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.

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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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Disclosure Synopsis date: 28 MAR 2014	**Trial No. / U No.:** 248.636 / U08-1964-01	**Dates of trial:** 01 NOV 07 – 22 MAY 08	**Date of revision** (if applicable):

Title of trial:	A double-blind, double-dummy, randomized, parallel groups study to assess the Efficacy, Safety and Tolerability of switching patients with early Parkinson's disease (PD) from Pramipexole IR to Pramipexole ER or Pramipexole IR.
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicenter Study, 3 countries, 26 active sites
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	- To assess if patients with early Parkinson's disease (PD) could be successfully switched (overnight switching) from Pramipexole IR to Pramipexole ER; - To establish if this successful switch could be obtained with or without dose-adaptation; - To provide information about the conversion ratio (mg:mg) from Pramipexole IR to Pramipexole ER.
Methodology:	A double-blind, double-dummy, randomized, parallel group design
No. of subjects:	
planned:	entered: 132 (120 for the PPS)
actual:	enrolled: 169 entered: 156 Treatment Pramipexole ER: entered: 104; treated: 104; analysed with FAS: 103; analysed with PPS: 100 Treatment Pramipexole IR: entered: 52; treated: 52; analysed with FAS: 52; analysed with PPS: 49
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. Patients should have been on Pramipexole IR for at least 3 months prior to

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Diagnosis and main criteria for inclusion: (continued)	baseline (V2). The Pramipexole dose should have been optimized (according to the investigator's judgement), greater or equal to 1.5 mg/day, stable and equally divided 3 times per day, for a least 4 weeks prior to baseline visit (V2). A concomitant treatment with levodopa was allowed, provided patients did not experience any motor complications (e.g. on-off phenomena, dyskinesia) under levodopa therapy. Patients should not have been treated with a dopamine agonist (except Pramipexole IR) within 3 months 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 provided the investigator did not intent to change this treatment during the study): - L-Dopa^{+} (i.e. standard and/or controlled release Levodopa/DDC inhibitor), or with a fixed combination of L-Dopa^{+} and entacapone, at an optimized dose according to the investigator's judgement; - anti-Parkinsonian anticholinergics; - MAOB-Inhibitors (e.g. selegiline, rasagiline); - amantadine; - entacapone (or other COMT-Inhibitors) - beta-blockers (e.g. propranolol) when used to treat PD (tremor symptoms). Patients should not have discontinued Pramipexole IR in the past due to any clinically significant adverse event related to Pramipexole IR, according to the 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, once a day, in the morning.
mode of admin.:	Per os
batch no.:	Please refer to Appendix 16.1.6.

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Reference therapy:	- Pramipexole IR (tablets of 0.125 mg, 0.25 mg, 0.50 mg, 1.0 mg and 1.5 mg) - Placebo tablets matching the Pramipexole ER tablets - Placebo tablets matching the Pramipexole IR tablets
dose:	- Tablets administered in equally divided doses three times per day, to achieve a total daily dose of 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg. - Matching placebos of Pramipexole ER - Matching placebos of Pramipexole IR
mode of admin.:	Per os
batch no.:	Please refer to Appendix 16.1.6.
Duration of treatment:	The maximum total trial duration was 14 weeks. After an up to 4-week open-label run-in phase with Pramipexole IR, patients were randomized to Pramipexole ER or Pramipexole IR in a 9-week double-blind phase, as described below: <u>Two-to-4 week open-label run-in phase</u> with Pramipexole IR. During this run-in phase (from Visit 1 to Visit 2), Pramipexole IR and all other anti-Parkinsonian treatments should be maintained at a stable dose. At the end of this run-in phase, patients were randomly switched with a 1:1 (mg mg) conversion ratio from Pramipexole IR, to either Pramipexole ER or Pramipexole IR. <u>Nine-week double-blind phase</u>, divided into two phases: - Maintenance phase N°1 (from Visit 2: day 0 to Visit 3: week 4). During this maintenance phase, Pramipexole and all other anti-Parkinsonian treatments had to be maintained at a stable dose. - Maintenance phase N°2 (from Visit 3: week 4 to Visit 4: week 5 then to Visit 5: week 9). During this maintenance phase, Pramipexole and all other anti-Parkinsonian treatments should had to be maintained at a stable dose. However, a possible dose adaptation of study medication could be performed at V3 and/or at V4 in case of worsening of the UPDRS II+III score by more than 15% compared to baseline. At the end of the double-blind maintenance treatment phase N°2, patients were eligible to enter an open-label extension study, where they received Pramipexole ER.

