daily in the morning
batch no.:	Refer to Appendices 16.1.6 and 16.1.7.
Reference therapy:	Pramipexole IR (tablets of 0.125 mg, 0.25 mg, 0.50 mg, 1.0 mg, and 1.5 mg)
dose:	0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg

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Name of finished product: Pramipexole extended release (ER)		**EudraCT No.:** 2007-000073-39	
Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAR 2009	**Trial No. / U No.:** 248.524 / U09-1232-03	**Dates of trial:** 23 MAY 2007 – 25 NOV 2008	**Date of revision:** 10 JUL 2009

mode of admin.:	Orally, in equally divided doses 3 times a day
batch no.:	Refer to Appendices 16.1.6 and 16.1.7
Reference therapy:	Placebo (matching pramipexole ER and pramipexole IR, double-dummy)
dose:	0 mg
mode of admin.:	Orally, once daily in the morning (ER placebo) Orally, in equally divided doses 3 times a day (IR placebo)
batch no.:	Refer to Appendices 16.1.6 and 16.1.7
Duration of treatment:	7 weeks flexible double-blind up-titration phase, followed by a 26 weeks double-blind maintenance phase. At the end of the maintenance phase eligible patients could enter an open-label extension study (248.633). Patients not entering the open-label extension study performed an additional 1-week down-titration phase.
Criteria for evaluation:	
Efficacy:	Primary efficacy criterion: UPDRS parts II+III score; change from baseline to end of the maintenance period at week 33 (Visit 11) for comparison of pramipexole ER vs. pramipexole IR (non-inferiority hypothesis). Key secondary efficacy criteria (confirmatory testing at week 18 and descriptive testing at week 33): - Responder rate for Clinical Global Impression of Improvement (CGI-I) - Responder rate for Patient Global Impression of Improvement (PGI-I) Other secondary efficacy criteria (at week 33): - UPDRS I, II and III scores separately (change from baseline) - Proportion of patients with at least 20% improvement relative to baseline in the UPDRS II+III total score - Proportion of patients requiring supplement Levodopa during the study - Beck's Depression Inventory (BDI) version IA (change from baseline) - Parkinson's Disease Sleep Scale (PDSS) total score (change from baseline) - 11-point Likert scale for pain related to PD (change from baseline) - Quality of life scales: Parkinson Disease Questionnaire- 39 items (PDQ-39)

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Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAR 2009	**Trial No. / U No.:** 248.524 / U09-1232-03	**Dates of trial:** 23 MAY 2007 – 25 NOV 2008	**Date of revision:** 10 JUL 2009

	and EuroQoL (EQ-5D) (change from baseline) - Cost effectiveness analysis to compare treatments. Results will be reported separately - Pramipexole plasma concentrations (exposure). Results have been reported separately, see Population PK report [U08-1904-01]
Safety:	Incidence of adverse events, proportion of withdrawals due to adverse events, vital signs (blood pressure and pulse rate), weight, Epworth Sleepiness Scale (ESS), PDSS question 15, Modified Minnesota Impulsive Disorders Interview (mMIDI), safety laboratory parameters.
Statistical methods:	A hierarchical statistical testing was used in this trial: Superiority of pramipexole ER vs. placebo on the primary efficacy endpoint (UPDRS II+III) after 18 weeks of treatment was already demonstrated at an interim analysis (1st step of the hierarchical testing). The results of this interim analysis have been reported separately; see interim CTR [U08-1826-01]. The following hierarchical tests were performed in this final analysis: Primary analysis 2nd step: Final analysis to test for non-inferiority of pramipexole ER vs. pramipexole IR on the primary efficacy endpoint at Week 33: Analysis of covariance (ANCOVA) for change from baseline at end of the maintenance phase (week 33, Visit 11) in the UPDRS II+III total score, adjusting for pooled country (fixed effect) and baseline (covariate). The primary analysis was based on both the full analysis set (FAS; using last observation carried forward [LOCF]) and the per protocol set (PPS). If the hypothesis of no difference between pramipexole ER and placebo could be rejected (1st step; interim report), a non-inferiority hypothesis comparing both pramipexole formulations was tested using a non-inferiority margin of -3 points in UPDRS part II+III (2nd step). Subsequently after establishing non-inferiority, superiority of pramipexole ER over placebo was assessed on the key secondary endpoints CGI-I and PGI-I analysed by Cochran Mantel Haenszel (CMH; 3rd step for CGI-I and 4th step for PGI-I). Secondary analyses ANCOVA, CMH test, or non-parametric treatment group comparisons as appropriate for secondary efficacy endpoints. The secondary analyses were

