

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-421**

**STATISTICAL REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA /Serial Number:** 22-421  
**Drug Name:** Mirapex (Pramipexole dihydrochloride)  
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**Applicant:** Boehringer Ingelheim  
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# **1 EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

Based on the results of the first interim analysis, there is evidence that Mirapex (pramipexole extended release) is effective as compared to placebo in the treatment of early Parkinson's Disease (PD), as assessed by the primary endpoint, change from baseline at week 18 in the UPDRS Part II+III total score.

## **1.2 Brief Overview of Clinical Studies**

This submission includes Interim Clinical Study Report for the on-going efficacy study 248.524.

Study 248.524 was a double-blind, double-dummy, placebo-controlled, randomized, three parallel-group efficacy and safety multinational multi-centre study evaluating PPX ER (in daily doses from 0.375mg to 4.5mg q.d.) compared with placebo and with PPX IR over a 26-week maintenance phase.

After a 1- to 2-week screening phase and a 7-week double-blind flexible up-titration phase, a double-blind maintenance phase of up to 26 weeks followed.

Patients included in the 18-week confirmatory interim analysis (1<sup>st</sup> interim analysis) had a 7-week flexible up-titration, followed by a maintenance phase of up to 11 weeks. Patients included in the 33-week descriptive interim analysis (2<sup>nd</sup> interim analysis) had a 7-week flexible up-titration, followed by a maintenance phase of up to 26 weeks.

This study was conducted in 95 active sites in 14 countries. It was planned that 500 patients entered the study (200 for PPX ER, 200 for PPX IR and 100 for placebo), including approximately 250 planned for the 18-week interim analysis (100 for PPX ER, 100 for PPX IR and 50 for placebo) and approximately 100 planned for the 33-week interim analysis (40 for PPX ER, 40 for PPX IR and 20 for placebo).

## **1.3 Statistical Issues and Findings**

The objective of the trial was to determine the efficacy, safety and tolerability of Pramipexole (PPX) ER compared with placebo and PPX IR in patients with early PD. Superiority of PPX ER to placebo (at 18 weeks) and non-inferiority of PPX ER to IR (at 33 weeks) are planned to be evaluated in a hierarchical system of hypotheses.

The objectives of the two interim analyses performed in this early PD study were:

- at 1<sup>st</sup> interim analysis: to determine the efficacy, safety and tolerability of PPX ER compared with placebo in approximately 250 patients treated for 18 weeks (or having discontinued treatment prior to week 18)

- at 2<sup>nd</sup> interim analysis: to confirm, in a sub-set of approximately 100 patients treated for 33 weeks, that efficacy was maintained up to 6 month maintenance treatment.

The primary efficacy endpoint was the change from baseline to week 18 or week 33 on the UPDRS Part II+III score combined. The only confirmatory test for superiority of PPX ER versus placebo was done on approximately the 250 sub-set at the 1<sup>st</sup> interim analysis (18-week data). That is, the full alpha (0.05) will be spent at the first interim analysis. There was no hypothesis testing on approximately the 100 sub-set from the 2<sup>nd</sup> interim analysis (33-week data). The statistical model was an analysis of covariance, controlling for baseline UPDRS Part II+III. Fixed terms in the model were treatment, country and UPDRS Part II+III score at baseline. The analysis for the primary endpoint was based on the Full Analysis Set (FAS) (using LOCF).

Key secondary efficacy endpoints were the responder rates in CGI-I and PGI-I at week 18 or week 33. The analyses for the key secondary efficacy endpoints were based on the Full Analysis Set using a Cochran-Mantel-Haenszel procedure.

A closed testing procedure spending the full  $\alpha=0.05$  was used in the first interim analysis. In the first step, superiority of PPX ER versus placebo was tested for the primary endpoint (change in the UPDRS II+III total score). If this was significant at the 2-sided 0.05 level, then in the second and third step the superiority of PPX ER versus placebo was tested for the key secondary endpoints (CGI-I and PGI-I response rates). If significance at the 2-sided 0.05 level was reached for CGI-I in step 2, then significance for PGI-I at the 2-sided 0.05 level was tested in step 3.

For the first interim analysis, the mean of UPDRS Part II+III total score at baseline was 30.1 points in the placebo group, 30.5 points in the PPX ER group and 28.3 points in the PPX IR group, and at Week 18, the means were 24.0, 21.3 and 19.3 points, respectively. The LS mean changes were -5.1, -8.1 and -8.4 points based on ANCOVA. The difference between PPX ER and placebo were statistically significant ( $p=0.0282$ ).

For the second interim analysis, maintenance of efficacy was investigated by comparing the mean change in UPDRS Part II+III total score from baseline at week 33 or at week 18 in these patients. It appears that there was almost no change in the mean change from baseline to week 33 compared to the mean change from baseline to week 18 in the PPX ER group, no change in the PPX IR group, compared to a worsening in the placebo group. Based on the descriptive results, it seems that the drug effect was maintained in both PPX groups.

The key secondary endpoints CGI-I and PGI-I responder rates were analyzed by Cochran-Mantel-Haenszel (CMH) test with country stratification. The results of the first interim analysis indicate that the difference between placebo and PPX ER in CGI-I and PGI-I were statistically significant ( $p=0.0400$ ,  $p=0.0040$ , respectively). Based on the descriptive results of the second interim analysis, it appears that the effect was maintained.

This reviewer conducted the following additional analyses. Please refer to Section 3.1.2 Reviewer's Analysis for more details.

- **Plot the Cumulative Distribution Function (CDF) for the primary endpoint.** It seems that the CDF for PPX ER group is generally above the CDF for placebo group, indicating that the patients in PPX ER group generally had larger improvement in UPDRS Part II+III score than those in placebo group.
- **Evaluate the impact of L-dopa use as a rescue medication on the primary efficacy analysis.** The number of patients who started treatment with L-dopa during the study was 3 for PPX ER group and 7 for placebo group. The data suggest that the introduction of L-dopa generally results in a larger improvement in UPDRS Part II+III score. As higher proportion of patients in placebo group took L-dopa as a rescue medication, this reviewer thinks the sponsor's primary efficacy analysis (simple LOCF) is more conservative.
- **Conduct subgroup analysis by country.** Since Study 248.524 was conducted in 14 countries, this reviewer conducted descriptive statistical analysis for the primary endpoint by county and treatment. Based on this subgroup analysis, this reviewer thinks there is no meaningful difference between countries in change from baseline in UPDRS Part II+III total score.

**Reviewer's notes: Since the second interim analysis is descriptive, it seems to this reviewer that the results of the second interim analysis should not be used for efficacy claim or can only be used with great caution.**

## 2 INTRODUCTION

### 2.1 Overview

Parkinson's disease (PD) is a chronic degenerative disorder of the central nervous system, with slowly progressive degeneration of the nigrostriatal dopaminergic systems. Classically, the symptoms are tremor, muscular rigidity and bradykinesia. The underlying pathophysiology is a deficiency of dopamine in the basal ganglia.

The estimated incidence of PD is 4.5 to 16/100,000 persons/year and PD is associated with severe disability or death. Current pharmacological intervention in PD is symptomatic. In general, a patient with early stages PD will start with dopamine agonists. If symptoms are insufficiently controlled, L-Dopa is added during the course of the disease. In advanced PD, most patients will receive both L-Dopa and a dopamine agonist.

Pramipexole (SND 919) is a dopamine D2 receptor agonist. It is structurally different from the ergot-derived drugs (e.g. bromocriptine, pergolide). It is also pharmacologically unique in that it is a full agonist and has receptor selectivity for the dopamine D2 family of dopamine receptors.

Pramipexole tablets were first authorized in the USA in 1997, followed over the course of years by marketing authorizations in the European Union (EU), Norway, Switzerland, Australia,

Canada, Japan, Eastern European countries, countries of the Middle and Far East and South America.

Boehringer-Ingelheim is developing an extended release (ER) formulation of Pramipexole that can be administered once daily. This alternate formulation will be beneficial to patients as the extended release delivery will allow patients to treat their symptoms with a single daily dose, thereby increasing patient convenience and compliance.

## **2.2 Data Sources**

The sponsor's original electronic submission was stored in the directory of \\CDSESUB1\EVSPROD\NDA022421\0000 of the center's electronic document room.

# **3 STATISTICAL EVALUATION**

## **3.1 Evaluation of Efficacy**

### **3.1.1 PROTOCOL 248.524**

#### **3.1.1.1 Study Objectives**

The objective of the trial was to determine the efficacy, safety and tolerability of Pramipexole (PPX) ER compared with placebo and PPX IR in patients with early PD. Superiority of PPX ER to placebo (at 18 weeks) and non-inferiority of PPX ER to IR (at 33 weeks) are planned to be evaluated in a hierarchical system of hypotheses.

The objectives of the two interim analyses performed in this early PD study were:

- at 1<sup>st</sup> interim analysis: to determine the efficacy, safety and tolerability of PPX ER compared with placebo in approximately 250 patients treated for 18 weeks (or having discontinued treatment prior to week 18)
- at 2<sup>nd</sup> interim analysis: to confirm, in a sub-set of approximately 100 patients treated for 33 weeks, that efficacy was maintained up to 6 month maintenance treatment.