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Duration of treatment: (continued)	Patients not entering the open-label extension study had two options: either to continue with Pramipexole IR at the same dose than in the double-blind treatment (V5 dose), or to receive another treatment according the investigator's judgement. In this last case, a 1-week down-titration phase of Pramipexole was performed.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary efficacy endpoint: The primary efficacy endpoint was the proportion of patients successfully switched from Pramipexole IR to Pramipexole ER or IR at the end of maintenance phase N°2 (visit 5), with a possible dose adaptation. Key-secondary efficacy endpoint: - Proportion of patients successfully switched at the end of maintenance phase N°1 (visit 3) without a dose adaptation; Secondary efficacy endpoints: - UPDRS (Unified Parkinson's Disease Rating Scale) parts II+III score (change from Baseline); - Clinical Global Impression of Improvement (CGI-I); - Patient Global Impression of Improvement (PGI-I); - UPDRS II and III separately (change from Baseline); - Percentage of patients requiring dose adaptation; - Proportion of patients being successfully switched at visit 4; - Pramipexole daily dose (change from baseline)
Safety:	Incidence of adverse events, proportion of withdrawals due to adverse events (either drug-related or not), vital signs (blood pressure and pulse rate), weight, Epworth Sleepiness Scale (ESS), Modified Minnesota Impulsive Disorders Interview (mMIDI).
Statistical methods:	Primary analysis: Treatment group comparisons were performed using a Cochran-Mantel-Haenszel (CMH) test for the percentage of patients successfully switched in the two treatment groups with country stratification. The difference in proportions between patients successfully switched from Pramipexole IR to IR or ER was

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Statistical methods: (continued)

tested with one-sided non inferiority statistical test at the 5 % level of significance and a non-inferiority margin of 15 %.

A patient was considered as successfully switched at week 9, with a possible dose adaptation, if the following condition was fulfilled:

- No worsening of the UPDRS II+III score by more than 15% from Visit 2 (week 0) to Visit 5 (week 9) and no drug-related adverse events leading to withdrawal.

Key-secondary analysis:

A patient was considered as successfully switched at week 4, without a dose-adaptation if the following condition was fulfilled:

- No worsening of the UPDRS II+III score by more than 15% from Visit 2 (week 0) to Visit 3 (week 4) and no drug-related adverse events leading to withdrawal.

The key-secondary endpoint was tested again with a non-inferiority statistical test within a closed testing procedure.

Secondary analyses:

An analysis of covariance (ANCOVA) was used for change from Visit 2 to Visit 3, Visit 4 and Visit 5 in the UPDRS II+III total score, adjusting for treatment and country (fixed effect) and baseline (covariate).

For UPDRS part II and III separately an ANCOVA analogously to their combination was performed. The global improvement as measured by CGI-I and PGI-I was analysed by a CMH test with country stratification.

The proportion of patients switched to the same, lower or higher dose in maintenance phase N°2 was calculated as well.

Sample size calculation:

Using a one-sided test level of 0.05 and about 80% power, a sample size of 120 patients (PPS) was sufficient to test the following two hypotheses:

- in case the success rate after switch was 95% for pramipexole IR and 91.5% for pramipexole ER, a non-inferiority margin of 15% was assumed,

- in case the success rate after switch was 90% for pramipexole IR and 85% for pramipexole ER, a non-inferiority margin of 20% was assumed.

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Statistical methods: (continued)

In order to observe more patients switching to PPX ER, the sample was randomized in relation 2:1 (PPX ER: PPX IR).

