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
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Report date: 23 FEB 2011	**Trial No. / U No.:** 248.633 /U11-1118-01	**Date of trial:** 17 JAN 2008 – 11 JUNE 2010	**Date of revision:** Not applicable

Title of trial:	Long-term safety study of open-label pramipexole extended release (ER) in patients with early Parkinson's disease (PD)
Coordinating Investigator:	[redacted]
Trial sites:	Multinational and multicentre study (15 countries, 105 sites)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The primary objective was to obtain long-term safety and tolerability data on PPX ER in patients who had previously completed a pramipexole double-blind (DB) study in early PD (248.524 or 248.636 trial). Long-term efficacy was also assessed.
Methodology:	This was an open-label (OL), long-term safety study of PPX ER (in daily doses from 0.375 mg to 4.5 mg per day q.d.) in patients with early Parkinson's disease (PD). The study was conducted in patients who had previously participated in a pramipexole double-blind (DB) study in early PD (either 248.524 or 248.636 trial). The trial duration (initially 33 weeks for patients from 248.524 trial and 25 weeks for patients from 248.636 trial) was prolonged to 81 weeks and 73 weeks respectively. This change was implemented by clinical trial protocol (CTP amendment 3 (dated 5 February 2008).

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No. of subjects	
planned:	entered: 520
actual:	enrolled: 511 PPX ER entered: 511 treated and analyses for safety • 368 previously from trial 248.524 • 143 previously from trial 248.636 completed treatment: 408 • 291 previously from trial 248.524 • 117 previously from trial 248.636.
Diagnosis and main criteria for inclusion:	Male or female patients, with early idiopathic PD, who had completed trial 248.524 or trial 248.636, and had a modified Hoehn and Yahr scale of I to III. Concomitant treatment with other anti-Parkinsonian drugs was allowed as specified in the CTP.
Test product:	PPX ER (tablets of 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg or 4.5 mg)
dose:	DB transfer phase and OL phase: 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg, once daily, in the morning (flexible dose during the up-titration and the OL phase).
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Placebo tablets matching the PPX ER tablets
dose:	DB transfer phase: tablets administered once daily, in the morning
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Duration of treatment:	For patients from trial 248.524: DB transfer phase of up to 6 weeks, followed by an OL treatment phase of 74 weeks and a down-titration phase of 1 week (or switch to commercial pramipexole at the same dose) for a total of up to 81 weeks of treatment. For patients from trial 248.636: OL treatment phase of 72 weeks and a down-titration phase of 1 week (or switch to commercial pramipexole at the same dose) for a total of up to 73 weeks of treatment.

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Criteria for evaluation: **Efficacy:**	The primary focus of data collection was safety information. However, efficacy measurements were also collected. The main efficacy endpoint was the combined UPDRS parts II+III score. Other efficacy parameters included the UPDRS parts II+III response rate, separate analyses of the UPDRS I, II and III scores, the Parkinson's fatigue scale (PFS-16), Levodopa (L-Dopa) supplementation and daily dose, and changes in PPX ER dose. The parameters persistence of effect, clinical global impression of improvement (CGI-I), patient global impression of improvement (PGI-I) were assessed up to 32 weeks; the results were described in the interim report for this trial [U10-1341-02] and are not repeated here.
Safety:	Incidence of treatment-emergent adverse events (AEs), proportion of withdrawals due to adverse events (AEs), vital signs (blood pressure and pulse rate), body mass index (BMI), Epworth Sleepiness Scale (ESS), modified Minnesota Impulsive Disorders Interview (mMIDI) (added in CTP amendment 3, dated 5 February 2008).
Statistical methods:	Statistical analysis: Data from this study were stratified based on previous trial and previous treatment group (placebo or PPX ER or pramipexole immediate release tablets [PPX IR]). As no randomized group was observed in this trial, all statistical results were analyzed exploratively. Sample size calculation: It was assumed that approximately 80% of patients who had previously participated in the pramipexole DB study in early PD (248.524 trial) and 90% of patients who had previously participated in the pramipexole DB switch study in early PD (248.636 trial) would enter the OL extension trial 248.633. As 500 entered patients were planned in the 248.524 trial and 132 patients in the 248.636, it was expected that 520 patients were expected to enter the 248.633 trial. Analysis sets: • TS (treated set): patients who received at least one dose of study medication • FAS (full analysis set): patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment The TS was the safety population. The main efficacy population was the FAS, with analyses done on an observed case (OC) basis.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Patients from trial 248.524 (N=368, TS): There were slightly more male (55.4%) than female (44.6%) patients, and a higher proportion of white patients (60.3%) than Asian patients (39.7%). The mean ± SD age was 62.2 ± 9.2 years. L-Dopa was received by only 9.0% of patients at baseline (mean ± SD dose: 337 ± 210 mg/day). The mean ± SD PD duration was 1.6 ± 1.1 years, and 63.6% of patients had received treatment for PD in the past. There were no large differences in baseline characteristics by previous treatment group.

