Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Mirapex® (Mirapex® US, Mirapexin® in UK, and Sifrol® in EU)		**EudraCT No.:** 2005-004949-34	**Synopsis No.:**
Name of active ingredient: pramipexole dihydrochloride		**Page:** 1 of 7	
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 15 APR 2014	**Trial No. / U No.:** 248.595 / U09-3780-01	**Date of trial:** 24 May 2006-22 April 2009	**Date of revision:** Not applicable

Title of trial:	A randomized, double-blind, placebo-controlled, parallel-group clinical trial to examine the efficacy and safety of early pramipexole treatment versus delayed pramipexole treatment in patients with new onset Parkinson's disease
Coordinating Investigators:	[redacted]
Trial sites:	Multicentre Study, cf. Appendix 16.1.4
Publication (reference):	Data of this study have not been published
Clinical phase:	IV
Objectives:	The objective of this study was to assess the effect of early vs. later treatment with pramipexole in early Parkinson's Disease (PD).
Methodology:	Multi-national, multi-centre, randomized, double-blind, placebo-controlled, parallel-group study
No. of subjects:	
planned:	entered: 500 randomised of which 150 were to enter an imaging sub-study enrolled: 800
actual:	Treatment early pramipexole: entered: 261 treated: 261 analysed (for primary endpoint): 211 Treatment delayed pramipexole: entered: 274 treated: 274 analysed (for primary endpoint): 200 <u>Substudy:</u> Treatment early pramipexole: entered: 81 treated: 81 analysed: 62 Treatment delayed pramipexole: entered: 79 treated: 79 analysed: 61

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Diagnosis and main criteria for inclusion:	Male and female patients, ages 30 to 75 years, newly diagnosed with Idiopathic Parkinson's Disease, having a modified Hoehn and Yahr stage of I to II at the time of screening, and who did not require PD medications and were not likely to need PD medications for at least 6 months.
Test product:	pramipexole (Mirapex®) tablets
dose:	Patients initially randomized to pramipexole were up-titrated from 0.375 mg pramipexole daily to 0.75 mg pramipexole daily and then to 1.5 mg pramipexole daily over a 6 week period, and then 1.5 mg pramipexole daily was continued for the remainder of the 15 months of the study. Patients initially randomized to placebo, received placebo for 6-9 months, then up-titrated from 0.375 mg pramipexole daily to 1.5 mg pramipexole daily over a 6 week period. These patients were then continued on 1.5 mg pramipexole daily for the remainder of the 15 months of the study.
mode of admin.:	p.o.
batch no.:	Pramipexole 0.125 mg B073001186 Pramipexole 0.25 mg B073001189 Pramipexole 0.25 mg B083000083 Pramipexole 0.5 mg B073001191
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	p.o.
batch no.:	Placebo matching pramipexole 0.125 mg B073001187 Placebo matching pramipexole 0.25 mg B073001188 Placebo matching pramipexole 0.5 mg B073001190 Placebo matching pramipexole 0.5 mg B073001192
Duration of treatment:	Up to 15 months