SUMMARY – CONCLUSIONS:

Efficacy results:

Demographic and baseline disease characteristics: Overall, there were 56.4% of male patients and patients' mean age was 63.7 years. Some characteristics were comparable between both treatment groups: the mean PD duration was 3.4 years for PPX ER and 3.2 years for PPX IR and most of the patients had a Hoehn&Yahr staging of 2 (43.3 % in PPX ER and 32.7% in PPX IR). The mean UPDRS part II+III total score was slightly lower in the PPX ER group (21.5 points) compared to the PPX IR group (23.4 points). The most common concomitant antiparkinsonian therapy was levodopa (taken by 56.7% of PPX ER patients and 51.9% of PPX IR patients), followed by MAOB-inhibitors (taken by 27.9% of PPX ER patients and 32.7% of PPX IR patients) and by amantadine (taken by 23.1% of patients in each group).

Overall compliance at all visits was good (99.7%) and comparable in both PPX ER and PPX IR groups.

Primary efficacy endpoint (FAS):
At 9 weeks, after a possible dose adaptation, 84.5% of patients in the PPX ER group were successfully switched, compared to 94.2% of patients in the PPX IR group. The between groups difference was -9.76%, 95%CI= [-18.81, 1.66].

Key-secondary efficacy endpoint (FAS):
At 4 weeks, without a possible dose adaptation, 81.6% of patients in the PPX ER group were successfully switched at the same daily dose (1:1 mg ratio) compared to 92.3% of patients in the PPX IR group. The difference between both groups was - 10.75%, 95%CI= [-20.51, 1.48].

Secondary efficacy endpoints (FAS):
The adjusted mean change in the UPDRS II+III total score from baseline to week 9 was greater in the PPX ER group (-1.6 points) compared to the PPX IR group (-0.5 points). An improvement over time was observed for PPX ER. At visit 3, patients in this group worsened by 0.7 point, whereas at the end of this trial an (unexpected) improvement of -1.6 points compared to baseline was observed.

The proportion of patients successfully switched at visit 4 (week 5) after one possible dose adaptation was almost comparable in both groups (PPX ER:

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Efficacy results: (continued)	84.5%, PPX IR: 86.5%). The percentage of CGI-I responders (i.e. from unchanged to very much improved) at week 9 in the PPX ER group was higher (87.4%) compared to the PPX IR group (78.8%). The percentage of PGI-I responders (i.e. from unchanged to very much better) at week 9 in the PPX ER group was also higher (81.6%) compared to the PPX IR group (71.2%). The adjusted mean change from baseline to week 9 for UPDRS II score was comparable in both groups (-0.3 points in PPX ER and -0.1 points in PPX IR). The adjusted mean change from baseline at week 9 for UPDRS III score was slightly larger in the PPX ER group (-1.2 points) than in the PPX IR group (-0.3 points). At week 9, 80.6% of patients in the PPX ER group and 84.6% of patients in the PPX IR group did not change their dose level compared to baseline. In the PPX ER group, the mean daily dose at final visit (week 9) was 2.75 mg, compared to 2.63 mg at the baseline visit, which represents an increase of 0.12 mg. In the PPX IR group, the mean daily dose at final visit (week 9) was 2.83 mg, compared to 2.74 mg at the baseline visit, which represents an increase of 0.09 mg. The conversion ratio from PPX IR to PPX ER at week 9 was 1:1.04 (Final dose / Baseline dose: 2.7476 mg / 2.6322 mg) (compared to 1:1.03 (Final dose / Baseline dose: 2.8269 mg / 2.7404 mg) for the conversion ratio from PPX IR to PPX IR). Based on these data, a switch from PPX IR to PPX ER at the same daily dose (1mg:1mg) can be recommended.
Safety results:	Overall, the incidence of AEs was low and comparable in both PPX ER (36.5%) and IR groups (30.8%). Based on system organ class, the most frequently reported AEs (at least 5% of both groups pooled) were by decreasing frequency: nervous system disorders (10.3% of pooled groups), psychiatric disorders (8.3%), gastrointestinal disorders (6.4%) and general disorders and administration site conditions (6.4%). Based on preferred terms (PT), the most frequently reported AEs (at least 2% of any treatment group), regardless of relationship to treatment, were by decreasing frequency: fatigue (3.8% of pooled groups), followed by headache (3.2%),

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Safety results: (continued)

somnolence (2.6%), nausea (2.6%).