The results confirmed maintenance of efficacy of long-term treatment with PPX ER. Maintenance in efficacy was shown for the main efficacy endpoint (UPDRS II+III total score) and other efficacy endpoints.

For patients coming from trial 248.524 (N=332, FAS, OC), mean UPDRS II+III values over time showed an improvement from DB baseline at all intervals during treatment, with only a slight decline in the level of improvement from week 56 to week 80. The LS mean change from DB baseline to the week 80 of OL treatment in the UPDRS II+III total score was -6.9 for patients who had previously received placebo, -6.6 for patients who had previously received PPX ER, and -6.3 for patients who had previously received PPX IR (FAS, OC).

Similar findings were observed for the UPDRS I, II and III combined scores, and the PFS-16 score.

Only a small proportion of patients coming from the 248.524 trial (9.0%, 33/367) were receiving L-Dopa at baseline; and the proportion of patients receiving L-Dopa at week 80 increased but remained low (20.4%, 75/367) (FAS).

Patients from trial 248.636 (N=143, TS): There were slightly more male (56.6%) than female (43.4%) patients; and most patients were white (97.2%), with only few Asian patients (2.8%). The mean ± SD age was 64.0 ± 9.0 years. L-Dopa was received by more than half (53.8%) of patients at baseline (mean ± SD dose: 389 ± 234 mg/day). The mean ± SD PD duration was 3.6 ± 2.1 years, and 80.4% of patients had received treatment for PD in the past. There were no large differences in baseline characteristics by previous treatment group.

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Efficacy results (continued):	For patients coming from trial 248.636 in the present study (N=113, FAS, OC), mean UPDRS II+III scores over time showed approximately the same level of improvement from DB baseline to the end of week 72 of OL treatment. The LS mean change from DB baseline to week 72 of OL treatment in the UPDRS II+III total score was 0.5 for patients who had previously received PPX ER, and -1.0 for patients who had previously received PPX IR (FAS, OC). Similar findings were observed with separate analysis of the UPDRS I, II and III combined scores, and the PFS-16 score. The majority of patients coming from the 248.636 trial (54.3%, 75/138) were receiving L Dopa at baseline of the present trial; and there was a modest increase in the proportion of patients receiving L Dopa at week 72 (60.9%, 84/138). Of the patients who had data available from the patient convenience survey (from both the 248.524 and 248.635 strata), once daily intake of treatment was considered to be much more convenient for 68.2% (255/374) of patients and more convenient by 26.2% (98/374) of patients. Three times daily intake was preferred by only 2.7% (10/374) of patients; and 2.9% (11/374) of patients had no preference (FAS).
Safety results:	For both strata combined (patients from both trials 248.524 and 248.636), 430/511 (84.1%) patients received study drug treatment for 60 weeks or longer, with 38.9% of patients having received treatment for 60 to <80 weeks and 45.2% of patients having received treatment for ≥80 weeks. This represents good agreement with the planned treatment period of up to 81 weeks for patients coming from trial 248.524 (with 62.5% [230/368] having completed ≥80 weeks and 21.7% [80/368] having completed 60 to <80 weeks) and with the planned treatment period of up to 73 weeks for patients coming from trial 248.636 (83.2% [119/143] having completed 60 to <80 weeks). With regard to dose level for all patients combined (N=511), 20.2% of patients received a low final dose (0.375-1.5 mg), 38.4% of patients received a medium final dose (2.25-3.0 mg), and 41.5% of patients received a high final dose (3.75-4.5 mg) of PPX ER during the present study.