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Criteria for evaluation: **Efficacy/clinical pharmacology:**	Primary efficacy endpoint: The change in parts I, II, and III UPDRS at 15 months relative to baseline value as performed by an independent blinded rater Secondary efficacy endpoints: Changes from baseline in the following: • Change in parts I, II, and III UPDRS at 3, 6, 9 and 15 months relative to baseline by the investigator or coordinator • Change in Motor and ADL components of UPDRS at 15 months relative to baseline by a blinded rater • Change in Motor and ADL components of UPDRS at 3, 6, 9 and 15 months relative to baseline by the investigator or coordinator • Change in mentation, behaviour and mood component of UPDRS at 15 months relative to baseline by a blinded rater • Change in mentation, behaviour and mood component of UPDRS at 3, 6, 9 and 15 months relative to baseline by the investigator or coordinator • Clinical response (CGI-I) at month 15 by a blinded rater. • Severity of illness (CGI-S) at month 15 relative to baseline by a blinded rater • BDI-IA total score at 3, 6, 9 and 15 months relative to baseline • Quality of life scales – PDQ-39, EQ-VAS and EQ-5D at 6-9 and 15 months relative to baseline • MMIDI at 1, 6, 9, 12 and 15 months relative to baseline. • Patient subset DAT SPECT imaging assessment at 15 months relative to baseline to determine the percent change in striatal dopamine transporter density as measured by the specific striatal uptake: background tissue ratio
Safety:	• Incidence and intensity of adverse events • Withdrawals due to adverse events • Change in vital signs (supine and standing - blood pressure and pulse rate) • Change in clinically significant clinical laboratory blood and urine determinations
Statistical methods:	Comparison of the change in the UPDRS between the early and later pramipexole group at 15 months. Sample size was calculated based on a 3 unit difference at 15 months.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Demographics for the treated set were similar for the two treatment groups with a mean age of 62.1 years for the early group and 62.9 years for the delayed pramipexole group. The majority of patients (67.8% early pramipexole; 60.6% delayed pramipexole) had PD 6 months or less. Of the 535 patients who entered Phase 1 (261 early pramipexole vs. 274 delayed pramipexole/placebo) 84.7% early pramipexole and 78.1% delayed pramipexole patients completed Phase 1 study treatment. Of the 435 patients who entered and were treated in Phase 2, 89.6% early pramipexole and 89.7% delayed pramipexole patients completed Phase 2 study treatment.

Primary endpoint: The adjusted mean blinded rater UPDRS Part I+II+III total scores at Month 15 were 24.5 for the early pramipexole treatment group and 24.9 for the Phase 2 Full Analysis Set (FAS). The Phase 2 FAS included all treated set patients who had a baseline and on-treatment blinded rater assessment of the UPDRS (I+II+III) during Phase 2. The adjusted mean change from baseline at Month 15 was 0.3 for the early pramipexole treatment group and 0.7 for the delayed pramipexole group. The difference in the adjusted means was -0.4 (95% CI: -2.2, 1.4; p=0.6503) in favor of the early pramipexole group, but not of statistical significance (p=0.6503). Thus, superiority of early pramipexole over delayed pramipexole treatment was not observed for the primary efficacy endpoint. This analysis for the Phase 2 FAS was confirmed by all sensitivity analyses and for the PPS.

Secondary endpoints:

The analyses of the secondary efficacy endpoints at the end of treatment on the whole supported the conclusions from the primary analysis with very little evidence of superiority of early pramipexole treatment over delayed pramipexole:

There was no significant difference between the two treatment groups in adjusted mean change from baseline to the end of treatment in UPDRS Part I+II+III total score (Investigator rated), UPDRS Parts I, II, III and II+III (Blinded rater).

There were no clinically or statistically significant differences at the end of treatment for the BDI-IA, CGI-I, CGI-S, PDQ-39, EQ-5D overall index score or SPECT imaging data. For the EQ-5D VAS general health state score the difference in medians was statistically significant (p=0.0489) in favour of early pramipexole.

- EQ-5D: The difference in the medians for the overall index score at Month 9 was statistically significant (p<0.0001). The difference in the medians for the VAS health score at Month 9 was statistically significant (p=0.0282) in favour of early pramipexole treatment.

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Efficacy / clinical pharmacology results (continued):

For the analysis of efficacy endpoints during and at the end of Phase 1, a consistent superior effect of early pramipexole over delayed pramipexole (placebo during Phase 1) was observed:

- UPDRS total score (Investigator rated): the difference in the adjusted mean change from baseline to Month 9 was statistically significant ($p<0.0001$). Statistically significant effects were also observed at Months 3 and 6 ($p<0.001$). An analysis of the slopes during Months 3 to 9 was also statistically significant ($p=0.0304$).
- UPDRS Parts II, III and II+III (Investigator rated): for the Part II+III score the difference in adjusted mean change from baseline to Month 9 was statistically significant ($p <0.0001$. Similar results were observed for the Part II ($p=0.0001$) and III ($p<0.0001$) individual analyses.
- UPDRS Part I (Investigator rated): the difference in the adjusted mean change from baseline to Month 9 was statistically significant ($p=0.0173$).
- BDI-1A total score: The difference in the adjusted means at Month 9 was statistically significant ($p=0.0009$).
- PDQ-39: Statistically significant differences at Month 9 in favour of early pramipexole were observed for the domains of activities of daily living, bodily discomfort, emotional well being, mobility and stigma. The reverse was seen for the cognitive impairment domain. The difference in the medians at Month 9 for the total score of -2.0 (95% CI: −3.1, -0.9) in favour of early pramipexole was statistically significant ($p=0.0001$).