Based on PT, the most common drug-related AEs in the PPX ER group were: somnolence (3 patients), fatigue (3 patients) and nausea (2 patients). In the PPX IR group, the most common drug-related AE was oedema peripheral (2 patients).

No patient had a SAE during the double-blind treatment phase.

Two patients (one in each group) had an AE leading to premature discontinuation.

One case of abnormal behaviour assessed with the mMIDI ("increased libido") was reported at Visit 5 (week 9) in the PPX IR group. In the PPX ER group, compulsive shopping was reported as an AE (lasting for 1 day) at Visit 3 (week 4). For this patient, the mMIDI sub-scale "compulsive buying" was negative.

Overall, mean values for systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate were comparable in both treatment groups at baseline and no relevant changes were observed at week 9 compared to baseline.

No relevant change was observed during the study for the ESS score.

Conclusions:

Overall, 81.6% of patients were successfully switched overnight from Pramipexole IR to Pramipexole ER without a dose adaptation and 84.5% of patients were successfully switched after a possible dose adaptation. Formally, non-inferiority between PPX ER and IR was not shown.

For some secondary endpoints, the PPX ER group showed numerically better results than the PPX IR group, e.g. adjusted mean change from baseline in UPDRS II+III total score of -1.6 points in the PPX ER group, compared to -0.5 points in the PPX IR group; 87.4% of PPX ER patients were CGI-I responders compared to 78.8% of PPX IR patients; and 81.6% of PPX ER patients were PGI-I responders compared to 71.2% of PPX IR patients.

In the PPX ER group, 19.4% (2.9% + 16.5%) of patients adapted their Pramipexole daily dose during the trial, compared to 15.4% (1.9% + 13.5%) of

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Conclusions: (continued)

patients in the PPX IR group. Therefore, there was no difference between the two groups.

The mean pramipexole dose at week 9 compared to baseline was almost unchanged, leading to a conversion ratio from PPX IR to PPX ER at week 9 of 1:1.04 (Final dose / Baseline dose: 2.7476 mg / 2.6322 mg). Therefore, a switch from PPX IR to PPX ER at the same daily dose (1 mg : 1 mg) can be recommended.

The overall safety profile was good for both PPX ER and PPX IR, without any notable difference between the 2 Pramipexole formulations.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the disposition results and the results for the secondary endpoints for 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
Analysis of change in UPDRS II+III Total Score after 9 weeks	Table 15.2.2.2: 1
Analysis of change in CGI-I Response Rate after 9 weeks	Table 15.2.2.3: 1
Analysis of change in PGI-I Response Rate after 9 weeks	Table 15.2.2.4: 1
Analysis of change in UPDRS II Total Score after 9 weeks	Table 15.2.2.5: 1
Analysis of change in UPDRS III Total Score after 9 weeks	Table 15.2.2.6: 1
Analysis of change in Pramipexole daily dose from baseline after 9 weeks	Table 15.2.2.9: 1
Analysis of amount of treatment taken (source data for calculation of conversion ratio from PPX IR to PPX ER)	Table 15.3.1: 2

Table 15.1.1: 1 Patient disposition and patient eligibilty, all patients

	Pramipexole ER	Pramipexole IR	Total
Enrolled			169
Not Randomised			13
Randomised	104	52	156
Not Treated	0	0	0
Treated with double-blind medication	104 (100.0)	52 (100.0)	156 (100.0)
NOT Prematurely Discontinued	100 (96.2)	49 (94.2)	149 (95.5)
Prematurely Discontinued	4 (3.8)	3 (5.8)	7 (4.5)
due to Adverse Events	1 (1.0)	1 (1.9)	2 (1.3)
Worsening of Disease Under Study	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of Other Pre-existing Disease	0 (0.0)	0 (0.0)	0 (0.0)
Other Adverse Event	1 (1.0)	1 (1.9)	2 (1.3)
due to Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
due to Administrative Reason	3 (2.9)	2 (3.8)	5 (3.2)
Non Compliant with Protocol	1 (1.0)	0 (0.0)	1 (0.6)
Lost to Follow-Up	0 (0.0)	0 (0.0)	0 (0.0)
Refused to Continue Medication	2 (1.9)	2 (3.8)	4 (2.6)
due to Other Reason	0 (0.0)	0 (0.0)	0 (0.0)