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Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAR 2009	**Trial No. / U No.:** 248.524 / U09-1232-03	**Dates of trial:** 23 MAY 2007 – 25 NOV 2008	**Date of revision:** 10 JUL 2009

based on the FAS (using LOCF).

Descriptive statistical methods were used for the analysis of safety endpoints and pharmacokinetics. Pharmacokinetic results were reported separately [U08-1904-01].

SUMMARY – CONCLUSIONS:

Efficacy results:

Primary endpoint

In the FAS (LOCF), treatment for 33 weeks with pramipexole ER was non-inferior to pramipexole IR as measured by UPDRS Part II+III total score. The lower bound of the 95% confidence interval (ANCOVA: -0.2 [-2.2, 1.7] and MMRM: -0.3 [-2.0, 1.3]) for the between groups difference was above the pre-specified non-inferiority margin of -3 points. The PPS (observed cases [OC]) analysis and the PPS (endpoint) analysis confirmed non-inferiority of pramipexole ER vs. pramipexole IR (PPS [OC] ANCOVA: -0.2 [-2.0, 1.7] and PPS [endpoint] ANCOVA: -0.9 [-2.7, 0.9]).

The FAS sensitivity analysis (censoring efficacy values after introduction of L-Dopa as rescue medication) for 33 weeks treatment showed a between group comparison of -0.5 [-2.3, 1.3], which confirmed also non-inferiority of pramipexole ER compared to pramipexole IR.

Additionally, exploratory comparisons between pramipexole ER and pramipexole IR vs. placebo at week 33 were done. At week 33, the mean UPDRS II+III scores (calculated with FAS [LOCF]) were 24.6, 20.4, and 19.4 points, in the placebo, pramipexole ER and pramipexole IR groups, respectively. The associated adjusted mean changes from baseline were -3.8, -8.6, and -8.8 points as calculated by ANCOVA and -4.1, -8.7, and -9.1 points as calculated with a MMRM analysis. The p-values for the adjusted mean changes from baseline to week 33 were $p = 0.0001$ (pramipexole ER vs placebo) and $p<0.0001$ (pramipexole IR vs placebo), using an ANCOVA model. Therefore, both pramipexole formulations were superior to placebo on this descriptive analysis.

Maintenance of efficacy in the subgroup of 437 patients treated for 33 weeks was demonstrated between week 18 and 33 (placebo 90 patients, pramipexole ER 173 patients, and pramipexole IR 174 patients; FAS [OC]).

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Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAR 2009	**Trial No. / U No.:** 248.524 / U09-1232-03	**Dates of trial:** 23 MAY 2007 – 25 NOV 2008	**Date of revision:** 10 JUL 2009