Safety results:

The mean exposure during Phase 1 was higher for the early pramipexole group, 219.1 days compared to 200.5 days for the delayed pramipexole treatment group. Patients in the delayed pramipexole group were more likely to enter Phase 2 of the trial prematurely due to symptoms of PD: 18.1% of patients in the early pramipexole group (active treatment) and 28.5% in the delayed pramipexole group (placebo). The mean exposure to study medication during Phase 2 of the trial was similar for the two treatment groups, 157.3 days for the early pramipexole treatment group and 157.2 days for the delayed pramipexole treatment group.

The frequencies of treatment emergent AEs reported during Phase 1 of the trial were similar for the two treatment groups (early pramipexole, 74.3%; delayed pramipexole, 71.5%); however, drug related AEs, according to the investigator, were higher for the early pramipexole treatment group (early pramipexole, 43.3%; delayed pramipexole, 26.3%). Adverse Events that led to discontinuation of study medication were reported at similar frequencies for the two groups (early pramipexole, 11.5%; delayed pramipexole, 10.6%). Serious Adverse Events were comparable in the two groups (early pramipexole, 6.5%; delayed pramipexole, 6.6%) during Phase 1.

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Safety results (continued):

Treatment emergent AEs were reported with similar frequencies for the two treatment groups for patients treated with Phase 2 study medication: early pramipexole, 81.4%; delayed pramipexole, 83.6%. Adverse Events considered drug-related by the investigator occurred in 46.2% of early pramipexole and 49.1% of delayed pramipexole. The frequencies of AEs leading to discontinuation of study medication were similar for the treatment groups (early pramipexole, 7.2%; delayed pramipexole, 7.9%). SAEs occurred in 6.5% of early pramipexole and 6.6% delayed pramipexole patients during Phase 1. Slightly higher incidences of SAEs occurred in the early pramipexole group (10.0% vs. 7.9% for delayed pramipexole) during Phase 1 or Phase 2. The most common SAEs were events that required hospitalization (early pramipexole, 9.5%; delayed pramipexole, 7.0%).

There were 3 deaths during the study, all in the delayed pramipexole treatment group. None were attributable to study drug, according to the investigator. One (1) patient who received treatment only with placebo completed suicide. This occurred while the patient was receiving placebo and is counted in Phase 1 of the study for Delayed Pramipexole Treatment Group. One (1) patient who received treatment with placebo and then with pramipexole (which was discontinued) died 13 days later of cardiac trauma (heart injury) secondary to an automobile accident. This was counted in the Post-treatment period following Phase 1 of the study for the Delayed Pramipexole Treatment Group. One (1) patient who received and then discontinued treatment with pramipexole died of a staphylococcal infection and sepsis 39 days later. This was counted in Phase 2 of the study for the Delayed Pramipexole Treatment Group, although the patient was not receiving study treatment at the time of the onset of the SAEs leading to death.

There were no unexpected laboratory abnormalities for any parameter assessed.

Vital signs and weight did not appreciably change during the study for either patient group.

There were no patients identified with a risk of gambling at any stage during the study for either treatment group. The occurrences of compulsive sexual behaviour (2 early pramipexole, 3 delayed pramipexole) and compulsive buying (5 early) were very low and in some cases already present at baseline.

The data obtained for this study were generally consistent with the known safety profile of pramipexole.

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Conclusions:

In summary there was no evidence that treatment with early pramipexole was superior to treatment with delayed pramipexole after 15 months treatment. As such the results did not support the hypothesis that early treatment, 6-9 months, with pramipexole would provide benefits consistent with a possible disease-modifying effect.

These results should be interpreted cautiously, as the delayed start study design has not been validated by correlation with neuronal survival; widely accepted clinical criteria are still lacking and inferences regarding neuroprotection remain problematic.

For the analysis of the efficacy endpoints during and at the end of the Phase 1 period of the study a consistent superior effect of early pramipexole over delayed pramipexole (placebo during Phase 1) was observed. This confirmed the symptomatic efficacy of treatment with pramipexole monotherapy over placebo in patients with newly diagnosed, very early PD.