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Safety results (continued):

The most frequently reported AEs, irrespective of causality (N=511), were somnolence (15.1%), oedema peripheral (11.7%), back pain (10.6%), nausea (9.2%), nasopharyngitis (7.2%), dizziness (6.8%), cataract (6.3%) and fall (5.7%).

- Previously from study 248.524 (N=368): somnolence (18.2%), oedema peripheral (12.2%), back pain (11.1%), nausea (10.1%), dizziness (8.7%), nasopharyngitis (7.9%), cataract (6.8%), fall (6.3%) and insomnia (5.2%)
- Previously from study 248.636 (N=143): oedema peripheral (10.5%), back pain (9.1%), PD (8.4%), nausea (7.0%), somnolence (7.0%), constipation (6.3%), hallucination (6.3%) and nasopharyngitis (5.6%).

The most frequently reported related AEs overall (N=511) were somnolence (12.7%), oedema peripheral (7.0%), nausea (6.7%), dizziness (3.3%), hallucination (2.7%), fatigue (2.5%) and vomiting (2.0%).

- Previously from study 248.524 (N=368): somnolence (15.8%), nausea (8.2%), oedema peripheral (7.6%), dizziness (4.3%), hallucination (2.4%), hallucinations, visual (2.4%), fatigue (3.3%), vomiting (2.4%) and abnormal dreams (2.2%).
- Previously from study 248.636 (N=143): oedema peripheral (5.6%), somnolence (4.9%), hallucination (3.5%), nausea (2.8%) and abdominal pain upper (2.1%).

Treatment-emergent mMIDI defined abnormal behaviours comprised 3 patients with compulsive buying and 1 patient with pathological gambling (N=511).

There were a total of 8 patients with SAEs that led to death (7 from patients coming from trial 248.524 and 1 of the patients coming from trial 248.636). None of the deaths was related to the study drug.

Related SAEs (6/511, 1.2%) comprised two patients with hallucination, one with sleep attacks and a road traffic accident; and one patient each with psychotic disorder, PD or hepatitis. Road traffic accident was an AE of special interest in Japan and this was the only such event that occurred during the study.

Overall, 25/511 (4.9%) patients had one or more related AEs that led to treatment discontinuation, and 4/511 (0.8%) had one or more related SAEs that led to discontinuation (two with hallucination, one a road traffic accident and sleep attack, and one with psychotic disorder).

Differences in mean blood pressure and mean body mass index (BMI) values between baseline and last visit were very small relative to standard ranges and not indicative of clinically relevant increases.

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Conclusions:	Results from this study confirm the maintenance of efficacy of long-term treatment of PD with PPX ER. Maintenance of efficacy was shown for the main efficacy endpoint (UPDRS II+III total score) and other efficacy endpoints (UPDRS I, II and III, PFS 16). The nature and incidence of AEs, including SAEs and AEs that led to treatment discontinuation, were as anticipated for a population of elderly patients with PD who are receiving dopamine agonist therapy. There was no significant safety information identified. It can be concluded from this study that long-term treatment with PPX ER was well tolerated.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The primary objective of this trial was to obtain long-term safety and tolerability data; this objective was specified as the following primary endpoints:

- Frequency of all adverse events
- Frequency of drug-related adverse events
- Frequency of serious adverse events

The appended tables provide the complete disposition results and results of additional primary and secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
UPDRS II + III change from baseline after 80 weeks/72 weeks	Table 15.2.1.1: 1
UPDRS I change from baseline after 80 weeks/72 weeks	Table 15.2.2: 1
UPDRS II change from baseline after 80 weeks/72 weeks	Table 15.2.3: 1
UPDRS III change from baseline after 80 weeks/72 weeks	Table 15.2.4: 1
UPDRS II + III percentage of patients with ≥20% improvement from baseline after 80 weeks/72 weeks	Table 15.2.1.1: 3
PFS−16 change from baseline after 80 weeks/72 weeks	Table 15.2.7: 1
Pramipexole doses after 80 weeks/72 weeks	Table 15.3.1: 3
Adverse event overall summary – treated set	Table 15.3.2: 1