#### **3.1.1.2 Study Design**

This was a double-blind, double-dummy, placebo-controlled, randomized, three parallel-group efficacy and safety multinational multi-centre study evaluating PPX ER (in daily doses from 0.375mg to 4.5mg q.d.) compared with placebo and with PPX IR over a 26-week maintenance phase.

After a 1- to 2-week screening phase and a 7-week double-blind flexible up-titration phase, a double-blind maintenance phase of up to 26 weeks followed. At the end of the double-blind

maintenance treatment phase, completer patients had the possibility to enter an open-label extension study with PPX ER.

Patients included in the 18-week confirmatory interim analysis (1<sup>st</sup> interim analysis) had a 7-week flexible up-titration, followed by a maintenance phase of up to 11 weeks. During this 18-week period, there were 8 visits and 4 Telephone Contacts (TCs). Patients included in the 33-week descriptive interim analysis (2<sup>nd</sup> interim analysis) had a 7-week flexible up-titration, followed by a maintenance phase of up to 26 weeks. During this 33-week period, there were 11 visits and 4 TCs.

This study was conducted in 95 active sites in 14 countries. It was planned that 500 patients entered the study (200 for PPX ER, 200 for PPX IR and 100 for placebo), including approximately 250 planned for the 18-week interim analysis (100 for PPX ER, 100 for PPX IR and 50 for placebo) and approximately 100 planned for the 33-week interim analysis (40 for PPX ER, 40 for PPX IR and 20 for placebo).

### 3.1.1.3 Efficacy Measures

Primary efficacy endpoint:

- Change from baseline in UPDRS (Unified Parkinson's Disease Rating Scale) Part II+III score.

Key secondary efficacy endpoints:

- Responder rate for Clinical Global Impression of Improvement (CGI-I);
- Responder rate for Patient Global Impression of Improvement (PGI-I).

Other secondary efficacy endpoints:

- UPDRS I, II and III scores separately (change from baseline);
- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score;
- Proportion of patients requiring L-Dopa supplementation during the study;
- Beck's Depression Inventory (BDI) version IA (change from baseline);
- Parkinson's Disease Sleep Scale (PDSS) (change from baseline);
- 11-point Likert scale for pain related to Parkinson's disease (change from baseline);
- Quality of life scales: PDQ-39 (Parkinson Disease Questionnaire- 39 items) and EQ-5D (EuroQoL) (change from baseline)

### 3.1.1.4 Statistical Analysis Plan

#### *Changes in the Planned Analysis Based on Protocol Amendment 5*

The sponsor states that, after regulatory consultancy, it was agreed that statistically significant data, showing superiority of pramipexole ER vs. placebo after 18 weeks, would support the demonstration of efficacy of pramipexole ER in early PD patients. In addition, a descriptive analysis will be performed in at least 100 completer patients (i.e. patients treated up to 33

weeks), in order to check for sustained efficacy at 6 months. Therefore, the Amendment 5 states that the confirmatory analysis for the superiority hypothesis (pramipexole ER vs. placebo) will be performed at Visit 8 (18 weeks), instead of at Visit 11 (33 weeks), as initially planned (Amendment 5).

### ***Statistical Analysis Methods Specified in Amendment 5***

The primary efficacy endpoint was the change from baseline to week 18 or week 33 on the UPDRS Part II+III score combined. The only confirmatory test for superiority of PPX ER versus placebo was done on approximately the 250 sub-set at the 1<sup>st</sup> interim analysis (18-week data). That is, the full alpha (0.05) will be spent at the first interim analysis. There was no hypothesis testing on approximately the 100 sub-set from the 2<sup>nd</sup> interim analysis (33-week data). The statistical model was an analysis of covariance, controlling for baseline UPDRS Part II+III. Fixed terms in the model were treatment, country and UPDRS Part II+III score at baseline. The analysis for the primary endpoint was based on the Full Analysis Set (FAS) (using LOCF).

Key secondary efficacy endpoints were the responder rates in CGI-I and PGI-I at week 18 or week 33. The analyses for the key secondary efficacy endpoints were based on the Full Analysis Set using a Cochran-Mantel-Haenszel procedure.

A closed testing procedure spending the full  $\alpha=0.05$  was used in the first interim analysis. In the first step, superiority of PPX ER versus placebo was tested for the primary endpoint (change in the UPDRS II+III total score). If this was significant at the 2-sided 0.05 level, then in the second and third step the superiority of PPX ER versus placebo was tested for the key secondary endpoints (CGI-I and PGI-I response rates). If significance at the 2-sided 0.05 level was reached for CGI-I in step 2, then significance for PGI-I at the 2-sided 0.05 level was tested in step 3.

Two interim analyses were done at 1<sup>st</sup> and 2<sup>nd</sup> cut-off dates, as described below. There were no stopping rules defined after these interim analyses.

First cut-off (April 2008): The objectives of this 1<sup>st</sup> interim analysis, conducted in all patients treated for 18 weeks (or prematurely withdrawn), were to show superiority of PPX ER versus placebo, and to describe safety and tolerability of PPX ER compared with placebo and PPX IR at week 18. This analysis was conducted in approximately the first 250 randomized patients. Efficacy data from patients randomized after the randomization date of approximately the 250<sup>th</sup> randomized patient were not included in this analysis (even if those efficacy data were available at the time of the 1<sup>st</sup> cut-off date).

Second cut-off (May 2008): The objectives of this 2<sup>nd</sup> interim analysis, conducted in all patients treated for 33 weeks (or prematurely withdrawn), were to show descriptively that the efficacy of PPX ER was maintained up to 6 months and to describe safety and tolerability of PPX ER compared with placebo and PPX IR at week 33. This analysis was conducted in approximately the first 100 randomized patients. Efficacy data from patients randomized after the randomization date of approximately the 100<sup>th</sup> randomized patient were not included in this analysis (even if those efficacy data were available at the time of the 2<sup>nd</sup> cut-off date). For this

second unblinded interim analysis, only descriptive statistics and descriptive p-values were to be provided for efficacy and safety endpoints.

### **3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics**

#### ***Patient Disposition***

A total of 259 patients were included in the first interim analysis (to ensure at least 250 evaluable patients in the FAS 1 analysis) and 101 were included in the second interim analysis.

A total of 296 patients were enrolled into the trial for the first interim analysis. Of those 296 patients, 37 patients (12.5%) were not randomized, and 259 were randomized and treated (TS1). Of the 259 randomized patients included in the first interim analysis, 219 patients completed the study until Week 18. A total of 40 (15.4%) patients prematurely discontinued the study, 4 patients (8.0%) in the placebo group, 21 patients (19.8%) in the PPX ER group and 15 patients (14.6%) in the PPX IR group. The most common reasons for premature discontinuation of the study were AE and refusal to continue study medication. Patient disposition for TS1 is summarized in Figure 1 below.

A total of 101 patients were randomized into the trial for the second interim efficacy analysis (TS 2). Of the 101 randomized patients in TS2, all patients were treated, and 84 patients completed the study until Week 33. A total of 17 patients (16.8%) prematurely discontinued the study, 1 patient (5.3%) in the placebo group, 7 patients (16.7%) in the PPX ER group and 9 patients (22.5%) in the PPX IR group. The most common reason for premature discontinuation of the study was AE.

Overall, a total of 599 patients were enrolled. Of those 599 patients, 60 patients (10.0%) were not randomized. Of the 539 randomized patients in TS3, all patients were treated, and 84 patients completed the study until Week 33 and 378 patients went on without termination page. A total of 77 patients (14.3%) prematurely discontinued the study, 9 patients (8.7%) in the placebo group, 43 patients (19.3%) in the PPX ER group and 25 patients (11.7%) in the PPX IR group. The most common reasons for premature discontinuation of the study were AE (6.5%) and refusal to continue intake of study medication (4.1%).