The safety data obtained for this study were generally consistent with the established favourable risk / benefit ratio of treatment of early PD patients with pramipexole.

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 at end of study treatment	Table 15.1.1: 2
UPDRS II+III (motor and ADL), assessed by investigator or coordinator - change from baseline to Month 9 - change from baseline to Month 15	Table 15.2.1.2: 8
UPDRS II+III (motor and ADL), assessed by blinded rater - change from baseline to Month 15	Table 15.2.1.1: 8
UPDRS I+II+III, assessed by investigator or coordinator - change from baseline to Month 9 - change from baseline to Month 15	Table 15.2.1.2: 10
CGI-I at Month 15	Table 15.2.3: 2
CGI-S at Month 15, relative to baseline	Table 15.2.3: 4
BDI-IA total score at Month 15, relative to baseline	Table 15.2.2: 2
Quality of Life Scale PDQ-39 at Month 15, relative to baseline	Table 15.2.4: 2
Patient subset DAT SPECT imaging assessment at Month 15	Table 15.2.7: 2

Table 15.1.1: 2 Disposition of patients at end of study treatment
– enrolled set

	Early PPX N (%)	Delayed PPX N (%)	Total N (%)
Enrolled			593
Not randomised			58
Randomised	261	274	535
Not treated	0	0	0
Treated	261 (100.0)	274 (100.0)	535 (100.0)
Not prematurely discontinued study treatment up to Visit 14*	198 (75.9)	192 (70.1)	390 (72.9)
Prematurely discontinued study treatment up to Visit 14*	63 (24.1)	82 (29.9)	145 (27.1)
Adverse event	41 (15.7)	43 (15.7)	84 (15.7)
AE study disease worsening	6 (2.3)	19 (6.9)	25 (4.7)
AE other disease worsening	2 (0.8)	1 (0.4)	3 (0.6)
AE other	33 (12.6)	23 (8.4)	56 (10.5)
Lack of efficacy	9 (3.4)	14 (5.1)	23 (4.3)
Non compliant with protocol	6 (2.3)	5 (1.8)	11 (2.1)
Lost to follow-up	0 (0.0)	2 (0.7)	2 (0.4)
Consent withdrawn	6 (2.3)	17 (6.2)	23 (4.3)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Not prematurely discontinued down titration treatment	172 (65.9)	165 (60.2)	337 (63.0)
Prematurely discontinued down titration treatment	89 (34.1)	109 (39.8)	198 (37.0)
Adverse event	14 (5.4)	18 (6.6)	32 (6.0)
AE study disease worsening	1 (0.4)	7 (2.6)	8 (1.5)
AE other disease worsening	1 (0.4)	1 (0.4)	2 (0.4)
AE other	12 (4.6)	10 (3.6)	22 (4.1)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Non compliant with protocol	68 (26.1)	74 (27.0)	142 (26.5)
Lost to follow-up	0 (0.0)	3 (1.1)	3 (0.6)
Consent withdrawn	7 (2.7)	13 (4.7)	20 (3.7)
Other	0 (0.0)	1 (0.4)	1 (0.2)

*: Excludes down titration treatment

Source data: Appendix 16.2, Listing 1.1

Table 15.2.1.2: 8 Analysis of change from baseline to each visit in investigator rated UPDRS Parts II+III total score - phase 2 full analysis set

Visit: Month 9

UPDRS parts II+III (Investigator)	Early PPX (N=210)#	Delayed PPX (N=200)#
Baseline		
Mean (SE)	22.2 (0.6)	22.1 (0.7)
Month 9		
Adjusted mean* (SE)	21.9 (0.6)	26.4 (0.6)
Change to Month 9		
Adjusted mean* (SE)	-0.3 (0.6)	4.2 (0.6)
Difference to Delayed PPX		
Adjusted mean* (SE)	-4.5 (0.8)	
95% confidence interval	(-6.0, -3.0)	
p-value	<.0001	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.1.2: 8 Analysis of change from baseline to each visit in investigator rated UPDRS Parts II+III total score - phase 2 full analysis set

