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 Interim Report**	Boehringer Ingelheim
Name of finished product: Sifrol®		**EudraCT No.:** 2007-004235-37	
Name of active ingredient: Pramipexole dihydrochloride		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 08 APR 2014	**Trial No. / U No.:** 248.634 / U11-1427-01	**Date of trial:** 04 JAN 2008 – 19 JUN 2010	**Date of revision :** Not applicable

Title of trial:	Long-term safety study of open-label pramipexole extended release (ER) in patients with advanced Parkinson's disease (PD)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial
Publication (reference):	Not applicable
Clinical phase:	III
Objectives:	The general aim of this study is to obtain long-term safety data on pramipexole ER. The objectives of this **final analysis** are summarized below: The primary objective was to obtain long-term safety and tolerability data on pramipexole ER (in daily doses from 0.375 mg to 4.5 mg q.d.) in patients who had previously completed a pramipexole double-blind (DB) study in advanced PD (248.525 trial). The secondary objectives were: - to evaluate the overnight switch from pramipexole IR to pramipexole ER after one week - to assess dose reduction in Levodopa - and to assess effects on efficacy criteria during long-term treatment with pramipexole ER
Methodology:	Double-blind transfer phase of up to six weeks followed by an open-label treatment phase of 74 weeks. The trial duration (initially 33 weeks) was prolonged to 81 weeks (change implemented by amendment (AM) 1 dated 21 January 2008)

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No. of subjects:	
planned:	entered: 390
actual:	enrolled: 391 entered and treated with pramipexole ER: 391 analysed (for efficacy, based on percent successfully switched): 228
Diagnosis and main criteria for inclusion:	Male or female patients with advanced idiopathic PD, who had completed trial 248.525, had a modified Hoehn and Yahr stage of II to IV at on-time and were concomitantly treated with L-Dopa^{+} (i.e. standard and/or controlled release Levodopa/DDC inhibitor), or with a combination of L-Dopa^{+} and entacapone. A concomitant treatment with one or more of the following drugs was allowed. If possible, it should have remained at a stable dose during the study, however patients were not dropped if the dose of such medication was altered: - 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 (for tremor symptoms).
Test product:	Pramipexole ER (tablets of 0.375 mg, 0.75 mg, 1.5 mg, 3.0 mg or 4.5 mg)
dose:	Double-blind transfer phase and open-label phase: 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg, once a day, in the morning (flexible dose during the up-titration and the open-label phase)
mode of admin.:	p.o.
batch no.:	Refer to 16.1.6

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Reference therapy:	Double-blind transfer phase : Placebo tablets matching the Pramipexole ER tablets Open label phase: No placebo tablets
dose:	Double-blind transfer phase: tablets administered once a day, in the morning
mode of admin.:	p.o.
batch no.:	Refer to 16.1.6
Duration of treatment:	Up to six week double-blind transfer phase, followed by an open-label treatment phase of 74 weeks. In this final report all patients treated up to visit 13 (week 80) or prematurely withdrawn before this visit have been analyzed.

Criteria for evaluation:

Efficacy / clinical pharmacology:

The primary focus of data collection was safety information. However, some efficacy measurements were collected:

Efficacy criteria:

- Percentage of patients successfully switched over night from pramipexole IR or ER to pramipexole ER, regarding UPDRS II+III score. A patient was assessed as successfully switched regarding UPDRS II+III score, if he/she had converted to ER without a worsening of UPDRS II+III score by more than 15% from baseline* (for patients with UPDRS II+III score >20 points at baseline of 248.634) or without a worsening of UPDRS II+III score by more than 3 points from baseline (for patients with UPDRS II+III score ≤20 points at baseline of 248.634).
-- Percentage of patients successfully switched over night from pramipexole IR or ER to pramipexole ER, regarding off-time. A patient was assessed as successfully switched regarding off-time, if he/she had converted to ER without a worsening of off-time by more than 12.5% from baseline* after one week;
- UPDRS parts II+III score (change from baseline*);
- Percentage off-time during waking hours – diary based (change from baseline*);

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Efficacy / clinical pharmacology (cont.):

- 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*);
- L-Dopa daily dose (change from baseline*);
- Response in Clinical Global Impression of Improvement (CGI-I);

  Response in Patient Global Impression of Improvement (PGI-I);
- Response in Patient Global Impression of Improvement (PGI-I) for early morning off-symptoms;
- UPDRS I, II, III and IV scores separately (change from baseline*);
- Parkinson's fatigue scale (PFS-16) (change from baseline*);
- Proportion of patients with at least a 20% improvement relative to baseline* in the UPDRS II+III total score;
- Pramipexole dose (change from baseline*)

*Baseline scores were either the scores at entrance in the previous double-blind trial (248.525), or the scores at entrance in the 248.634 trial, depending on the endpoints.