	Key secondary endpoints In the FAS 1 (LOCF) population (using the first cut-off from the interim analysis), superiority at week 18 was demonstrated for both pramipexole ER and pramipexole IR groups over placebo for the CGI-I responder rate. For the PGI-I responder rate, superiority at week 18 of pramipexole ER over placebo was also demonstrated. These results have to be interpreted as confirmatory as part of the hierarchical testing procedure. Exploratory comparisons between pramipexole vs. placebo at week 33 showed superiority at week 33 for both pramipexole ER and pramipexole IR groups over placebo, for both the CGI-I responder rate and the PGI-I responder rate. Maintenance of efficacy between week 18 and 33 was confirmed in both pramipexole groups for the key secondary efficacy endpoints (FAS [OC]). Other secondary endpoints All comparisons between pramipexole groups vs. placebo at week 33 for the other secondary efficacy endpoints were exploratory in nature. In FAS (LOCF), the differences between the pramipexole groups and the placebo group were statistically significant for UPDRS Part II+III responder rate, UPDRS Part II score, UPDRS Part III score, and intake of L-Dopa rescue medication, all in favour of pramipexole. For the UPDRS Part II and Part III scores, the results on the FAS sensitivity analysis were more in favour of both pramipexole groups compared to the results from the FAS (LOCF). Overall, no treatment effect was observed on the non-motor symptoms of PD, due to the mild severity of these symptoms in this population, reflected by the non-motor scale baseline scores.
Safety results:	Overall, treatment with pramipexole ER or IR was safe and well tolerated, and no new or unexpected safety findings were observed. The mean exposure time was higher in the placebo group (215.2 days) compared to the active treatment groups (208.2 days pramipexole IR and 199.0 days pramipexole ER); however the median was identical in all 3 treatment groups (231 days).

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Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAR 2009	**Trial No. / U No.:** 248.524 / U09-1232-03	**Dates of trial:** 23 MAY 2007 – 25 NOV 2008	**Date of revision:** 10 JUL 2009

The numbers of patients reporting at least one treatment emergent AE were overall higher in the active treatment groups than in the placebo group. More patients in the pramipexole ER group (189 patients, 84.8%) reported AEs than in the pramipexole IR group (172 patients, 80.8%) or in the placebo group (80 patients, 77.7%). The majority of AEs was of mild or moderate intensity. The most frequently reported AEs (and more frequent in pramipexole pooled groups than placebo) were reported in the following system organ classes (SOCs): nervous system disorders (48.2% total pramipexole vs. 32.0% placebo), gastrointestinal disorders (46.6% total pramipexole vs. 19.4% placebo), psychiatric disorders (24.8% total pramipexole vs. 10.7% placebo) and general disorders and administration site conditions (19.7% total pramipexole vs. 14.6% placebo). The most frequently (at least 3% in any treatment group) reported AEs by MedDRA preferred term (PT) and more common (at least 2% difference) under pramipexole treatment than in the placebo group were: somnolence (34.6% total pramipexole vs. 14.6% placebo), dizziness (11.7% total pramipexole vs. 6.8% placebo), nausea (22.7% total pramipexole vs. 8.7% placebo), constipation (13.1% total pramipexole vs. 1.9% placebo), peripheral oedema (6.9% total pramipexole vs. 3.9% placebo), fatigue (6.0% total pramipexole vs. 3.9% placebo), and dry mouth (4.6% total pramipexole vs. 1.0% placebo). Most common (PT ≥3%) AEs with placebo and more common (difference ≥2%) with placebo than in the pooled pramipexole group were nasopharyngitis (7.8% placebo vs. 5.3% total pramipexole), cataract (4.9% placebo vs. 1.4% total pramipexole), and pruritus (3.9% placebo vs. 0.9% total pramipexole).

In the pramipexole ER group 16 patients (7.2%) reported SAEs, in the pramipexole IR group 11 patients (5.2%), and in the placebo group 4 patients (3.9%). Only 7 SAEs experienced by 4 patients (2 patients in each active treatment group) were considered to be drug related. There were 2 cases of death, both were assessed as not drug related (one patient receiving pramipexole ER experienced lip and/or oral cavity cancer which resulted in death, and one patient who had been receiving pramipexole IR died during the post treatment period due to an acute respiratory distress syndrome).