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

	248.524				
	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total PPX N (%)	Total PPX ER N (%)
Enrolled				292	368
Not entered/randomised				0	0
Entered/randomised	76	153	139	292	368
Not treated	0	0	0	0	0
Treated	76 (100.0)	153 (100.0)	139 (100.0)	292 (100.0)	368 (100.0)
Treated transfer and/or OL phase	76 (100.0)	153 (100.0)	139 (100.0)	292 (100.0)	368 (100.0)
Not prematurely discontinued transfer and/or OL phase	57 (75.0)	118 (77.1)	116 (83.5)	234 (80.1)	291 (79.1)
Prematurely discontinued transfer and/or OL phase	19 (25.0)	35 (22.9)	23 (16.5)	58 (19.9)	77 (20.9)
Adverse event	13 (17.1)	17 (11.1)	12 (8.6)	29 (9.9)	42 (11.4)
AE study dis. worse	1 (1.3)	1 (0.7)	0 (0.0)	1 (0.3)	2 (0.5)
AE other dis. worse	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
AE other	11 (14.5)	16 (10.5)	12 (8.6)	28 (9.6)	39 (10.6)
Lack of efficacy	0 (0.0)	0 (0.0)	3 (2.2)	3 (1.0)	3 (0.8)
Non compl. protocol	1 (1.3)	3 (2.0)	1 (0.7)	4 (1.4)	5 (1.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Refused cont. medic.	3 (3.9)	10 (6.5)	5 (3.6)	15 (5.1)	18 (4.9)
Other	2 (2.6)	5 (3.3)	2 (1.4)	7 (2.4)	9 (2.4)
Treated taper down phase	30 (39.5)	70 (45.8)	67 (48.2)	137 (46.9)	167 (45.4)
Not prematurely discontinued taper down phase	30 (39.5)	69 (45.1)	67 (48.2)	136 (46.6)	166 (45.1)
Prematurely discontinued taper down phase	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Adverse event	0 (0.0)	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)	0 (0.0)
AE other dis. worse	0 (0.0)	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)	0 (0.0)
Lack of efficacy	0 (0.0)	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)	0 (0.0)
Lost to follow-up	0 (0.0)	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)	0 (0.0)
Other	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)

Number of patients treated in transfer and/or OL phase but with no taper down performed: 201

Source data: Section 15, Table 1.1: 3 eot\dispt.sas 27AUG2010

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

	248.636		
	PPX ER N (%)	PPX IR N (%)	Total PPX N (%)
Enrolled			143
Not entered/randomised			0
Entered/randomised	95	48	143
Not treated	0	0	0
Treated	95 (100.0)	48 (100.0)	143 (100.0)
Treated OL phase	95 (100.0)	48 (100.0)	143 (100.0)
Not prematurely discontinued OL phase	78 (82.1)	39 (81.3)	117 (81.8)
Prematurely discontinued OL phase	17 (17.9)	9 (18.8)	26 (18.2)
Adverse event	8 (8.4)	6 (12.5)	14 (9.8)
AE study dis. worse	1 (1.1)	2 (4.2)	3 (2.1)
AE other dis. worse	0 (0.0)	0 (0.0)	0 (0.0)
AE other	7 (7.4)	4 (8.3)	11 (7.7)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Non compl. protocol	1 (1.1)	0 (0.0)	1 (0.7)
Lost to follow-up	0 (0.0)	1 (2.1)	1 (0.7)
Refused cont. medic.	7 (7.4)	2 (4.2)	9 (6.3)
Other	1 (1.1)	0 (0.0)	1 (0.7)
Treated taper down phase	5 (5.3)	3 (6.3)	8 (5.6)
Not prematurely discontinued taper down phase	5 (5.3)	3 (6.3)	8 (5.6)
Prematurely discontinued taper down phase	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)
AE study dis. worse	0 (0.0)	0 (0.0)	0 (0.0)
AE other dis. worse	0 (0.0)	0 (0.0)	0 (0.0)
AE other	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Non compl. protocol	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Refused cont. medic.	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients treated in OL phase but with no taper down performed: 135