Figure 1: Patient Disposition, Treated Set at first interim analysis, 18 weeks

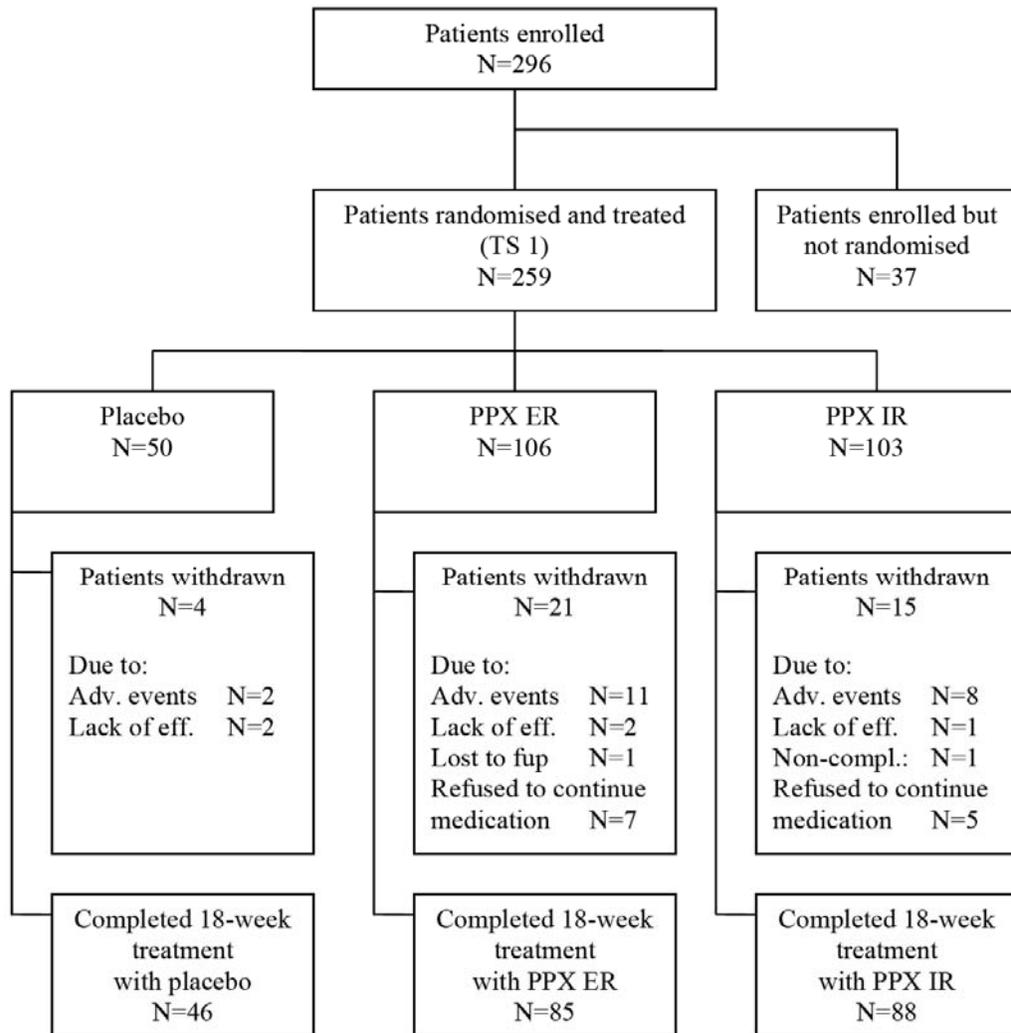


Figure 10.1: 1 Patient disposition, Treated Set at first interim analysis, 18 weeks

Source Data: [Table 15.1.1.1: 1](#)

Source: Figure 10.1:1 of sponsor’s Clinical Study Report

***Demographic and Other Baseline Characteristics for TS1 Population***

Demographic data and selected PD-related baseline characteristics are presented in Table 1 and Table 2 below.

In general, the 3 treatment groups were comparable regarding demographic and baseline characteristics. The exceptions were sex and time since PD was known:

- The placebo group consisted of 46.0% males compared to 58.5% males in the PPX ER group and 57.3% males in the PPX IR group.

- PD was known between 0 and < 2 years in 84.0% of the patients in the placebo group compared to 71.7% in the PPX ER group and 80.6% in the PPX IR group, and between 2 and < 5 years in 14.0% of the patients in the placebo group compared to 25.5% in the PPX ER group and 16.5% in the PPX IR group.

Table 1: Demographic data, Treated Set at first interim analysis (TS1), 18 weeks

		Placebo	PPX ER	PPX IR	Total
Number of Patients		50	106	103	259
Sex					
Male	[N (%)]	23 (46.0)	62 (58.5)	59 (57.3)	144 (55.6)
Female	[N (%)]	27 (54.0)	44 (41.5)	44 (42.7)	115 (44.4)
Age [years]					
Age	mean (SD)	63.2 (8.7)	61.6 (9.4)	62.0 (8.3)	62.1 (8.8)
Age classes					
Age < 65 years	[N (%)]	23 (46.0)	57 (53.8)	57 (55.3)	137 (52.9)
Age ≥ 65 years	[N (%)]	27 (54.0)	49 (46.2)	46 (44.7)	122 (47.1)
Race					
White	[N (%)]	32 (64.0)	67 (63.2)	62 (60.2)	161 (62.2)
Black	[N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	[N (%)]	18 (36.0)	39 (36.8)	41 (39.8)	98 (37.8)
BMI [kg/m <sup>2</sup> ]					
BMI	mean (SD)	26.7 (4.4)	26.0 (4.7)	26.2 (4.5)	26.2 (4.5)

Source data: [Table 15.1.4.1:1](#)

Source: Table 11.2.1:1 of sponsor's Clinical Study Report

Table 2: Selected PD-related baseline characteristics, Treated Set at first interim analysis (TS1), 18 weeks

	Placebo	PPX ER	PPX IR	Total
PD duration [years]				
Number of patients	50	106	103	259
Duration mean(SD)	0.8 (1.1)	1.1 (1.3)	0.9 (1.2)	0.9 (1.2)
PD known since*				
Number of patients	50 (100.0)	106 (100.0)	103 (100.0)	259 (100.0)
0-< 2 [y] [N (%)]	42 (84.0)	76 (71.7)	83 (80.6)	201 (77.6)
2-< 5 [y] [N (%)]	7 (14.0)	27 (25.5)	17 (16.5)	51 (19.7)
> 5 [y] [N (%)]	1 (2.0)	3 (2.8)	3 (2.9)	7 (2.7)
PD pre-treated				
Number of patients	50 (100.0)	106 (100.0)	103 (100.0)	259 (100.0)
No [N (%)]	43 (86.0)	96 (90.6)	96 (93.2)	235 (90.7)
Yes [N (%)]	7 (14.0)	10 (9.4)	7 (6.8)	24 (9.3)
Hoehn&Yahr Staging				
Number of Patients	50 (100.0)	106 (100.0)	103 (100.0)	259 (100.0)
1-1.5 [N (%)]	14 (28.0)	31 (29.2)	27 (26.2)	72 (27.8)
2-3 [N (%)]	36 (72.0)	75 (70.8)	76 (73.8)	187 (72.2)
4-5 [N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
UPDRS Part II+III total score				
Number of Patients	50	106	103	259
Mean (SD)	30.1 (17.0)	30.4 (13.4)	28.2 (11.9)	29.5 (13.6)
UPDRS Part I total score				
Number of Patients	50	106	103	259
Mean (SD)	1.0 (1.0)	1.2 (1.3)	0.9 (1.2)	1.0 (1.2)
UPDRS Part II total score				
Number of Patients	50	106	103	259
Mean (SD)	7.6 (4.3)	7.9 (4.3)	7.8 (3.7)	7.8 (4.1)
UPDRS Part III total score				
Number of Patients	50	106	103	259
Mean (SD)	22.4 (13.6)	22.6 (10.1)	20.4 (9.0)	21.7 (10.5)
PDSS				
Number of Patients	49	105	102	256
Mean (SD)	112.9 (23.8)	117.3 (22.7)	110.2 (24.7)	113.6 (23.8)

Source data: [Tables 15.1.4.1: 2](#) and [15.1.4.1: 4](#)

\*numbers (%) of patients are based on calculations of PD duration without decimals

Source: Table 11.2.1:2 of sponsor's Clinical Study Report

### ***Demographic and Other Baseline Characteristics for TS2 Population***

Table 3, Table 4 and Table 5 present the demographic data and selected PD-related baseline characteristics.

The numerical difference between groups in the demographic data and baseline characteristics can be summarized as follows:

- The placebo group consisted of 52.6% males compared to 64.3% males in the PPX ER group and 52.5% males in the PPX IR group.
- In the placebo group, 42.1% of the patients were < 65 years of age compared to 64.3% in the PPX ER group and 52.5% in the PPX IR group.
- PD was known between 0 and < 2 years for 89.5% patients in the placebo group, 69.0% patients in the PPX ER group and 80.0% in the PPX IR group.
- In the placebo group, 21.1% patients were pre-treated compared to 9.5% in the PPX ER group and 2.5% in the PPX IR group
- A total of 57.9% patients in the placebo group had a Hoehn&Yahr Staging of 2 to 3 compared to 69.0% in the PPX ER group and 72.5% in the PPX IR group.
- The overall mean baseline UPDRS Part II+III total score was 29.1 points in TS2, 23.6 points in the placebo group compared to 32.3 points in the PPX ER group and 28.3 points in the PPX IR group.
- The mean baseline PDSS was 117.7 mm in the placebo group compared to 121.4 mm in the PPX ER group and 110.0 mm in the PPX IR group.