As anticipated, a smaller proportion of patients experienced drug related AEs in the placebo group (40 patients, 38.8%), compared to the pramipexole ER group (141 patients, 63.2%) or the pramipexole IR group (134 patients, 62.9%). Also a

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Name of active ingredient: Pramipexole dihydrochloride monohydrate		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
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	smaller proportion of patients experienced AEs leading to premature discontinuation in the placebo group (4 patients, 3.9%), compared to the pramipexole ER (24 patients, 10.8%) and pramipexole IR (20 patients, 9.4%) groups. Four patients of the pramipexole ER group had a positive mMIDI, 3 patients (1.3%) reported pathological gambling and one patient reported compulsive buying (0.4%) and other abnormal behaviour. In the pramipexole IR group, 3 patients had a positive mMIDI, one patient was reported with compulsive buying and sexual behaviour, one patient with compulsive buying, and one patient with compulsive sexual behaviour. One patient (1.0%) of the placebo group was reported with a confirmed mMIDI for compulsive buying and other abnormal behaviour. Other abnormal behaviour or urges, or AE qualifying for an abnormal behaviour were reported by 2 patients (0.9%) of the pramipexole ER group, 3 patients (1.4%) of the pramipexole IR group, and 2 patients (1.9%) of the placebo group. One patient (1.0%) in the placebo group, 2 patients (0.9%) in the pramipexole ER group, and 3 patients (1.4%) in the pramipexole IR group were reported with sudden onset sleep (SOS). Sleep attacks were reported by 5 patients (2.2%) in the pramipexole ER group and 3 patients (1.4%) in the pramipexole IR group. There were no notable differences between treatment groups regarding ESS and question 15 of the PDSS. Laboratory analyses (haematology and blood chemistry) and vital signs did not reveal any clinically significant findings.
Conclusions:	Non-inferiority of pramipexole ER to pramipexole IR was statistically demonstrated, as measured by UPDRS Part II+III total score at week 33. Superiority at week 18 was also demonstrated for the pramipexole ER and pramipexole IR groups over placebo for the CGI-I responder rate. For the PGI-I responder rate in the pramipexole ER group superiority over placebo was established. The overall safety evaluation showed that both pramipexole formulations were safe and well tolerated. No notable differences were seen between the two active treatments and no new or unexpected adverse events were observed. These results were observed at comparable mean daily dose and duration of treatment for both pramipexole formulations.

Trial Synopsis – Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide information as summarized below.

Results for	Presented in
Disposition	Table 15.1.1: 1
Responder Rate for CGI-I at 33 Weeks	Table 15.2.2.1.1: 1
Responder Rate for PGI-I at 33 Weeks	Table 15.2.2.2.1: 1
UPDRS I Total Score at Baseline and Change from Baseline after 33 Weeks	Table 15.2.2.3: 1
UPDRS II Total Score at Baseline and Change from Baseline after 33 Weeks	Table 15.2.2.4: 1
UPDRS III Total Score at Baseline and Change from Baseline: after 33 Weeks	Table 15.2.2.5: 1
Number (and Percentage) of Patients Requiring L-Dopa Rescue Medication	Table 15.2.2.8: 1
UPDRS II+III Response (>=20% Improvement), 33 Weeks Treatment	Table 15.2.1.1: 5
BDI-1A Total Score, 33 Weeks Treatment	Table 15.2.2.6: 1
PDSS Total Score (cm), 33 Weeks Treatment	Table 15.2.2.9: 1
Likert Scale for Pain Control Related to PD, 33 Weeks Treatment	Table 15.2.2.7: 1