Safety: Incidence of adverse events, proportion of withdrawals due to adverse events, vital signs (blood pressure and pulse rate), weight, Epworth Sleepiness Scale (ESS) and the modified Minnesota Impulsive Disorders Interview (mMIDI).

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Statistical methods:

Statistical analyses:

All efficacy criteria were stratified based on previous treatment group (placebo or pramipexole IR/ER) in the previous DB trial.

- Based on UPDRS II+ III score and percent off-time during waking time, the percentage of patients successfully switched from the IR or ER double-blind treatment to ER open-label treatment was descriptively analysed by a centre stratified Cochran-Mantel-Haenszel test.

As no randomised groups were observed in this trial, all statistical results had to be interpreted exploratively.

Sample size calculation:

It was assumed that approximately 75% of patients who had previously participated in a pramipexole double-blind (DB) study in advanced PD (248.525 trial) would enter the open-label extension trial 248.634. As 516 entered patients were planned in the 248.525 trial, 390 patients were expected in the 248.634 trial.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The results confirmed maintenance of efficacy of an open-label treatment with pramipexole ER as assessed on the mean change in UPDRS II+III total score and the percentage off-time.

Maintenance of efficacy of pramipexole ER was confirmed by mean change on the UPDRS II+III total score and the percentage off-time after 80 weeks of treatment. Efficacy remained stable with long-term open-label treatment with pramipexole ER, the adjusted mean changes from open label (OL) baseline to week 80 in the UPDRS II+III score being: 1.1 point in the ex-PPX ER and 2.5 points in the ex-PPX IR groups.

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Efficacy / clinical pharmacology results (cont.):	Based on UPDRS II+III total score, the percentage of patients successfully switched to PPX ER open-label within one week was comparable in Ex-PPX IR and Ex-PPX ER groups: 86.2% of patients (95% CI 78.8 to 91.7) were successfully switched double-blind from PPX IR to PPX ER compared to 83.8% of patients (95% CI 75.3 to 90.3) successfully switched double-blind from PPX ER to PPX ER (p=0.9039). Based on percentage off time, the percentage of patients successfully switched to PPX ER open label within one week was slightly higher in Ex-PPX IR group than in Ex-PPX ER group: 63.6% of patients (95% CI 53.9 to 72.6) were successfully switched double-blind from PPX IR to PPX ER compared to 60.0% of patients (95% CI 49.4 to 69.9) successfully switched double blind from PPX ER to PPX ER (p=0.3996). The percentage of patients successfully switched (for both endpoints) was even slightly higher in patients switched from PPX IR to PPX ER (86.2% for UPDRS II+III and 63.6% for off-time), compared to those switched from PPX ER to PPX ER (the 'pseudo-switch' control group) (83.8 % for UPDRS II+II and 60.0% for off-time). Based on these data, an overnight switch from PPX IR to PPX ER at the same daily dose can be recommended in patients with advanced PD.
Safety results:	Overall, 324 patients (82.9%) experienced at least one AE under the mean PPX ER dose of 2.90 mg/day. As expected, the proportion of patients experiencing any AE was slightly higher in the Ex-placebo group (110 patients (85.3%)) compared to the Ex-PPX total group (214 patients (81.7%)). Most AEs were of mild or moderate intensity; 47 patients (12.0%) experienced at least one severe AE. Most frequent (≥5%) AEs with a long-term open-label treatment with PPX ER were, by decreasing frequency: dyskinesia, somnolence, dizziness, fall, insomnia, cataract, nausea, hallucination, and dystonia. The system organ classes (SOCs) in which AEs were most frequently reported were nervous system disorders, followed by psychiatric disorders Thirty-one patients (on treatment) (7.9%) experienced an AE leading to discontinuation. Overall, 191 patients (48.8%) experienced drug related AEs; they were most frequently reported in the SOCs nervous system disorders, psychiatric disorders, and gastrointestinal disorders.