Table 3: Demographic data, Treated Set at second interim analysis (TS2), 33 weeks

		Placebo	PPX ER	PPX IR	Total
Number of Patients		19	42	40	101
Sex					
Male	[N (%)]	10 (52.6)	27 (64.3)	21 (52.5)	58 (57.4)
Female	[N (%)]	9 (47.4)	15 (35.7)	19 (47.5)	43 (42.6)
Age [years]					
Age	mean (SD)	61.4 (8.3)	61.4 (6.2)	63.6 (5.6)	62.3 (6.4)
Age classes					
Age < 65 years	[N (%)]	8 (42.1)	27 (64.3)	21 (52.5)	56 (55.4)
Age ≥ 65 years	[N (%)]	11 (57.9)	15 (35.7)	19 (47.5)	45 (44.6)
Race					
White	[N (%)]	8 (42.1)	18 (42.9)	17 (42.5)	43 (42.6)
Black	[N (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	[N (%)]	11 (57.9)	24 (57.1)	23 (57.5)	58 (57.4)
BMI [kg/m <sup>2</sup> ]					
BMI	mean (SD)	26.0 (3.7)	25.3 (4.9)	25.1 (3.9)	25.4 (4.2)

Source data: [Table 15.1.4.2.1: 1](#)

Source: Table 11.2.1:1 of sponsor's Clinical Study Report

Table 4: Selected PD-related baseline characteristics, Treated Set at second interim analysis (TS2), 33 weeks (Part I)

	Placebo	Pramipexole ER	Pramipexole IR	Total
PD duration [years]				
Mean (SD)	0.7 (1.3)	1.0 (1.3)	0.8 (1.1)	0.9 (1.2)
PD known since [N (%)]				
0 - <2 [y]	17 (89.5)	29 (69.0)	32 (80.0)	78 (77.2)
2 - <5 [y]	1 ( 5.3)	11 (26.2)	7 (17.5)	19 (18.8)
> 5 [y]	1 ( 5.3)	2 ( 4.8)	1 ( 2.5)	4 ( 4.0)
PD pre-treated [N (%)]				
No	15 (78.9)	38 (90.5)	39 (97.5)	92 (91.1)
Yes	4 (21.1)	4 ( 9.5)	1 ( 2.5)	9 ( 8.9)

Source: Table 15.1.4.2.1: 4 of sponsor's Clinical Study Report

Table 5: Selected PD-related baseline characteristics, Treated Set at second interim analysis (TS2), 33 weeks (Part II)

	Placebo	Pramipexole ER	Pramipexole IR	Total
Hoehn & Yahr Staging [N (%)]				
Number of patients	19 (100.0)	42 (100.0)	40 (100.0)	101 (100.0)
1 - 1.5	8 ( 42.1)	13 ( 31.0)	11 ( 27.5)	32 ( 31.7)
2 - 3	11 ( 57.9)	29 ( 69.0)	29 ( 72.5)	69 ( 68.3)
4 - 5	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
UPDRS Part II+III total score				
Number of patients	19	42	40	101
Mean (SD)	23.6 (13.1)	32.3 (14.4)	28.3 (13.1)	29.1 (13.9)
UPDRS Part I total score				
Number of patients	19	42	40	101
Mean (SD)	0.8 (1.2)	1.0 (1.3)	0.6 (1.0)	0.8 (1.2)
UPDRS Part II total score				
Number of patients	19	42	40	101
Mean (SD)	6.5 (4.0)	8.8 (4.5)	7.5 (4.2)	7.9 (4.3)
UPDRS Part III total score				
Number of patients	19	42	40	101
Mean (SD)	17.1 ( 9.8)	23.5 (11.0)	20.8 ( 9.7)	21.2 (10.4)
PDSS				
Number of patients	19	42	40	101
Mean (SD)	117.7 (24.8)	121.4 (21.2)	110.0 (25.8)	116.2 (24.1)

Source: Table 15.1.4.2.1: 2 of sponsor's Clinical Study Report

**Reviewer's notes:**

Based on this reviewer's discussion with the medical reviewer, Dr. Kenneth Bergmann, the numerical differences between groups in the demographic data and baseline characteristics for TS1 and TS2 populations are not clinically meaningful differences. Please refer to Dr. Kenneth Bergmann's review for details.

**3.1.1.6 Sponsor's Primary Efficacy Results at First Interim Analysis**

The change from baseline to week 18 and to week 33 in the UPDRS Part II+III score was analyzed by Analysis of Covariance (ANCOVA) with treatment and country as factors and with baseline UPDRS Part II+III score as covariate. The sum of the UPDRS Part II+III score ranges from 0-160.

Two FAS 1 analyses were performed:

- The FAS 1 LOCF analysis, in which all efficacy values were kept in the analysis.
- The FAS 1 LOCF sensitivity analysis, in which efficacy values after introduction of L-dopa rescue were censored, to account for the unbalanced proportions of patients who started L-dopa rescue during the study.

Table 6 displays the results of the primary efficacy analysis. The mean of UPDRS Part II+III total score at baseline was 30.1 points in the placebo group, 30.5 points in the PPX ER group and 28.3 points in the PPX IR group. At Week 18, the means were 24.0, 21.3 and 19.3 points, respectively. The LS mean changes were -5.1, -8.1 and -8.4 points based on ANCOVA. The difference between PPX ER and placebo were statistically significant (p=0.0282).

Table 6: UPDRS Part II+III total score, 18 weeks treatment, FAS 1 (LOCF)

Primary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo
UPDRS Part II+III total score				
Number of Patients	50	102	101	
Baseline, Mean (SD)	30.1 (17.0)	30.5 (13.6)	28.3 (12.0)	
Week 18, Mean (SD)	24.0 (14.9)	21.3 (14.0)	19.3 (9.8)	
LS Mean Change (SE) – ANCOVA*	-5.1 (1.3)	-8.1 (1.1)	-8.4 (1.1)	0.0282
LS Mean Change (SE) – MMRM*	-4.0 (1.2)	-8.0 (1.0)	-8.0 (1.0)	0.0016

\*ANCOVA and MMRM with factors treatment and country and covariate baseline

Negative changes imply improvement in UPDRS Part II+III total score

Source data: [Table 15.2.1.1.1: 1](#)

Source: Excerpt from Table 11.4.1.1.1:1 of sponsor's Clinical Study Report

To account for the intake of L-dopa in the study as rescue medication, a sensitivity analysis was carried out. In this sensitivity analysis, the last efficacy value before the first intake of

L-dopa was carried forward. Table 7 displays the results from the FAS 1 sensitivity analysis. Based on this sensitivity analysis, the difference between PPX ER and placebo were also statistically significant (p=0.0010).

Table 7: UPDRS Part II+III total score, 18 weeks treatment, FAS 1 (LOCF) sensitivity analysis

Primary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo
UPDRS Part II+III total score				
Number of Patients	50	102	101	
Baseline, Mean (SD)	30.1 ( 17.0)	30.5 ( 13.6)	28.3 ( 12.0)	
Week 18, Mean (SD)	25.7 ( 16.7)	21.2 ( 14.0)	19.3 ( 9.8)	
LS Mean Change (SE) – ANCOVA*	-2.7 (1.3)	-7.4 (1.1)	-7.5 (1.1)	0.0010
LS Mean Change (SE) – MMRM*	-3.1 (1.2)	-7.8 (1.0)	-7.8 (1.0)	0.0003

\*ANCOVA and MMRM with factors treatment and country and covariate baseline

Negative changes imply improvement in UPDRS Part II+III total score

Source data: [Table 15.2.1.1.3: 1](#)

Source: Excerpt from Table 11.4.1.1.2: 1 of sponsor's Clinical Study Report

The difference in the UPDRS Part II+III total scores in the primary analysis (with “simple” LOCF) and the sensitivity analysis (with LOCF before first intake of L-dopa) is due to the mean change in UPDRS Part II+III total score in the placebo group: In the placebo group, it increased between Week 13 and Week 18 in the primary analysis and decreased in the sensitivity analysis, but not in the PPX groups, in which the mean changes between Week 13 and 18 were comparable in both analyses. This is most probably due to the higher proportion of patients in the placebo group who started treatment with L-dopa during the study and to the resulting large improvement in UPDRS Part II+III score once L-dopa was introduced in the 7 placebo patients.

In addition, Per Protocol Set observed cases (PPS 1 OC) analysis was performed, which was carried out with exclusion of all patients with at least one important protocol violations for efficacy and was based on observed cases, i.e. without imputation of missing values. The results are presented in Table 8. Like the FAS 1 (LOCF) and FAS 1 sensitivity analyses, the PPS 1 analysis (OC) also showed superiority of PPX ER over placebo.

Table 8: UPDRS II+III, 18 weeks treatment, PPS1 (OC)

Primary Endpoint	Placebo	Pramipexole ER	Pramipexole IR	PPX ER vs. Placebo
UPDRS II+III total score				
Number of patients	37	81	87	
Baseline, Mean (SD)	30.0 ( 16.6)	29.6 ( 13.2)	28.5 ( 12.6)	
Week 18, Mean (SD)	23.8 ( 14.3)	18.4 ( 12.0)	18.3 ( 9.6)	
LS Mean Change (SE) - ANCOVA*	-5.2 ( 1.4)	-9.9 ( 1.1)	-9.6 ( 1.0)	0.0010
LS Mean Change (SE) - MMRM**	-4.5 ( 1.4)	-8.7 ( 1.1)	-9.1 ( 1.1)	0.0016

Negative change implies improvement

\* ANCOVA and MMRM with factors treatment and country and covariate baseline

\*\* LS means per treatment group over visits 6 7 and 8

Source: Excerpt from Table 15.2.1.1.2: 1 of sponsor's Clinical Study Report

### 3.1.1.7 Sponsor's Primary Efficacy Results at Second Interim Analysis

The main efficacy objective of this second interim analysis was to assess maintenance of efficacy at 6 months in the sub-group of patients treated for 33 weeks (i.e. completers).