Table 15.1.1: 1 Disposition of patients - Termination of trial medication - TS

	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total N (%)
Enrolled				599
Not entered/randomised				60
Entered/randomised	103	223	213	539
Not treated	0	0	0	0
Treated	103 (100.0)	223 (100.0)	213 (100.0)	539 (100.0)
Treated titration-maintenance	103 (100.0)	223 (100.0)	213 (100.0)	539 (100.0)
Not prematurely discontinued titration-maintenance	91 (88.3)	174 (78.0)	176 (82.6)	441 (81.8)
Prematurely discontinued titration-maintenance	12 (11.7)	49 (22.0)	37 (17.4)	98 (18.2)
Adverse event	4 (3.9)	24 (10.8)	20 (9.4)	48 (8.9)
AE study dis. worse	1 (1.0)	2 (0.9)	2 (0.9)	5 (0.9)
AE other dis. worse	0 (0.0)	4 (1.8)	1 (0.5)	5 (0.9)
AE other	3 (2.9)	18 (8.1)	17 (8.0)	38 (7.1)
Lack of efficacy	4 (3.9)	2 (0.9)	2 (0.9)	8 (1.5)
Non compl. protocol	1 (1.0)	2 (0.9)	1 (0.5)	4 (0.7)
Lost to follow-up	1 (1.0)	1 (0.4)	1 (0.5)	3 (0.6)
Refused cont. medic.	2 (1.9)	16 (7.2)	10 (4.7)	28 (5.2)
Other	0 (0.0)	4 (1.8)	3 (1.4)	7 (1.3)
Treated taper-down phase	20 (19.4)	38 (17.0)	47 (22.1)	105 (19.5)
Not prematurely discontinued taper-down phase	20 (19.4)	38 (17.0)	47 (22.1)	105 (19.5)
Prematurely discontinued taper-down phase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
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)	0 (0.0)	0 (0.0)
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: 66
Number of patients treated in titration-maintenance but have switched to open-label trial: 368

Table 15.2.2.1.1: 1 CGI-I Responders, 33 weeks of treatment,
FAS (LOCF)

Secondary endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
CGI-I responder					
Week 33					
Number of patients	102	210	206		
Responder [N,(%)]	30 (29.4)	91 (43.3)	95 (46.1)	0.0256	0.0078
% Responder [95% CI]	[20.8, 39.3]	[36.5, 50.3]	[39.2, 53.2]		

Pooled country used for CMH stratification
Exploratory test

Table 15.2.2.2.1: 1 PGI-I Responders, 33 weeks of treatment, FAS (LOCF)

Secondary endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
PGI-I responder					
Week 33					
Number of patients	103	212	207		
Responder [N,(%)]	22 (21.4)	73 (34.4)	69 (33.3)	0.0148	0.0193
% Responder [95% CI]	[13.9, 30.5]	[28.1, 41.2]	[27.0, 40.2]		

Pooled country used for CMH stratification
Exploratory test

Table 15.2.2.3: 1 UPDRS I total score, 33 weeks treatment,
FAS (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS I score total Number of patients	103	213	207	Wilcoxon	Wilcoxon
Baseline, Median (IQR)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)		
Week 33, Median (IQR)	0.0 (1.0)	0.0 (2.0)	0.0 (1.0)		
Change from Baseline, Median (IQR)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.2378	0.9075

Negative change implies improvement
Exploratory test

Table 15.2.2.4: 1 UPDRS II total score, 33 weeks treatment, FAS (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS II total score Number of patients	103	213	207		
Baseline, Mean (SD)	7.6 (4.4)	8.0 (4.3)	7.8 (3.7)		
Week 33, Mean (SD)	6.6 (4.3)	5.6 (4.1)	5.2 (3.7)		
Change from Baseline, Mean [95% CI]	-1.0 [-1.7, -0.3]	-2.4 [-2.8, -1.9]	-2.6 [-3.1, -2.1]		
LS Mean Change [95% CI] - ANCOVA*	-0.9 [-1.5, -0.3]	-2.2 [-2.6, -1.7]	-2.4 [-2.9, -2.0]	0.0005	<.0001