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Safety results (cont.):	Thirty-nine patients reported SAEs, five of them were considered to be drug related. Four patients died due to an SAE; none of these SAEs was considered as drug-related. No patient experienced sudden onset of sleep (SOOS), three patients reported a sleep attack during the trial. Eleven patients experienced a treatment emergent symptomatic orthostatic hypotension during a study visit assessment. Nine patients (2.3%) had a treatment emergent abnormal behaviour (3 Ex-Placebo, 2 Ex-PPX ER and 4 Ex-PPX IR). No new, unexpected, or increased safety risk was identified with pramipexole ER in this open-label long-term trial, compared to the data reported in the previous DB trial 248.525.
Conclusions:	In summary, long term efficacy of pramipexole ER in advanced PD patients was demonstrated after 80 weeks of treatment. In addition, patients can be safely switched overnight from PPX IR to PPX ER at the same total daily dose, while maintaining efficacy. The overall safety profile showed that PPX ER at the mean dose of 2.90 mg/day was well tolerated by patients with advanced PD. No new, unexpected, or increased safety risk was identified with pramipexole ER in this open-label long-term trial, compared to data reported in the previous DB trial 248.525. Long-term treatment added the following most common (≥5%) AEs: insomnia, dizziness, fall, and cataract while the following two most common AEs reported in previous DB trial 248.525, headache and constipation, were no longer reported as most common AEs in trial 248.634.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and/or 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**
Patient Disposition	Table 15.1.1: 1
UPDRS II + III change from baseline after 80 weeks treatment	Table 15.2.1: 12
Percentage off time during waking hours, change from baseline after 80 weeks treatment	Table 15.2.2.1: 12
UPDRS II + III Response (>=20% improvement) from OL baseline, 80 weeks treatment	Table 15.2.1: 41
Percentage on time without dyskinesia during waking hours after 80 weeks, change from baseline	Table 15.2.3.1: 1
Percentage on time with non troublesome dyskinesia during waking hours after 80 weeks, change from baseline	Table 15.2.4: 1
Percentage on time without dyskinesia or with non troublesome dyskinesia during waking hours after 80 weeks, change from baseline	Table 15.2.5: 1
Percentage on time with troublesome dyskinesia during waking hours at baseline, after 80 weeks, change from baseline	Table 15.2.6: 1
Response in CGI−I over 32 weeks	Table 15.2.7: 13
Response in PGI−I over 32 weeks	Table 15.2.8: 13
Response in PGI−I for early morning off symptoms over 32 weeks	Table 15.2.9: 13

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

	248.525				
	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total PPX N (%)	Total PPX ER N (%)
Enrolled				262	391
Not entered/randomised				0	0
Entered/randomised	129	123	139	262	391
Not treated	0	0	0	0	0
Treated	129 (100.0)	123 (100.0)	139 (100.0)	262 (100.0)	391 (100.0)
Treated transfer and/or OL phase	129 (100.0)	123 (100.0)	139 (100.0)	262 (100.0)	391 (100.0)
Not prematurely discontinued transfer and/or OL phase	113 (87.6)	104 (84.6)	112 (80.6)	216 (82.4)	329 (84.1)
Prematurely discontinued transfer and/or OL phase	16 (12.4)	19 (15.4)	27 (19.4)	46 (17.6)	62 (15.9)
Adverse event	11 (8.5)	7 (5.7)	14 (10.1)	21 (8.0)	32 (8.2)
AE study dis. worse	3 (2.3)	1 (0.8)	4 (2.9)	5 (1.9)	8 (2.0)
AE other dis. worse	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	1 (0.3)
AE other	8 (6.2)	6 (4.9)	9 (6.5)	15 (5.7)	23 (5.9)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non compl. protocol	0 (0.0)	1 (0.8)	1 (0.7)	2 (0.8)	2 (0.5)
Lost to follow-up	0 (0.0)	3 (2.4)	4 (2.9)	7 (2.7)	7 (1.8)
Refused cont. medic.	5 (3.9)	5 (4.1)	6 (4.3)	11 (4.2)	16 (4.1)
Other	0 (0.0)	3 (2.4)	2 (1.4)	5 (1.9)	5 (1.3)
Treated taper down phase	91 (70.5)	88 (71.5)	98 (70.5)	186 (71.0)	277 (70.8)
Not prematurely discontinued taper down phase	86 (66.7)	84 (68.3)	92 (66.2)	176 (67.2)	262 (67.0)
Prematurely discontinued taper down phase	5 (3.9)	4 (3.3)	6 (4.3)	10 (3.8)	15 (3.8)
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	5 (3.9)	4 (3.3)	6 (4.3)	10 (3.8)	15 (3.8)
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)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Number of patients treated in transfer and/or OL phase but with no taper down performed: 114