Maintenance of efficacy was investigated by comparing the mean change in UPDRS Part II+III total score from baseline at week 33 or at week 18 in these patients. Maintenance of efficacy was defined as no worsening by more than 15% in the mean change from baseline to week 33, compared to the mean change from baseline to week 18, and no drug-related AE leading to withdrawal, within each PPX treatment.

The main analysis for the assessment of maintenance of effect was done on FAS (OC), because any imputation of missing values by a carry forward algorithm would have decreased the difference in means at week 18 and week 33 artificially. There were 84 completer patients (i.e. patients not prematurely withdrawn before week 33).

Data in Table 9 indicate that there was almost no change in the mean change from baseline to week 33 compared to the mean change from baseline to week 18 in the PPX ER group, no change in the PPX IR group, compared to a worsening in the placebo group. Based on the descriptive results, it seems that the drug effect was maintained in both PPX groups.

Table 9: Maintenance of effect in UPDRS Part II+III totals score at week 18 and week 33, FAS2 (OC)

Primary Endpoint (maintenance of effect)		Placebo	PPX ER	PPX IR
UPDRS Part II+III total score				
Number of Patients		18	35	31
Baseline	Mean (SD)	23.6 (13.5)	31.3 (13.9)	29.0 (14.5)
Week 18	Mean (SD)	19.3 (12.7)	19.5 (12.5)	17.1 (10.9)
Change from baseline	Mean (SD)	-4.2 (7.0)	-11.8 (8.1)	-11.9 (8.8)
Week 33	Mean (SD)	20.9 (12.9)	19.8 (13.4)	17.1 (10.3)
Change from baseline	Mean (SD)	-2.7 (6.7)	-11.5 (8.5)	-11.9 (9.6)

Negative changes imply improvement in UPDRS Part II+III total score

Source data: [Table 15.2.1.2.1: 9](#)

Source: Table 11.4.1.1.5: 1 of sponsor's Clinical Study Report

The percentage of patients with/without a worsening by more than 15% in the change from baseline to week 33, compared to the change from baseline to week 18, in the UPDRS Part II+III score is displayed below in Table 10.

Table 10: Percentage of patients with / without worsening in UPDRS Part II+III total score, FAS2 (OC)

Primary Endpoint (maintenance of effect)		Placebo	PPX ER	PPX IR
% of patients with worsening or maintenance in UPDRS Part II+III total score				
Number of Patients		18	35	31
Worsening	[N (%)]	5 ( 27.8)	5 ( 14.3)	7 ( 22.6)
Without worsening	[N (%)]	13 ( 72.2)	30 ( 85.7)	24 ( 77.4)

Maintenance of effect defined as no worsening by more than 15% in the % change from baseline to week 33 compared to week 18 % change

Source data: [Table 15.2.1.2.1: 10](#)

Source: Table 11.4.1.1.5: 2 of sponsor's Clinical Study Report

In FAS 2 (OC), 13 patients (72.2%) of the placebo group, 30 patients (85.7%) of the PPX ER group and 24 patients (77.4%) in the PPX IR group did not have a worsening by more than 15% in the change from baseline to week 33, compared to the change from baseline to week 18, in the UPDRS Part II+III score.

### 3.1.1.8 Sponsor's Key Secondary Efficacy Results at First Interim Analysis

The key secondary endpoints CGI-I and PGI-I responder rates were analyzed by Cochran-Mantel-Haenszel (CMH) test with country stratification on FAS populations.

The two items ‘very much improved’ and ‘much improved’ (for CGI-I), or ‘very much better’ and ‘much better’ (for PGI-I) were pooled and these patients were considered as responders for CGI-I and PGI-I, respectively.

Table 11 below displays the results for CGI-I at week 18 in the FAS 1 population. In FAS 1 (LOCF), the responder rate as assessed by CGI-I at Week 18 was 18.0% in the placebo group compared to 37.0% in the PPX ER group and 48.0% in the PPX IR group. The difference between placebo and PPX ER were statistically significant ( $p=0.0400$ ).

Table 11: CGI-I responders, 18 weeks treatment, FAS 1 (LOCF)

Key secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo
CGI-I Responders				CMH
Number of Patients	50	100	100	
Responder [N,(%)]	9 (18.0)	37 (37.0)	48 (48.0)	0.0400
% Responder [95% CI]	[8.6, 31.4]	[27.6, 47.2]	[37.9, 58.2]	

Source data: Table 15.2.2.1.1.1: 1

Source: Excerpt from Table 11.4.1.2.1: 1 of sponsor’s Clinical Study Report

Table 12 below displays the results for PGI-I at week 18 in the FAS 1 population. In FAS 1, the responder rate as assessed by PGI-I at Week 18 was 12.0% in the placebo group compared to 35.6% in the PPX ER group and 23.8% in the PPX IR group. The difference between placebo and PPX ER was statistically significant ( $p=0.0040$ ).

Table 12: PGI-I responders, 18 weeks treatment, FAS 1 (LOCF)

Key secondary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo
PGI-I Responders				CMH
Number of Patients	50	101	101	
Responder [N(%)]	6 (12.0)	36 (35.6)	24 (23.8)	0.0040
% Responder [95% CI]	[4.5, 24.3]	[26.4, 45.8]	[15.9, 33.3]	

Source data: [Table 15.2.2.2.1.1: 1](#)

Source: Excerpt from Table 11.4.1.2.1: 2 of sponsor’s Clinical Study Report

### 3.1.1.9 Sponsor’s Key Secondary Efficacy Results at Second Interim Analysis

Out of the 101 patients included in the 2<sup>nd</sup> interim analysis, 17 patients were prematurely withdrawn from the study before the final visit (V11, week 33). Maintenance of efficacy was evaluated by comparing the CGI-I responder rate and the PGI-I responder rate at week 33 and at week 18, in the sub-group of 84 (83.2%) completer patients with observed data at week 33 (Table 13 and Table 14).

Table 13: CGI-I responders at week 18 and week 33, FAS 2 (OC)

Key secondary Endpoint		Placebo	PPX ER	PPX IR
CGI-I Responders				
Number of patients at week 18		18 (100.0)	35 (100.0)	31 (100.0)
Responders at week 18	[N,(%)]	3 (16.7)	15 (42.9)	20 (64.5)
% Responder	[95% CI]	[3.6, 41.4]	[26.3, 60.6]	[45.4, 80.8]
Number of patients at week 33		18 (100.0)	35 (100.0)	31 (100.0)
Responders at week 33	[N,(%)]	2 (11.1)	13 (37.1)	16 (51.6)
% Responder	[95% CI]	[1.4, 34.7]	[21.5, 55.1]	[33.1, 69.8]

Source data: [Appendix 16.1.2.9, Table 6.3.11.2](#)

Source: Table 11.4.1.2.1: 3 of sponsor's Clinical Study Report

Table 14: PGI-I responders at week 18 and week 33, FAS 2 (OC)

Key secondary Endpoint		Placebo	PPX ER	PPX IR
PGI-I Responders				
Number of patients at week 18		18 (100.0)	35 (100.0)	31 (100.0)
Responder at week 18	[N,(%)]	2 (11.1)	16 (45.7)	11 (35.5)
% Responder	[95% CI]	[1.4, 34.7]	[28.8, 63.4]	[19.2, 54.6]
Number of patients at week 33		18 (100.0)	35 (100.0)	31 (100.0)
Responder at week 33	[N,(%)]	2 (11.1)	15 (42.9)	13 (41.9)
% Responder	[95% CI]	[1.4, 34.7]	[26.3, 60.6]	[24.5, 60.9]

Source data: [Appendix 16.1.2.9, Table 6.3.11.5](#)

Source: Table 11.4.1.2.1: 4 of sponsor's Clinical Study Report

In FAS 2 (OC), there was no large numerical difference between the CGI-I responder rate and the PGI-I responder rate at week 33 compared to week 18 in the PPX ER group.

### 3.1.2 REVIEWER'S ANALYSIS

This reviewer verified the sponsor's efficacy analysis presented in this review.