Source data: Section 15, Table 1.1: 3

Table 15.2.1.1: 1 UPDRS II + III total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.524	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS II+III total score					
Number of patients, DB analysis	56	119	115		
DB Baseline, Mean (SD)	26.2 (11.1)	30.0 (13.4)	29.0 (12.4)		
Number of patients, OL analysis	56	119	115		
OL Baseline, Mean (SD)	21.8 (12.8)	18.2 (11.5)	17.1 (10.5)		
Number of patients	56	119	115		
Week 80, Mean (SD)	19.3 (12.1)	20.7 (14.3)	21.2 (13.1)		
Number of patients	56	119	115		
Change from DB Baseline, Mean (SD)	-6.9 (12.7)	-9.3 (12.3)	-7.8 (12.6)		
Number of patients	56	119	115		
Change from OL Baseline, Mean (SD)	-2.5 (11.2)	2.5 (8.9)	4.1 (8.4)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-6.9 (1.5)	-6.6 (1.1)	-6.3 (1.1)	0.8679	0.7489
LS Mean Change from OL baseline (SE) - ANCOVA*	-1.9 (1.3)	3.1 (0.9)	3.9 (0.9)	0.0004	<.0001

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.1.1: 1 UPDRS II + III total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.636	PPX ER	PPX IR	PPX ER vs.PPX IR
UPDRS II+III total score			
Number of patients, DB analysis	76	37	
DB Baseline, Mean (SD)	21.0 (9.4)	22.9 (10.6)	
Number of patients, OL analysis	76	37	
OL Baseline, Mean (SD)	19.1 (10.3)	22.2 (10.7)	
Number of patients	76	37	
Week 72, Mean (SD)	21.5 (12.2)	21.9 (11.5)	
Number of patients	76	37	
Change from DB Baseline, Mean (SD)	0.5 (7.8)	-1.0 (5.9)	
Number of patients	76	37	
Change from OL Baseline, Mean (SD)	2.4 (8.4)	-0.3 (5.7)	
LS Mean Change from DB baseline (SE) - ANCOVA*	0.5 (1.0)	-1.0 (1.3)	0.3047
LS Mean Change from OL baseline (SE) - ANCOVA*	2.6 (1.0)	0.2 (1.3)	0.1336

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.2: 1 UPDRS I total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.524	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS I score total					
Number of patients, DB analysis	56	119	115		
DB Baseline, Mean (SD)	1.1 (1.0)	1.0 (1.3)	1.0 (1.2)		
Number of patients, OL analysis	55	118	114		
OL Baseline, Mean (SD)	0.5 (0.9)	0.7 (1.0)	0.5 (1.0)		
Number of patients	56	119	115		
Week 80, Mean (SD)	0.8 (1.0)	0.9 (1.3)	0.9 (1.1)		
Number of patients	56	119	115		
Change from DB Baseline, Mean (SD)	-0.4 (1.1)	-0.1 (1.3)	-0.1 (1.2)		
Number of patients	55	118	114		
Change from OL Baseline, Mean (SD)	0.2 (1.0)	0.2 (1.1)	0.4 (1.0)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-0.3 (0.1)	-0.0 (0.1)	-0.1 (0.1)	0.1036	0.2374
LS Mean Change from OL baseline (SE) - ANCOVA*	0.2 (0.1)	0.4 (0.1)	0.4 (0.1)	0.3246	0.2550

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.2: 1 UPDRS I total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.636	PPX ER	PPX IR	PPX ER vs.PPX IR
UPDRS I score total			
Number of patients, OL analysis	76	35	
OL Baseline, Mean (SD)	1.0 (1.4)	0.9 (0.9)	
Number of patients	76	35	
Week 72, Mean (SD)	1.0 (1.2)	1.1 (1.7)	
Number of patients	76	35	
Change from OL Baseline, Mean (SD)	0.0 (1.2)	0.2 (1.7)	
LS Mean Change from OL baseline (SE) - ANCOVA*	0.0 (0.2)	0.2 (0.2)	0.6067

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate OL baseline
For UPDRS I, no DB baseline data for patients from 248.636 available