Source data: Section 15, Table 1.1: 3 eot\dispt.sas 02SEP2010

Table 15.2.1: 12 UPDRS II + III total score at baseline, after 80 weeks and change from baseline, FAS, OC

248.525	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
UPDRS II+III total score					
Number of patients, DB analysis	113	103	111		
DB Baseline, Mean (SD)	38.0 (17.1)	40.3 (16.9)	37.6 (16.5)		
Number of patients, OL analysis	113	102	112		
OL Baseline, Mean (SD)	30.5 (16.3)	27.1 (15.9)	25.6 (17.2)		
Number of patients	113	103	112		
Week 80, Mean (SD)	27.1 (16.2)	28.8 (18.7)	28.9 (21.1)		
Number of patients	113	103	111		
Change from DB Baseline, Mean (SD)	-10.9 (13.8)	-11.4 (18.2)	-8.7 (15.8)		
Number of patients	113	102	112		
Change from OL Baseline, Mean (SD)	-3.4 (10.5)	1.9 (12.2)	3.2 (12.7)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-11.1 (1.8)	-11.5 (2.0)	-9.1 (1.9)	0.8229	0.3275
LS Mean Change from OL baseline (SE) - ANCOVA*	-3.6 (1.5)	1.1 (1.6)	2.5 (1.5)	0.0039	0.0001

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

Table 15.2.2.1: 12 Percentage off time during waking hours total score at baseline, after 80 weeks and change from baseline, FAS, OC

248.525	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% off time during waking hours					
Number of patients, DB analysis	110	100	108		
DB Baseline, Mean (SD)	38.0 (14.4)	35.9 (15.4)	37.3 (12.6)		
Number of patients, OL analysis	108	100	108		
OL Baseline, Mean (SD)	28.0 (18.5)	22.4 (17.2)	20.3 (14.8)		
Number of patients	110	100	108		
Week 80, Mean (SD)	25.1 (17.0)	24.1 (18.0)	24.4 (17.8)		
Number of patients	110	100	108		
Change from DB Baseline, Mean (SD)	-13.0 (19.2)	-11.9 (19.6)	-12.9 (20.1)		
Number of patients	108	100	108		
Change from OL Baseline, Mean (SD)	-2.8 (17.1)	1.7 (19.8)	4.0 (14.4)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-13.8 (2.1)	-14.6 (2.3)	-13.8 (2.2)	0.7331	0.9965
LS Mean Change from OL baseline (SE) - ANCOVA*	-1.5 (2.0)	-0.3 (2.1)	1.7 (2.0)	0.5590	0.1289

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

Table 15.2.1: 41 UPDRS II + III Response (>=20% improvement) from OL baseline, 80 weeks treatment, FAS, OC

	248.525				
	Placebo	PPX ER	PPX IR	Total PPX	TOTAL PPX ER
UPDRS II+III responder					
Week 80					
Number of patients	113	102	112	214	327
Responder [N,(%)]	35 (31.0)	30 (29.4)	31 (27.7)	61 (28.5)	96 (29.4)

UPDRS II+III Response: At least 20% improvement relative to Baseline (OL) in the UPDRS II+III total score
The interesting baseline is OL baseline

Table 15.2.3.1: 1 Percentage on time without dyskinesia during waking hours at baseline, after 80 weeks and change from baseline, FAS, OC