Visit: Month 15

UPDRS parts II+III (Investigator)	Early PPX (N=210)#	Delayed PPX (N=200)#
Baseline		
Mean (SE)	22.2 (0.6)	22.1 (0.7)
Month 15		
Adjusted mean* (SE)	23.0 (0.7)	22.8 (0.7)
Change to Month 15		
Adjusted mean* (SE)	0.8 (0.7)	0.6 (0.7)
Difference to Delayed PPX		
Adjusted mean* (SE)	0.2 (0.9)	
95% confidence interval	(-1.5, 1.9)	
p-value	0.8155	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.1.1: 8 Analysis of change from baseline to end of treatment in blinded rater UPDRS Parts II+III total score - phase 2 full analysis set

UPDRS parts II+III (Blinded rater)	Early PPX (N=211)#	Delayed PPX (N=200)#
Baseline		
Mean (SE)	22.9 (0.7)	22.8 (0.7)
Month 15		
Adjusted mean* (SE)	23.5 (0.7)	23.6 (0.7)
Change to Month 15		
Adjusted mean* (SE)	0.6 (0.7)	0.7 (0.7)
Difference to Delayed PPX		
Adjusted mean* (SE)	-0.1 (0.9)	
95% confidence interval	(-1.8, 1.5)	
p-value	0.8693	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.1.2: 10 Analysis of change from baseline to each visit in investigator rated UPDRS Parts I+II+III total score - phase 2 full analysis set

Visit: Month 9

UPDRS total score (Investigator)	Early PPX (N=210)#	Delayed PPX (N=200)#
Baseline		
Mean (SE)	23.3 (0.7)	23.3 (0.7)
Month 9		
Adjusted mean* (SE)	22.8 (0.6)	27.6 (0.6)
Change to Month 9		
Adjusted mean* (SE)	-0.5 (0.6)	4.3 (0.6)
Difference to Delayed PPX		
Adjusted mean* (SE)	-4.8 (0.8)	
95% confidence interval	(-6.3, -3.2)	
p-value	<.0001	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.1.2: 10 Analysis of change from baseline to each visit in investigator rated UPDRS Parts I+II+III total score - phase 2 full analysis set

Visit: Month 15

UPDRS total score (Investigator)	Early PPX (N=210)#	Delayed PPX (N=200)#
Baseline		
Mean (SE)	23.3 (0.7)	23.3 (0.7)
Month 15		
Adjusted mean* (SE)	23.9 (0.7)	23.8 (0.7)
Change to Month 15		
Adjusted mean* (SE)	0.6 (0.7)	0.5 (0.7)
Difference to Delayed PPX		
Adjusted mean* (SE)	0.0 (0.9)	
95% confidence interval	(-1.7, 1.8)	
p-value	0.9568	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.3: 2 Analysis of blinded rater CGI-I categories at end of treatment
- phase 2 full analysis set

	Early PPX (N=200)#	Delayed PPX (N=184)#
CGI improvement		
N	200 (100.0)	184 (100.0)
Much improved	18 (9.0)	21 (11.4)
Essentially unchanged	176 (88.0)	158 (85.9)
Much worse	6 (3.0)	5 (2.7)
Comparison vs. Delayed PPX*		
p-value	0.4961	
Odds ratio	0.811	
95% CI	(0.444, 1.482)	

Much improved = CGI-I scores of 1 or 2, Essentially unchanged = scores of 3, 4 or 5, Much worse = scores of 6 or 7
* - from logistic regression, adjusted for effects of baseline severity of illness score and country
# - N's exclude patients from the analysis set with incomplete data

Table 15.2.3: 4 Analysis of blinded rater CGI-S categories at end of treatment
- phase 2 full analysis set

	Early PPX (N=209)#	Delayed PPX (N=198)#
CGI severity		
N	209 (100.0)	198 (100.0)
Improved	4 (1.9)	3 (1.5)
Essentially unchanged	200 (95.7)	191 (96.5)
Worsened	5 (2.4)	4 (2.0)
Comparison vs. Delayed PPX*		
p-value	0.7913	
Odds ratio	1.153	
95% CI	(0.403, 3.299)	