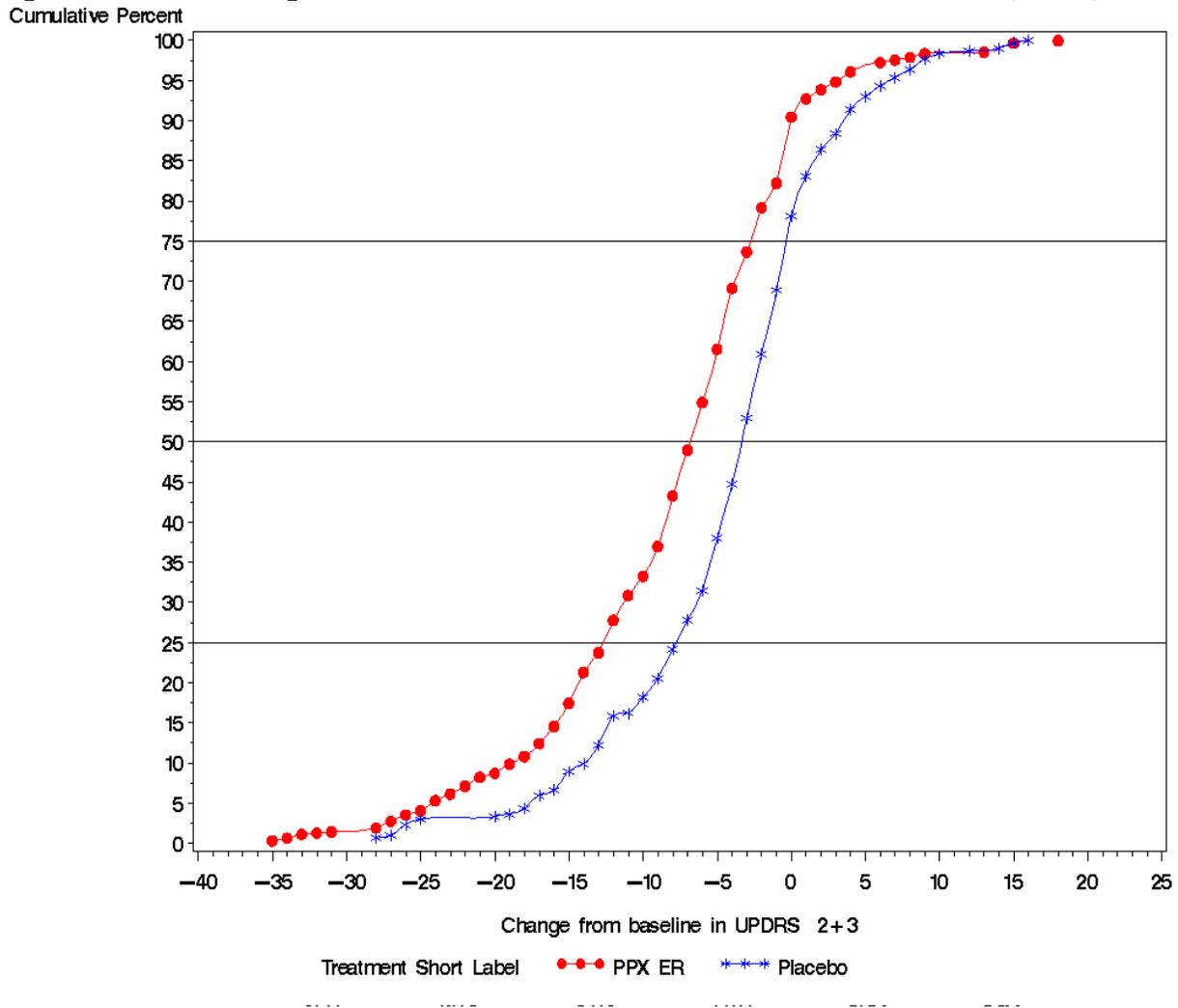
***This reviewer would like to emphasize that since the second interim analysis is descriptive, it seems to this reviewer that the results of the second interim analysis should not be used for efficacy claim or can only be used with great caution.***

In addition, this reviewer conducted the following analyses.

#### 3.1.2.1 Cumulative Distribution Function (CDF) for Primary Efficacy Endpoint

The Cumulative Distribution Function (CDF) for the primary endpoint, change from baseline in UPDRS Part II+III at week 18, is presented in Figure 2. It seems that the CDF for PPX ER group is generally above the CDF for placebo group, indicating that the patients in PPX ER group generally had larger improvement in UPDRS Part II+III score than those in placebo group.

Figure 2: CDF for change from baseline in UPDRS Part II+III at Week 18, FAS1 (LOCF)



Source: Reviewer’s Analysis

**3.1.2.2 The Impact of L-dopa Intake on Primary Efficacy Analysis**

The impact of L-dopa use as a rescue medication on the primary efficacy analysis is displayed in Table 15. The number of patients who started treatment with L-dopa during the study was 3 for PPX ER group and 7 for placebo group. As shown in the table below, the introduction of L-dopa generally results in a larger improvement in UPDRS Part II+III score. As higher proportion of patients in placebo group took L-dopa as a rescue medication, the sponsor’s primary efficacy analysis (simple LOCF) is more conservative.

Table 15: The Impact of L-dopa intake on primary efficacy analysis

Patient No.	Visit No.	Was L-dopa taken since previous visit?	Baseline UPDRS II+III	UPDRS II+III at visit	Change in UPDRS II+III from baseline (Primary endpoint, simple LOCF) <sup>1</sup>	Change in UPDRS II+III from baseline (LOCF before L-dopa) <sup>2</sup>
<b>PPX ER (3 patients)</b>						
2102	6	N	21	7	-14	.
	7	Y	21	8	-13	-14
	8	Y	21	14	<b>-7</b>	<b>-14</b>
<b>2700</b>						
	6	N	32	31	-1	.
	7	Y	32	25	-7	-1
	8	Y	32	38	<b>6</b>	<b>-1</b>
<b>3660</b>						
	7	N	35	27	-8	.
	8	Y	35	18	<b>-17</b>	<b>-8</b>
<b>Placebo (7 patients)</b>						
2204	7	N	43	45	2	.
	8	Y	43	26	<b>-17</b>	<b>2</b>
<b>2580</b>						
	7	N	74	64	-10	.
	8	Y	74	54	<b>-20</b>	<b>-10</b>
<b>2601</b>						
	6	N	25	29	4	.
	7	Y	25	37	12	4
	8	Y	25	16	<b>-9</b>	<b>4</b>
<b>2839</b>						
	6	N	20	30	10	.
	7	Y	20	36	16	-10
	8	Y	20	18	<b>-2</b>	<b>-10</b>
<b>3642</b>						
	7	N	35	33	-2	.
	8	Y	35	32	<b>-3</b>	<b>-2</b>
<b>4201</b>						
	7	N	18	15	-3	.
	8	Y	18	15	<b>-3</b>	<b>-3</b>
<b>4561</b>						
	5	N	25	22	-3	.
	6	Y	25	24	-1	-3
	7	Y	25	16	-9	-3
	8	Y	25	11	<b>-14</b>	<b>-3</b>

Source: Reviewer's Analysis

<sup>1</sup>: Simple LOCF, i.e., the last non-missing value was carried forward.

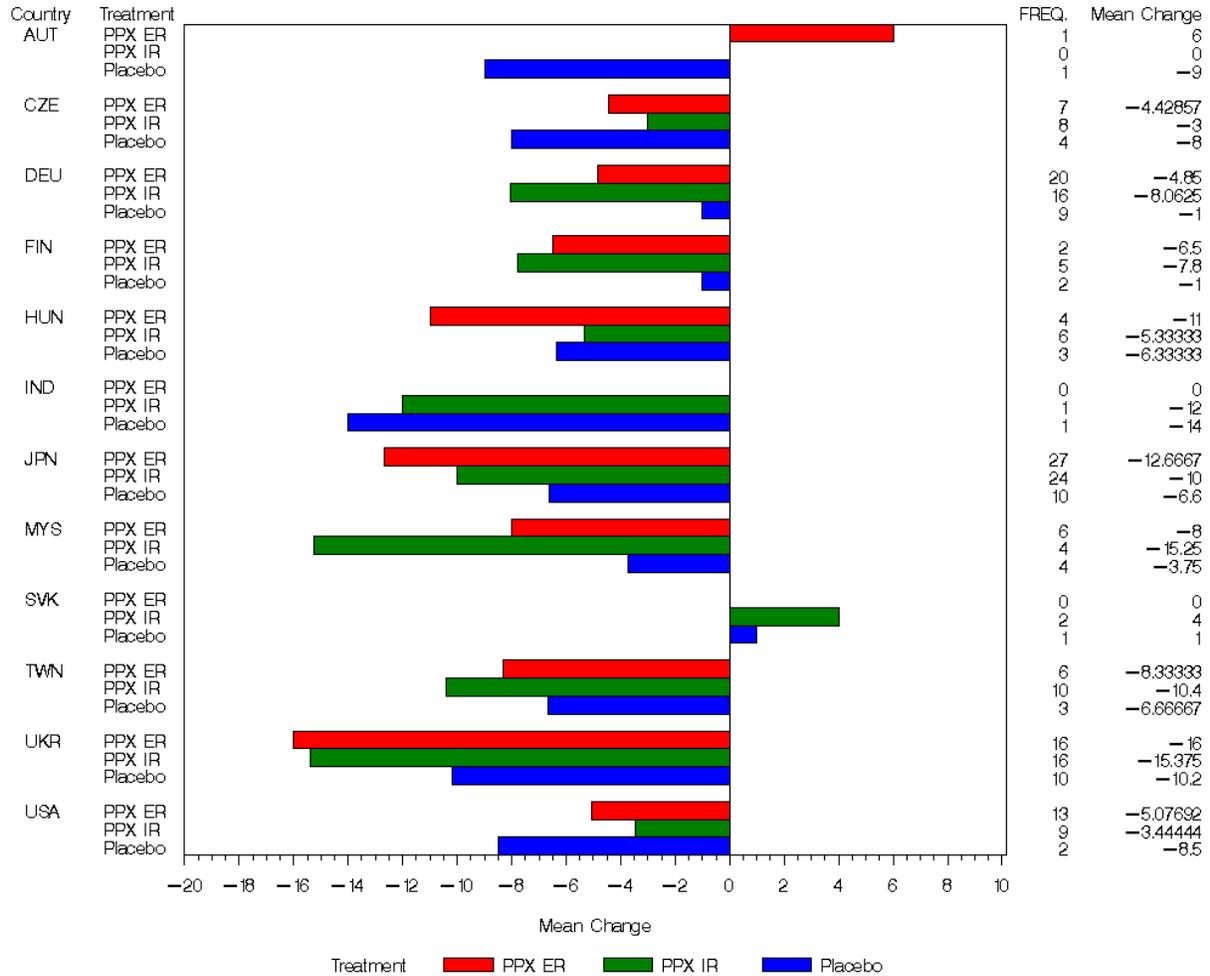
<sup>2</sup>: If L-dopa was taken this is set to the last non-missing change in UPDRS II+III from baseline before L-dopa intake.