248.525	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on without dyskinesia					
Number of patients, DB analysis	110	100	108		
DB Baseline, Mean (SD)	51.2 (21.0)	52.7 (19.0)	53.2 (17.4)		
Number of patients, OL analysis	108	100	108		
OL Baseline, Mean (SD)	62.5 (22.9)	66.5 (23.8)	66.9 (24.3)		
Number of patients	110	100	108		
Week 80, Mean (SD)	60.5 (26.4)	67.1 (22.9)	63.3 (24.9)		
Number of patients	110	100	108		
Change from DB Baseline, Mean (SD)	9.3 (26.5)	14.4 (22.2)	10.1 (23.6)		
Number of patients	108	100	108		
Change from OL Baseline, Mean (SD)	-1.8 (24.1)	0.6 (20.4)	-3.6 (18.6)		
LS Mean Change from DB baseline (SE) - ANCOVA*	9.5 (2.9)	16.1 (3.1)	11.3 (3.0)	0.0399	0.5736
LS Mean Change from OL baseline (SE) - ANCOVA*	-1.6 (2.5)	2.9 (2.7)	-2.0 (2.6)	0.1073	0.8694

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

Table 15.2.4: 1 Percentage on time with non troublesome dyskinesia during waking hours at baseline, after 80 weeks and change from baseline, FAS, OC

248.525	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on with non troublesome dyskinesia					
Number of patients, DB analysis	110	100	108		
DB Baseline, Mean (SD)	8.1 (15.0)	7.7 (13.6)	7.0 (13.8)		
Number of patients, OL analysis	108	100	108		
OL Baseline, Mean (SD)	7.3 (14.0)	8.1 (16.1)	9.9 (19.1)		
Number of patients	110	100	108		
Week 80, Mean (SD)	12.1 (22.3)	6.0 (14.0)	10.0 (15.3)		
Number of patients	110	100	108		
Change from DB Baseline, Mean (SD)	4.0 (20.8)	-1.7 (13.4)	3.0 (13.9)		
Number of patients	108	100	108		
Change from OL Baseline, Mean (SD)	4.4 (15.8)	-2.1 (12.8)	0.0 (15.1)		
LS Mean Change from DB baseline (SE) - ANCOVA*	5.2 (2.0)	-0.9 (2.1)	3.5 (2.1)	0.0047	0.4227
LS Mean Change from OL baseline (SE) - ANCOVA*	3.8 (1.8)	-2.7 (1.9)	0.2 (1.8)	0.0009	0.0573

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

Table 15.2.5: 1 Percentage on time without dyskinesia or with non troublesome dyskinesia during waking hours at baseline, after 80 weeks and change from baseline, FAS, OC

248.525	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on w/o dysk. or with non tbl. dysk.					
Number of patients, DB analysis	110	100	108		
DB Baseline, Mean (SD)	59.3 (15.0)	60.4 (16.1)	60.2 (13.7)		
Number of patients, OL analysis	108	100	108		
OL Baseline, Mean (SD)	69.8 (18.9)	74.6 (19.2)	76.9 (17.9)		
Number of patients	110	100	108		
Week 80, Mean (SD)	72.6 (18.9)	73.1 (19.7)	73.3 (18.6)		
Number of patients	110	100	108		
Change from DB Baseline, Mean (SD)	13.3 (20.6)	12.7 (22.4)	13.1 (21.3)		
Number of patients	108	100	108		
Change from OL Baseline, Mean (SD)	2.7 (19.2)	-1.5 (22.9)	-3.6 (15.8)		
LS Mean Change from DB baseline (SE) - ANCOVA*	14.7 (2.3)	15.4 (2.5)	14.9 (2.5)	0.7949	0.9526
LS Mean Change from OL baseline (SE) - ANCOVA*	1.8 (2.2)	0.7 (2.3)	-0.9 (2.3)	0.6434	0.2469

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

Table 15.2.6: 1 Percentage on time with troublesome dyskinesia during waking hours at baseline, after 80 weeks and change from baseline, FAS, OC