Source data: Appendix 16.1.9.2, Table 1.1

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'Not Randomised' includes 2 screening failures and 11 open-label run-in drop-outs.
One open-label run-in drop-out did not take any open label medication.
'Randomised' is referring to double-blind treatment randomisation.

Table 15.2.2.2: 1 Analysis of covariance for UPDRS II+III total score change from baseline over time, FAS (LOCF) at visit 5 (after 9 weeks)

UPDRS 2+3 total score	PPX ER	PPX IR
Number of patients	103	52
Baseline		
Mean (SD)	21.3 (9.8)	23.4 (11.0)
Treatment phase		
Mean (SD)	19.8 (10.9)	22.9 (10.5)
Change from baseline		
Mean (SD)	-1.5 (5.3)	-0.5 (4.2)
Adjusted mean (SE)	-1.6 (0.5)	-0.5 (0.7)
Diff. from PPX IR°		
Adjusted mean (SE)	-1.1 (0.8)	
95% CI	[-2.8, 0.6]	
p-value	0.2061	_

°ANCOVA with factors treatment and country, and covariate baseline

Table 15.2.2.3: 1 Analysis of CGI-I Response rate over time, FAS (LOCF)
CMH test with country stratification
at visit 5 (after 9 weeks)

		CGI-I Response					
		PPX ER		PPX IR		PPX Total	
Country	Response	N	%	N	%	N	%
-All-	All	103	100.0	52	100.0	155	100.0
	Non-responder	13	12.6	11	21.2	24	15.5
	Responder	90	87.4	41	78.8	131	84.5
France	All	38	100.0	19	100.0	57	100.0
	Non-responder	7	18.4	2	10.5	9	15.8
	Responder	31	81.6	17	89.5	48	84.2
Germany	All	50	100.0	26	100.0	76	100.0
	Non-responder	4	8.0	6	23.1	10	13.2
	Responder	46	92.0	20	76.9	66	86.8
Netherlands	All	15	100.0	7	100.0	22	100.0
	Non-responder	2	13.3	3	42.9	5	22.7
	Responder	13	86.7	4	57.1	17	77.3
p-value	CMH	vs.	PPX IR		0.1623		

Responder are patients with answers between 'very much improved/better' and 'unchanged'

Table 15.2.2.4: 1 Analysis of PGI-I Response rate over time, FAS (LOCF)
CMH test with country stratification
at visit 5 (after 9 weeks)

		PGI-I Response					
		PPX ER		PPX IR		PPX Total	
Country	Response	N	%	N	%	N	%
-All-	All	103	100.0	52	100.0	155	100.0
	Non-responder	19	18.4	15	28.8	34	21.9
	Responder	84	81.6	37	71.2	121	78.1
France	All	38	100.0	19	100.0	57	100.0
	Non-responder	9	23.7	4	21.1	13	22.8
	Responder	29	76.3	15	78.9	44	77.2
Germany	All	50	100.0	26	100.0	76	100.0
	Non-responder	6	12.0	7	26.9	13	17.1
	Responder	44	88.0	19	73.1	63	82.9
Netherlands	All	15	100.0	7	100.0	22	100.0
	Non-responder	4	26.7	4	57.1	8	36.4
	Responder	11	73.3	3	42.9	14	63.6
p-value	CMH	vs.	PPX IR		0.1299		

Responder are patients with answers between 'very much improved/better' and 'unchanged'

Table 15.2.2.5: 1 Analysis of covariance for UPDRS II total score change from baseline over time, FAS (LOCF) at visit 5 (after 9 weeks)