Improved: >1 category improvement, Unchanged: not improved or worsened by >1 category, Worsened: >1 category worsening
* - from logistic regression, adjusted for effects of baseline severity of illness score and country
# - N's exclude patients from the analysis set with incomplete data

Table 15.2.2: 2 Analysis of change from baseline to each visit in BDI total score
- phase 2 full analysis set

Visit: Month 15

BDI total score	Early PPX (N=211)#	Delayed PPX (N=197)#
Baseline		
Mean (SE)	6.1 (0.4)	6.4 (0.4)
Month 15		
Adjusted mean* (SE)	5.2 (0.3)	5.8 (0.3)
Change to Month 15		
Adjusted mean* (SE)	-1.0 (0.3)	-0.5 (0.3)
Difference to Delayed PPX		
Adjusted mean* (SE)	-0.5 (0.4)	
95% confidence interval	(-1.3, 0.2)	
p-value	0.1702	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.4: 2 Analysis of change from baseline to each visit in PDQ-39 domain and total scores - phase 2 full analysis set

PDQ-39 total score

	Early PPX (N=211)#	Delayed PPX (N=200)#
Baseline		
Median	9.8	9.3
(Q1, Q3)	(4.5, 15.5)	(4.8, 16.5)
Month 15		
Median	9.1	9.1
(Q1, Q3)	(4.2, 17.7)	(5.3, 18.0)
Change to Month 15		
Median	-0.4	0.3
(Q1, Q3)	(-3.2, 3.8)	(-3.6, 4.4)
Comparison vs. Delayed PPX*		
p-value	0.2149	
Shift in location**	-0.573	
95% confidence interval***	(-1.823, 0.677)	

\# - N's exclude patients from the analysis set with incomplete data
* - Stratified for country Wilcoxon rank sum test (Van Elteren's test)
** - Hodges-Lehmann estimate of difference in medians
*** - Distribution-free CI (Moses)
Domain and total scores range from 0 (no problem at all) to 100 (maximum level of the problem)
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.7: 2 Analysis of percentage change from baseline to end of treatment in beta-CIT uptake by region - substudy set

Endpoint: Caudate uptake

	Early PPX (N=62)#	Delayed PPX (N=61)#
Baseline		
Mean (SE)	2.2406 (0.0840)	2.2052 (0.1010)
Month 15		
Adjusted mean* (SE)	1.8704 (0.0490)	1.8465 (0.0464)
% Change to Month 15		
Adjusted mean* (SE)	-15.7 (2.2)	-15.4 (2.1)
Difference to Delayed PPX		
Adjusted mean* (SE)	-0.3 (2.5)	
95% confidence interval	(-5.3, 4.7)	
p-value	0.8997	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.7: 2 Analysis of percentage change from baseline to end of treatment in beta-CIT uptake by region - substudy set

Endpoint: Putamen uptake

	Early PPX (N=62)#	Delayed PPX (N=61)#
Baseline		
Mean (SE)	1.0535 (0.0678)	1.0087 (0.0683)
Month 15		
Adjusted mean* (SE)	0.8899 (0.0362)	0.8767 (0.0346)
% Change to Month 15		
Adjusted mean* (SE)	-13.6 (3.4)	-12.0 (3.3)
Difference to Delayed PPX		
Adjusted mean* (SE)	-1.7 (4.0)	
95% confidence interval	(-9.5, 6.2)	
p-value	0.6778	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication

Table 15.2.7: 2 Analysis of percentage change from baseline to end of treatment in beta-CIT uptake by region - substudy set

Endpoint: Striatum uptake

	Early PPX (N=62)#	Delayed PPX (N=61)#
Baseline		
Mean (SE)	1.6471 (0.0697)	1.6070 (0.0805)
Month 15		
Adjusted mean* (SE)	1.3791 (0.0364)	1.3598 (0.0346)
% Change to Month 15		
Adjusted mean* (SE)	-15.1 (2.1)	-14.6 (2.0)
Difference to Delayed PPX		
Adjusted mean* (SE)	-0.5 (2.5)	
95% confidence interval	(-5.4, 4.4)	
p-value	0.8397	

- N's exclude patients from the analysis set with incomplete data
* - Adjusted for baseline and country effect
Note: Month 15 assessment recorded at completion/premature withdrawal of Phase 2 study medication