248.525	Placebo	PPX ER	PPX IR	PPX ER vs.Placebo	PPX IR vs.Placebo
% on with troublesome dyskinesia					
Number of patients, DB analysis	110	100	108		
DB Baseline, Mean (SD)	2.7 (7.3)	3.7 (8.0)	2.5 (7.8)		
Number of patients, OL analysis	108	100	108		
OL Baseline, Mean (SD)	2.2 (6.9)	3.0 (10.6)	2.8 (10.0)		
Number of patients	110	100	108		
Week 80, Mean (SD)	2.3 (7.6)	2.8 (11.2)	2.3 (7.3)		
Number of patients	110	100	108		
Change from DB Baseline, Mean (SD)	-0.3 (9.1)	-0.8 (12.5)	-0.2 (10.0)		
Number of patients	108	100	108		
Change from OL Baseline, Mean (SD)	0.1 (7.7)	-0.2 (12.3)	-0.5 (9.4)		
LS Mean Change from DB baseline (SE) - ANCOVA*	-0.9 (1.1)	-0.7 (1.2)	-1.1 (1.1)	0.8695	0.8961
LS Mean Change from OL baseline (SE) - ANCOVA*	-0.4 (1.0)	-0.3 (1.1)	-0.7 (1.1)	0.9741	0.7620

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

Table 15.2.7: 13 Response in CGI-I
FAS, OC

	248.525				
	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
Week 1					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	139 (100.0)	262 (100.0)	391 (100.0)
Responder [N (%)]	20 (15.5)	102 (82.9)	125 (89.9)	227 (86.6)	247 (63.2)
Week 3					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	139 (100.0)	262 (100.0)	391 (100.0)
Responder [N (%)]	30 (23.3)	110 (89.4)	116 (83.5)	226 (86.3)	256 (65.5)
Week 5					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	135 (100.0)	258 (100.0)	387 (100.0)
Responder [N (%)]	44 (34.1)	114 (92.7)	120 (88.9)	234 (90.7)	278 (71.8)
Week 8					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	133 (100.0)	256 (100.0)	385 (100.0)
Responder [N (%)]	55 (42.6)	117 (95.1)	128 (96.2)	245 (95.7)	300 (77.9)
Week 14					
Number of patients [N (%)]	127 (100.0)	120 (100.0)	131 (100.0)	251 (100.0)	378 (100.0)
Responder [N (%)]	58 (45.7)	114 (95.0)	120 (91.6)	234 (93.2)	292 (77.2)
Week 20					
Number of patients [N (%)]	126 (100.0)	119 (100.0)	128 (100.0)	247 (100.0)	373 (100.0)
Responder [N (%)]	53 (42.1)	102 (85.7)	113 (88.3)	215 (87.0)	268 (71.8)

The interesting baseline is OL baseline
Responders for Placebo = At least Much improved - Responders for PPX = No change to Very much improved
According to amendment 1, it was not required to record CGI at week 80

Source data: Appendix 16.2, Listing 6.10 eot\second_eot.sas 03SEP2010

Table 15.2.7: 13 Response in CGI-I
FAS, OC

	248.525				
	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
Week 26					
Number of patients [N (%)]	126 (100.0)	117 (100.0)	128 (100.0)	245 (100.0)	371 (100.0)
Responder [N (%)]	49 (38.9)	104 (88.9)	118 (92.2)	222 (90.6)	271 (73.0)
Week 32					
Number of patients [N (%)]	124 (100.0)	115 (100.0)	124 (100.0)	239 (100.0)	363 (100.0)
Responder [N (%)]	50 (40.3)	106 (92.2)	114 (91.9)	220 (92.1)	270 (74.4)

The interesting baseline is OL baseline
Responders for Placebo = At least Much improved - Responders for PPX = No change to Very much improved
According to amendment 1, it was not required to record CGI at week 80