### **3.1.2.3 Subgroup Analysis by Country**

Study 248.524 was conducted in 14 countries. The data used in first interim analysis were from patients in 12 countries. This reviewer conducted descriptive statistical analyses for the primary endpoint (change from baseline in UPDRS Part II+III totals score) by county and treatment.

Figure 3 displays FAS1 LOCF analysis for change in UPDRS Part II+II total score by country and treatment at week 18. It appears that that the point estimates of treatment effect are in the same direction as the overall patients except for Czechia, India and USA, in which the treatment effect for placebo group is numerically larger than that for PPX ER group. However, the number of patients in placebo group for these three countries is fairly small (4 in Czechia, 1 in India and 2 in USA).

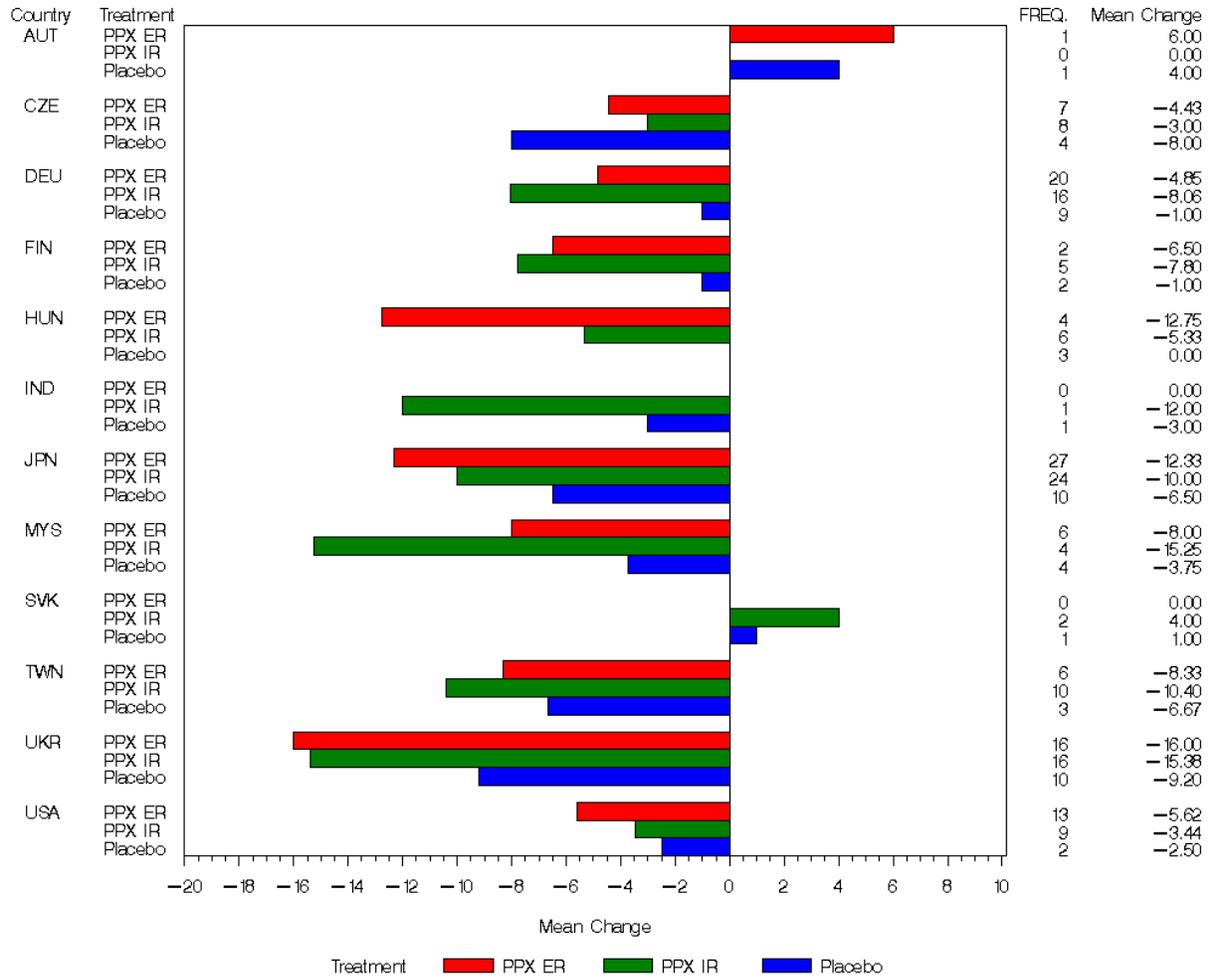
Figure 3: Change in UPDRS Part II+II total score by country and treatment, at week 18, FAS1 (LOCF)



Source: Reviewer’s Analysis

To account for the intake of L-dopa in the study as rescue medication, a sensitivity analysis was carried out. In this sensitivity analysis, the last efficacy value before the first intake of L-dopa was carried forward. Figure 4 displays this sensitivity analysis for change in UPDRS Part II+II total score by country and treatment at week 18. After taking into account the intake of L-dopa, it seems that that the point estimates of treatment effect are in the same direction as the overall patients except for Czechia. However, there were only 4 patients in placebo group in Czechia.

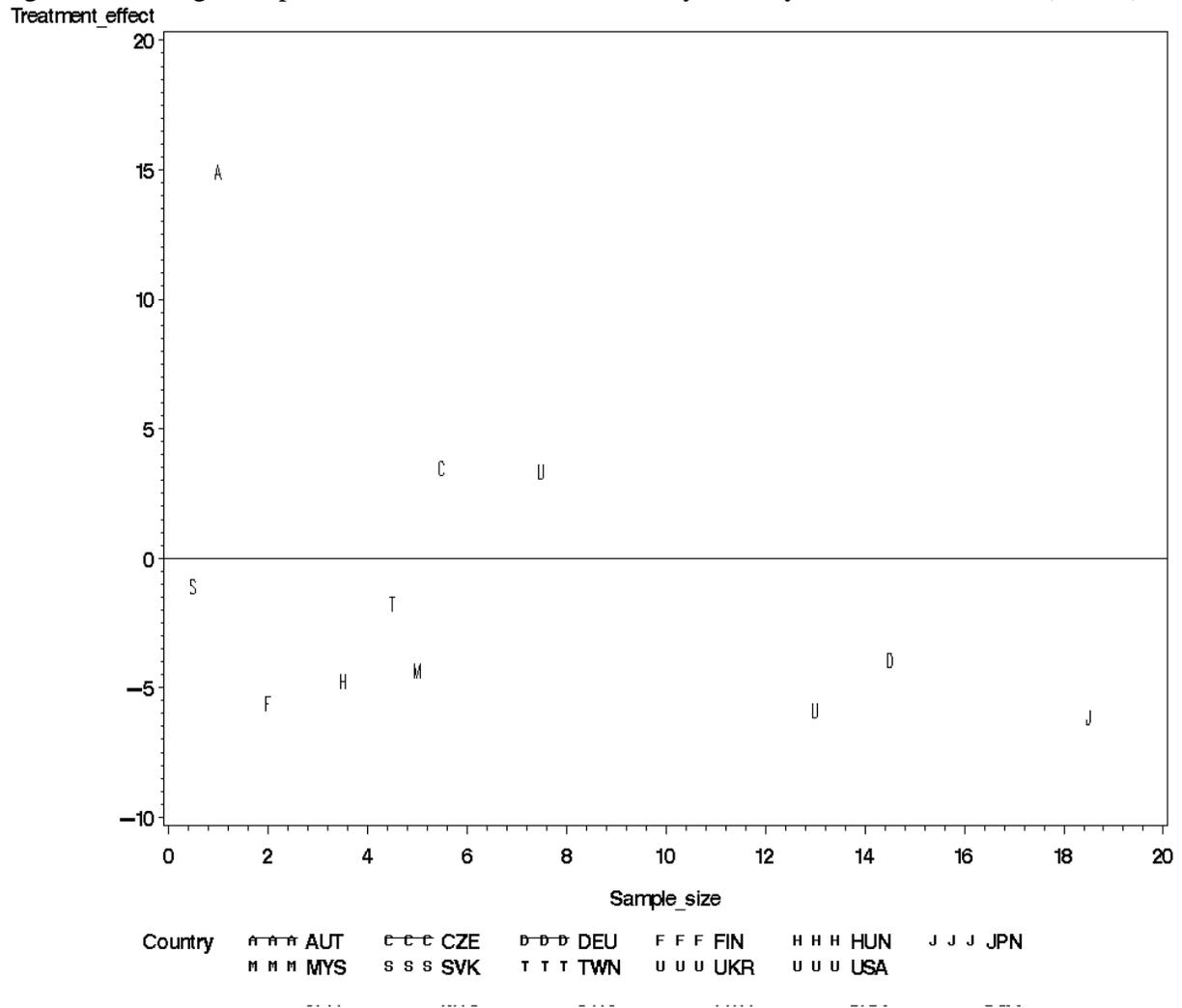
Figure 4: Change in UPDRS Part II+II total score by country and treatment, at week 18, FAS1 sensitivity analysis