Table 15.2.3: 1 UPDRS II total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.524	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS II total score					
Number of patients, DB analysis	56	119	115		
DB Baseline, Mean (SD)	6.7 (3.5)	7.9 (4.3)	7.7 (3.8)		
Number of patients, OL analysis	56	119	115		
OL Baseline, Mean (SD)	6.0 (3.7)	5.0 (3.6)	4.7 (3.5)		
Number of patients	56	119	115		
Week 80, Mean (SD)	5.7 (3.6)	6.2 (4.7)	6.2 (4.2)		
Number of patients	56	119	115		
Change from DB Baseline, Mean (SD)	-1.0 (3.9)	-1.7 (3.7)	-1.5 (4.1)		
Number of patients	56	119	115		
Change from OL Baseline, Mean (SD)	-0.3 (3.7)	1.2 (3.1)	1.5 (2.8)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-1.2 (0.5)	-1.3 (0.4)	-1.3 (0.4)	0.9524	0.9020
LS Mean Change from OL baseline (SE) - ANCOVA*	-0.3 (0.4)	1.1 (0.3)	1.3 (0.3)	0.0042	0.0014

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.3: 1 UPDRS II total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.636	PPX ER	PPX IR	PPX ER vs.PPX IR
UPDRS II total score			
Number of patients, DB analysis	76	37	
DB Baseline, Mean (SD)	6.8 (3.8)	7.1 (3.4)	
Number of patients, OL analysis	76	37	
OL Baseline, Mean (SD)	6.4 (3.9)	6.8 (3.3)	
Number of patients	76	37	
Week 72, Mean (SD)	7.5 (5.2)	6.5 (3.5)	
Number of patients	76	37	
Change from DB Baseline, Mean (SD)	0.7 (4.0)	-0.5 (2.3)	
Number of patients	76	37	
Change from OL Baseline, Mean (SD)	1.1 (4.0)	-0.3 (2.1)	
LS Mean Change from DB baseline (SE) - ANCOVA*	0.8 (0.5)	-0.5 (0.6)	0.0742
LS Mean Change from OL baseline (SE) - ANCOVA*	1.2 (0.5)	-0.1 (0.6)	0.0614

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.4: 1 UPDRS III total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.524	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS III total score					
Number of patients, DB analysis	56	119	115		
DB Baseline, Mean (SD)	19.5 (8.6)	22.1 (10.3)	21.3 (9.7)		
Number of patients, OL analysis	56	119	115		
OL Baseline, Mean (SD)	15.8 (9.8)	13.2 (8.5)	12.4 (7.7)		
Number of patients	56	119	115		
Week 80, Mean (SD)	13.6 (9.4)	14.5 (10.4)	15.0 (9.7)		
Number of patients	56	119	115		
Change from DB Baseline, Mean (SD)	-5.9 (9.7)	-7.6 (9.9)	-6.3 (10.0)		
Number of patients	56	119	115		
Change from OL Baseline, Mean (SD)	-2.2 (8.6)	1.3 (6.6)	2.5 (6.5)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-5.7 (1.2)	-5.3 (0.8)	-5.1 (0.9)	0.7301	0.6076
LS Mean Change from OL baseline (SE) - ANCOVA*	-1.5 (0.9)	2.0 (0.7)	2.6 (0.7)	0.0010	0.0002

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.4: 1 UPDRS III total score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.636	PPX ER	PPX IR	PPX ER vs.PPX IR
UPDRS III total score			
Number of patients, DB analysis	76	37	
DB Baseline, Mean (SD)	14.2 (6.6)	15.9 (8.4)	
Number of patients, OL analysis	76	37	
OL Baseline, Mean (SD)	12.7 (7.2)	15.4 (8.5)	
Number of patients	76	37	
Week 72, Mean (SD)	14.0 (8.3)	15.4 (9.6)	
Number of patients	76	37	
Change from DB Baseline, Mean (SD)	-0.2 (5.6)	-0.4 (5.4)	
Number of patients	76	37	
Change from OL Baseline, Mean (SD)	1.3 (5.8)	-0.0 (5.0)	
LS Mean Change from DB baseline (SE) - ANCOVA*	-0.2 (0.7)	-0.4 (1.0)	0.8850
LS Mean Change from OL baseline (SE) - ANCOVA*	1.3 (0.7)	0.4 (1.0)	0.3880

Negative change implies improvement
* ANCOVA with factors treatment and country and covariate DB or OL baseline

Table 15.2.1.1: 3 UPDRS II + III Response (>=20% improvement) from DB baseline, 80 weeks for previously 248.524 patients and 72 weeks for previously 248.636 patients, FAS, OC