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

Table 15.2.2.5: 1 UPDRS III total score, 33 weeks treatment, FAS (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS III total score Number of patients	103	213	207		
Baseline, Mean (SD)	21.4 (11.7)	22.0 (10.0)	21.1 (9.4)		
Week 33, Mean (SD)	18.0 (11.6)	14.8 (9.7)	14.1 (8.6)		
Change from Baseline, Mean [95% CI]	-3.4 [-4.9, -1.9]	-7.2 [-8.3, -6.1]	-7.0 [-8.1, -5.8]		
LS Mean Change [95% CI] - ANCOVA*	-2.8 [-4.2, -1.4]	-6.4 [-7.4, -5.4]	-6.4 [-7.4, -5.4]	<.0001	<.0001

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

Table 15.2.2.8: 1 Number (and percentage) of patients requiring L-Dopa rescue medication
FAS (LOCF)

Secondary endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
Patients requiring L-Dopa rescue med.					
Week 33					
Number of patients	103	213	207		
Patient with rescue medication [N,(%)]	22 (21.4)	15 (7.0)	9 (4.3)	<.0001	<.0001
[95% CI]	[13.9, 30.5]	[4.0, 11.3]	[2.0, 8.1]		

Pooled country used for CMH stratification
Exploratory test

Table 15.2.1.1: 5 UPDRS II+III Response (>=20% improvement), 33 weeks treatment
FAS (LOCF)

Secondary endpoint	Placebo	Pramipexole ER	Pramipexole IR
UPDRS II+III responder			
Week 33			
Number of patients	103	213	207
Responder [N,(%)]	50 (48.5)	146 (68.5)	136 (65.7)
% Responder [95% CI]	[38.6, 58.6]	[61.8, 74.7]	[58.8, 72.1]

Pooled country used for CMH stratification

Table 15.2.2.6: 1 BDI-1A total score, 33 weeks treatment,
FAS (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
BDI total score Number of patients	102	208	206		
Baseline, Mean (SD)	9.1 (7.5)	8.9 (6.4)	8.8 (6.7)		
Week 33, Mean (SD)	7.0 (7.3)	7.0 (6.1)	6.3 (6.1)		
Change from Baseline, Mean [95% CI]	-2.1 [-3.2, -0.9]	-1.9 [-2.6, -1.1]	-2.6 [-3.3, -1.8]		
LS Mean Change [95% CI] - ANCOVA*	-2.1 [-3.1, -1.2]	-2.0 [-2.7, -1.3]	-2.7 [-3.4, -2.0]	0.7646	0.3527

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

Table 15.2.2.9: 1 PDSS total score [cm], 33 weeks treatment,
FAS (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
PDSS total score Number of patients	101	207	205		
Baseline, Mean (SD)	113.5 (22.7)	112.8 (24.7)	111.7 (25.3)		
Week 33, Mean (SD)	119.0 (25.2)	115.9 (25.5)	118.1 (23.8)		
Change from Baseline, Mean [95% CI]	5.6 [1.3, 9.9]	3.0 [-0.0, 6.1]	6.4 [3.5, 9.4]		
LS Mean Change [95% CI] - ANCOVA*	5.6 [1.8, 9.4]	2.3 [-0.4, 5.0]	5.6 [2.8, 8.4]	0.1559	0.9929

Positive change implies improvement
* ANCOVA with factors treatment and pooled country and covariate baseline
Exploratory test

Table 15.2.2.7: 1 Likert scale for pain related to PD, 33 weeks treatment, FAS (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs.Placebo	PPX IR vs.Placebo
Likert pain score Number of patients	102	208	206		
Baseline, Mean (SD)	1.9 (2.3)	1.9 (2.3)	1.7 (2.1)		
Week 33, Mean (SD)	2.0 (2.5)	1.6 (2.0)	1.6 (2.1)		
Change from Baseline, Mean [95% CI]	0.1 [-0.3, 0.5]	-0.3 [-0.6, 0.0]	-0.1 [-0.4, 0.1]		
LS Mean Change [95% CI] - ANCOVA*	0.2 [-0.2, 0.5]	-0.2 [-0.4, 0.1]	-0.1 [-0.4, 0.1]	0.1114	0.1738

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