Source data: Appendix 16.2, Listing 6.10 eot\second_eot.sas 03SEP2010

Table 15.2.8: 13 Response in PGI-I
FAS, OC

	248.525				
	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
Week 1					
Number of patients [N (%)]	129 (100.0)	122 (100.0)	139 (100.0)	261 (100.0)	390 (100.0)
Responder [N (%)]	14 (10.9)	100 (82.0)	117 (84.2)	217 (83.1)	231 (59.2)
Week 2 (TC1)					
Number of patients [N (%)]	129 (100.0)	121 (100.0)	139 (100.0)	260 (100.0)	389 (100.0)
Responder [N (%)]	14 (10.9)	105 (86.8)	128 (92.1)	233 (89.6)	247 (63.5)
Week 3					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	139 (100.0)	262 (100.0)	391 (100.0)
Responder [N (%)]	30 (23.3)	103 (83.7)	111 (79.9)	214 (81.7)	244 (62.4)
Week 4 (TC2)					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	135 (100.0)	258 (100.0)	387 (100.0)
Responder [N (%)]	21 (16.3)	114 (92.7)	117 (86.7)	231 (89.5)	252 (65.1)
Week 5					
Number of patients [N (%)]	129 (100.0)	122 (100.0)	135 (100.0)	257 (100.0)	386 (100.0)
Responder [N (%)]	39 (30.2)	110 (90.2)	113 (83.7)	223 (86.8)	262 (67.9)
Week 6 (TC3)					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	133 (100.0)	256 (100.0)	385 (100.0)
Responder [N (%)]	31 (24.0)	119 (96.7)	120 (90.2)	239 (93.4)	270 (70.1)

The interesting baseline is OL baseline
Responders for Placebo = At least Much better - Responders for PPX = No change to Very much better
According to amendment 1, it was not required to record PGI at week 80

Source data: Appendix 16.2, Listing 6.10 eot\second_eot.sas 03SEP2010

Table 15.2.8: 13 Response in PGI-I
FAS, OC

	248.525				
	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
Week 8					
Number of patients [N (%)]	129 (100.0)	123 (100.0)	133 (100.0)	256 (100.0)	385 (100.0)
Responder [N (%)]	51 (39.5)	114 (92.7)	123 (92.5)	237 (92.6)	288 (74.8)
Week 14					
Number of patients [N (%)]	127 (100.0)	120 (100.0)	131 (100.0)	251 (100.0)	378 (100.0)
Responder [N (%)]	50 (39.4)	108 (90.0)	117 (89.3)	225 (89.6)	275 (72.8)
Week 20					
Number of patients [N (%)]	126 (100.0)	119 (100.0)	129 (100.0)	248 (100.0)	374 (100.0)
Responder [N (%)]	43 (34.1)	99 (83.2)	111 (86.0)	210 (84.7)	253 (67.6)
Week 26					
Number of patients [N (%)]	126 (100.0)	116 (100.0)	128 (100.0)	244 (100.0)	370 (100.0)
Responder [N (%)]	43 (34.1)	101 (87.1)	119 (93.0)	220 (90.2)	263 (71.1)
Week 32					
Number of patients [N (%)]	124 (100.0)	115 (100.0)	124 (100.0)	239 (100.0)	363 (100.0)
Responder [N (%)]	45 (36.3)	102 (88.7)	113 (91.1)	215 (90.0)	260 (71.6)

The interesting baseline is OL baseline
Responders for Placebo = At least Much better - Responders for PPX = No change to Very much better
According to amendment 1, it was not required to record PGI at week 80

Source data: Appendix 16.2, Listing 6.10 eot\second_eot.sas 03SEP2010

Table 15.2.9: 13 Response in PGI-I for early morning off symptoms
FAS, OC

	248.525				
	Placebo	PPX ER	PPX IR	TOTAL PPX	TOTAL PPX ER
Week 8					
Number of patients [N (%)]	129 (100.0)	122 (100.0)	135 (100.0)	257 (100.0)	386 (100.0)
Responder [N (%)]	42 (32.6)	114 (93.4)	125 (92.6)	239 (93.0)	281 (72.8)
Week 20					
Number of patients [N (%)]	126 (100.0)	120 (100.0)	129 (100.0)	249 (100.0)	375 (100.0)
Responder [N (%)]	47 (37.3)	105 (87.5)	111 (86.0)	216 (86.7)	263 (70.1)
Week 32					
Number of patients [N (%)]	125 (100.0)	116 (100.0)	125 (100.0)	241 (100.0)	366 (100.0)
Responder [N (%)]	45 (36.0)	103 (88.8)	112 (89.6)	215 (89.2)	260 (71.0)

The interesting baseline is OL baseline
Responders for Placebo = At least Much better - Responders for PPX = No change to Very much better

Source data: Appendix 16.2, Listing 6.10 eot\second_eot.sas 03SEP2010