	248.524				
248.524	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
UPDRS II+III responder					
Week 80					
Number of patients	56	119	115	234	290
Responder [N,(%)]	31 (55.4)	76 (63.9)	65 (56.5)	141 (60.3)	172 (59.3)

UPDRS II+III Response: At least 20% improvement relative to Baseline (DB) in the UPDRS II+III total score.
The interesting baseline is DB baseline. Patients with UPDRS II+III total score equal to 0 at DB Baseline are not taken into account

Table 15.2.1.1: 3 UPDRS II + III Response (>=20% improvement) from DB baseline, 80 weeks for previously 248.524 patients and 72 weeks for previously 248.636 patients, FAS, OC

	248.636		
248.636	PPX ER	PPX IR	TOTAL PPX
UPDRS II+III responder			
Week 72			
Number of patients	76	37	113
Responder [N,(%)]	25 (32.9)	9 (24.3)	34 (30.1)

UPDRS II+III Response: At least 20% improvement relative to Baseline (DB) in the UPDRS II+III total score
The interesting baseline is DB baseline. Patients with UPDRS II+III total score equal to 0 at DB Baseline are not taken into account

Table 15.2.7: 1 PFS-16 score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.524	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
PFS total score					
Number of patients, OL analysis	60	123	120		
OL Baseline, Mean (SD)	37.4 (14.9)	36.9 (15.3)	35.7 (15.2)		
Number of patients	60	123	120		
Week 80, Mean (SD)	36.3 (13.6)	40.0 (14.8)	38.0 (13.3)		
Number of patients	60	123	120		
Change from OL Baseline, Mean (SD)	-1.1 (11.3)	3.1 (12.6)	2.4 (12.7)		
LS Mean Change from OL baseline (SE) - ANCOVA*	-2.0 (1.5)	2.4 (1.1)	0.8 (1.1)	0.0096	0.0925

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

Table 15.2.7: 1 PFS-16 score at baseline, after 80 weeks for previously 248.524 patients and after 72 weeks for previously 248.636 patients and change from baseline, FAS, OC

248.636	PPX ER	PPX IR	PPX ER vs.PPX IR
PFS total score			
Number of patients, OL analysis	73	37	
OL Baseline, Mean (SD)	38.1 (15.1)	41.5 (13.8)	
Number of patients	73	37	
Week 72, Mean (SD)	40.7 (14.9)	43.0 (15.2)	
Number of patients	73	37	
Change from OL Baseline, Mean (SD)	2.6 (10.2)	1.4 (9.2)	
LS Mean Change from OL baseline (SE) - ANCOVA*	2.9 (1.2)	2.4 (1.6)	0.7946

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

Table 15.3.1: 3 Pramipexole doses respectively after 80 weeks compared to pramipexole doses at week 8 for previously 248.524 patients and after 72 weeks compared to pramipexole doses at week 0 for previously 248.636 patients - TS

Distribution of daily dose at week 8	248.524				
	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
N [N (%)]	76 (100.0)	153 (100.0)	139 (100.0)	292 (100.0)	368 (100.0)
0.375 mg [N (%)]	2 (2.6)	1 (0.7)	1 (0.7)	2 (0.7)	4 (1.1)
0.75 mg [N (%)]	1 (1.3)	9 (5.9)	9 (6.5)	18 (6.2)	19 (5.2)
1.5 mg [N (%)]	15 (19.7)	27 (17.6)	20 (14.4)	47 (16.1)	62 (16.8)
2.25 mg [N (%)]	6 (7.9)	15 (9.8)	13 (9.4)	28 (9.6)	34 (9.2)
3 mg [N (%)]	11 (14.5)	28 (18.3)	32 (23.0)	60 (20.5)	71 (19.3)
3.75 mg [N (%)]	4 (5.3)	15 (9.8)	15 (10.8)	30 (10.3)	34 (9.2)
4.5 mg [N (%)]	37 (48.7)	58 (37.9)	49 (35.3)	107 (36.6)	144 (39.1)
Dose in mg					
Mean (SD)	3.32 (1.34)	3.15 (1.30)	3.16 (1.26)	3.16 (1.28)	3.19 (1.29)

Pramipexole dose at week 8 corresponds to final pramipexole dose at end of 248.524 study