UPDRS 2 total score	PPX ER	PPX IR
Number of patients	103	52
Baseline		
Mean (SD)	6.7 (3.6)	7.0 (3.6)
Treatment phase		
Mean (SD)	6.5 (3.9)	6.9 (3.5)
Change from baseline		
Mean (SD)	-0.3 (2.2)	-0.1 (1.0)
Adjusted mean (SE)	-0.3 (0.2)	-0.1 (0.3)
Diff. from PPX IR°		
Adjusted mean (SE)	-0.2 (0.3)	
95% CI	[-0.8, 0.4]	
p-value	0.4694	_

°ANCOVA with factors treatment and country, and covariate baseline

Table 15.2.2.6: 1 Analysis of covariance for UPDRS III total score change from baseline over time, FAS (LOCF) at visit 5 (after 9 weeks)

UPDRS 3 total score	PPX ER	PPX IR
Number of patients	103	52
Baseline		
Mean (SD)	14.6 (7.2)	16.4 (8.4)
Treatment phase		
Mean (SD)	13.4 (7.9)	16.0 (8.2)
Change from baseline		
Mean (SD)	-1.2 (4.1)	-0.5 (3.7)
Adjusted mean (SE)	-1.2 (0.4)	-0.3 (0.6)
Diff. from PPX IR°		
Adjusted mean (SE)	-0.9 (0.7)	
95% CI	[-2.3, 0.4]	
p-value	0.1804	_

°ANCOVA with factors treatment and country, and covariate baseline

Table 15.2.2.9: 1 Analysis of Pramipexole daily dose change from baseline, FAS (LOCF) at visit 5 (after 9 weeks)

		Change in PPX daily dose					
		PPX ER		PPX IR		PPX Total	
Country	Response	N	%	N	%	N	%
-All-	All	103	100.0	52	100.0	155	100.0
	increased	17	16.5	7	13.5	24	15.5
	unchanged/reduced	86	83.5	45	86.5	131	84.5
France	All	38	100.0	19	100.0	57	100.0
	increased	4	10.5	2	10.5	6	10.5
	unchanged/reduced	34	89.5	17	89.5	51	89.5
Germany	All	50	100.0	26	100.0	76	100.0
	increased	10	20.0	4	15.4	14	18.4
	unchanged/reduced	40	80.0	22	84.6	62	81.6
Netherlands	All	15	100.0	7	100.0	22	100.0
	increased	3	20.0	1	14.3	4	18.2
	unchanged/reduced	12	80.0	6	85.7	18	81.8
p-value	CMH	vs.	PPX IR		0.6190		

Table 15.3.1: 2 Amount of treatment taken - number of tablets, total dose [mg], baseline dose [mg], final dose [mg] within 9 weeks, TS

Treated set

	Pramipexole ER	Pramipexole IR	Total
Number of patients	104 (100.0)	52 (100.0)	156 (100.0)
Number of tablets			
Mean	82.4	233.3	132.7
SD	28.3	85.5	89.6
Min	14	15	14
Q1	63.0	189.0	63.0
Median	68.5	193.5	98.0
Q3	98.0	286.5	189.0
Max	142	468	468
Total dose [mg]			
Mean	169.2548	171.5481	170.0192
SD	63.6399	60.3538	62.3780
Min	15.750	15.000	15.000
Q1	114.0000	121.5000	115.8750
Median	171.0000	187.5000	181.5000
Q3	210.0000	195.0000	205.1250
Max	310.500	292.500	310.500
Baseline dose [mg]			
Mean	2.6322	2.7404	2.6683
SD	0.9578	0.8772	0.9303
Min	1.500	1.500	1.500
Q1	1.5000	2.2500	1.5000
Median	3.0000	3.0000	3.0000
Q3	3.0000	3.0000	3.0000
Max	4.500	4.500	4.500
Final dose [mg]			
Mean	2.7476	2.8269	2.7740
SD	0.9499	0.8611	0.9192
Min	1.500	1.500	1.500
Q1	2.2500	2.2500	2.2500
Median	3.0000	3.0000	3.0000
Q3	3.0000	3.0000	3.0000
Max	4.500	4.500	4.500

Source data: Appendix 16.1.9.2, Table 7.1.1.2