Source data: Appendix 16.2, Listing 7.1.2 eot\exposure.sas 27AUG2010

Table 15.3.1: 3 Pramipexole doses respectively after 80 weeks compared to pramipexole doses at week 8 for previously 248.524 patients and after 72 weeks compared to pramipexole doses at week 0 for previously 248.636 patients - TS

Distribution of daily dose at week 0	248.636		
	PPX ER	PPX IR	TOTAL PPX
N [N (%)]	95 (100.0)	48 (100.0)	143 (100.0)
1.5 mg [N (%)]	21 (22.1)	9 (18.8)	30 (21.0)
2.25 mg [N (%)]	23 (24.2)	9 (18.8)	32 (22.4)
3 mg [N (%)]	29 (30.5)	21 (43.8)	50 (35.0)
3.75 mg [N (%)]	11 (11.6)	4 (8.3)	15 (10.5)
4.5 mg [N (%)]	11 (11.6)	5 (10.4)	16 (11.2)
Dose in mg			
Mean (SD)	2.75 (0.95)	2.80 (0.89)	2.76 (0.93)

Pramipexole dose at week 0 corresponds to final pramipexole dose at end of 248.636 study

Table 15.3.2: 1 Adverse event overall summary - TS

Treatment analysis: On-treatment (Taper inc.), by rando. TRT + TOTAL (WO=2d)

	248.524				
	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	TOTAL PPX N (%)	TOTAL PPX ER N (%)
Number of patients	76 (100.0)	153 (100.0)	139 (100.0)	292 (100.0)	368 (100.0)
Patients with any AE	63 (82.9)	125 (81.7)	123 (88.5)	248 (84.9)	311 (84.5)
Patients with severe AEs	9 (11.8)	14 (9.2)	14 (10.1)	28 (9.6)	37 (10.1)
Patients with investigator defined drug-related AEs	40 (52.6)	68 (44.4)	60 (43.2)	128 (43.8)	168 (45.7)
Patients with other significant AEs (according to ICH E3)	16 (21.1)	27 (17.6)	28 (20.1)	55 (18.8)	71 (19.3)
Patient with other significant AEs (without allowed dose reductions)	14 (18.4)	25 (16.3)	27 (19.4)	52 (17.8)	66 (17.9)
Patients with AEs leading to discontinuation of trial drug	12 (15.8)	15 (9.8)	10 (7.2)	25 (8.6)	37 (10.1)
Patients with serious AEs	13 (17.1)	23 (15.0)	17 (12.2)	40 (13.7)	53 (14.4)
Fatal	1 (1.3)	4 (2.6)	2 (1.4)	6 (2.1)	7 (1.9)
Imm life-threatening	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Disability/incap.	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Req.hospitalisation	10 (13.2)	19 (12.4)	15 (10.8)	34 (11.6)	44 (12.0)
Prol.hospitalisation	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.3)	2 (1.3)	1 (0.7)	3 (1.0)	4 (1.1)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 13.0

Table 15.3.2: 1 Adverse event overall summary - TS

Treatment analysis: On-treatment (Taper inc.), by rando. TRT + TOTAL (WO=2d)

	248.636		
	PPX ER N (%)	PPX IR N (%)	TOTAL PPX N (%)
Number of patients	95 (100.0)	48 (100.0)	143 (100.0)
Patients with any AE	72 (75.8)	37 (77.1)	109 (76.2)
Patients with severe AEs	10 (10.5)	2 (4.2)	12 (8.4)
Patients with investigator defined drug-related AEs	22 (23.2)	11 (22.9)	33 (23.1)
Patients with other significant AEs (according to ICH E3)	15 (15.8)	6 (12.5)	21 (14.7)
Patient with other significant AEs (without allowed dose reductions)	7 (7.4)	3 (6.3)	10 (7.0)
Patients with AEs leading to discontinuation of trial drug	7 (7.4)	6 (12.5)	13 (9.1)
Patients with serious AEs	16 (16.8)	5 (10.4)	21 (14.7)
Fatal	1 (1.1)	0 (0.0)	1 (0.7)
Imm life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	1 (1.1)	0 (0.0)	1 (0.7)
Req.hospitalisation	16 (16.8)	5 (10.4)	21 (14.7)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 13.0