Source: Reviewer’s Analysis

Furthermore, Figure 5 presents average sample size of PPX ER group and placebo group versus treatment effect by country. The treatment effect is defined as the difference between the mean change from baseline of PPX ER and mean change from baseline of placebo. India was not included in this Figure because there was only 1 patient on placebo and no one was on PPX ER.

Figure 5: Average sample size versus treatment effect by country, at week 18, FAS1 (LOCF)



Source: Reviewer’s Analysis

Based on the subgroup analyses by country presented above, this reviewer thinks there is no meaningful difference between countries in change from baseline in UPDRS Part II+III total score.

### 3.2 Evaluation of Safety

Please read Dr. Bergmann’s review for safety assessment.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Age, Gender and Ethnic group

#### 4.1.1 PROTOCOL 248.524

Subgroups analyses are only presented below for the first interim analysis. Data for the second interim analysis are not presented, due to the small number of patients in the subgroups. Results of the sub-group analyses for the primary endpoint (UPDRS Part II+III total score) are displayed below in Table 16.

Table 16: Summary of subgroup analyses for UPDRS Part II+III total score, 18 weeks treatment, FAS 1 (LOCF)

Subgroup	Placebo			PPX ER			PPX IR		
	N	Baseline	Change*	N	Baseline	Change*	N	Baseline	Change*
Age group									
< 65 year	23	26.9	-4.6	55	29.8	-10.0	56	27.4	-10.4
≥ 65 years	27	32.8	-7.4	47	31.4	-8.3	45	29.5	-7.3
Race									
Asian	18	22.1	-6.4	39	30.2	-11.3	39	26.7	-10.7
White	32	34.6	-5.9	63	30.7	-8.0	62	29.3	-8.0
Sex									
Female	27	31.0	-5.9	43	31.6	-10.8	42	23.5	-6.3
Male	23	29.0	-6.3	59	29.7	-8.1	59	31.8	-10.9

Source: Excerpt from Table 11.4.1.3.1: 4 of sponsor's Clinical Study Report

It seems that that the point estimates of treatment effect are in the same direction as the overall patients across the patient subgroups investigated.

### 4.2 Other Subgroup Populations

Study 248.524 was conducted in 14 countries. The data used in first interim analysis were from patients in 12 countries. This reviewer conducted descriptive statistical analyses for the primary endpoint (change from baseline in UPDRS Part II+III totals score) by county and treatment.

Based on the subgroup analyses by country presented in Section 3.1.2.3, this reviewer thinks there is no meaningful difference between countries in change from baseline in UPDRS Part II+III total score. Please refer to Section 3.1.2.3 for details.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The objective of the trial was to determine the efficacy, safety and tolerability of Pramipexole (PPX) ER compared with placebo and PPX IR in patients with early PD. Superiority of PPX ER to placebo (at 18 weeks) and non-inferiority of PPX ER to IR (at 33 weeks) are planned to be evaluated in a hierarchical system of hypotheses.

The objectives of the two interim analyses performed in this early PD study were:

- at 1<sup>st</sup> interim analysis: to determine the efficacy, safety and tolerability of PPX ER compared with placebo in approximately 250 patients treated for 18 weeks (or having discontinued treatment prior to week 18)
- at 2<sup>nd</sup> interim analysis: to confirm, in a sub-set of approximately 100 patients treated for 33 weeks, that efficacy was maintained up to 6 month maintenance treatment.

The primary efficacy endpoint was the change from baseline to week 18 or week 33 on the UPDRS Part II+III score combined. The only confirmatory test for superiority of PPX ER versus placebo was done on approximately the 250 sub-set at the 1<sup>st</sup> interim analysis (18-week data). That is, the full alpha (0.05) will be spent at the first interim analysis. There was no hypothesis testing on approximately the 100 sub-set from the 2<sup>nd</sup> interim analysis (33-week data). The statistical model was an analysis of covariance, controlling for baseline UPDRS Part II+III. Fixed terms in the model were treatment, country and UPDRS Part II+III score at baseline. The analysis for the primary endpoint was based on the Full Analysis Set (FAS) (using LOCF).

Key secondary efficacy endpoints were the responder rates in CGI-I and PGI-I at week 18 or week 33. The analyses for the key secondary efficacy endpoints were based on the Full Analysis Set using a Cochran-Mantel-Haenszel procedure.

A closed testing procedure spending the full  $\alpha=0.05$  was used in the first interim analysis. In the first step, superiority of PPX ER versus placebo was tested for the primary endpoint (change in the UPDRS II+III total score). If this was significant at the 2-sided 0.05 level, then in the second and third step the superiority of PPX ER versus placebo was tested for the key secondary endpoints (CGI-I and PGI-I response rates). If significance at the 2-sided 0.05 level was reached for CGI-I in step 2, then significance for PGI-I at the 2-sided 0.05 level was tested in step 3.

For the first interim analysis, the mean of UPDRS Part II+III total score at baseline was 30.1 points in the placebo group, 30.5 points in the PPX ER group and 28.3 points in the PPX IR group, and at Week 18, the means were 24.0, 21.3 and 19.3 points, respectively. The LS mean changes were -5.1, -8.1 and -8.4 points based on ANCOVA. The difference between PPX ER and placebo were statistically significant ( $p=0.0282$ ).

For the second interim analysis, maintenance of efficacy was investigated by comparing the mean change in UPDRS Part II+III total score from baseline at week 33 or at week 18 in these patients. It appears that there was almost no change in the mean change from baseline to week 33 compared to the mean change from baseline to week 18 in the PPX ER group, no change in the

PPX IR group, compared to a worsening in the placebo group. Based on the descriptive results, it seems that the drug effect was maintained in both PPX groups.

The key secondary endpoints CGI-I and PGI-I responder rates were analyzed by Cochran-Mantel-Haenszel (CMH) test with country stratification. The results of the first interim analysis indicate that the difference between placebo and PPX ER in CGI-I and PGI-I were statistically significant ( $p=0.0400$ ,  $p=0.0040$ , respectively). Based on the descriptive results of the second interim analysis, it appears that the effect was maintained.

This reviewer conducted the following additional analyses. Please refer to Section 3.1.2 Reviewer's Analysis for more details.

- **Plot the Cumulative Distribution Function (CDF) for the primary endpoint.** It seems that the CDF for PPX ER group is generally above the CDF for placebo group, indicating that the patients in PPX ER group generally had larger improvement in UPDRS Part II+III score than those in placebo group.
- **Evaluate the impact of L-dopa use as a rescue medication on the primary efficacy analysis.** The number of patients who started treatment with L-dopa during the study was 3 for PPX ER group and 7 for placebo group. The data suggest that the introduction of L-dopa generally results in a larger improvement in UPDRS Part II+III score. As higher proportion of patients in placebo group took L-dopa as a rescue medication, this reviewer thinks the sponsor's primary efficacy analysis (simple LOCF) is more conservative.
- **Conduct subgroup analysis by country.** Since Study 248.524 was conducted in 14 countries, this reviewer conducted descriptive statistical analysis for the primary endpoint by county and treatment. Based on this subgroup analysis, this reviewer thinks there is no meaningful difference between countries in change from baseline in UPDRS Part II+III total score.

**Reviewer's notes: Since the second interim analysis is descriptive, it seems to this reviewer that the results of the second interim analysis should not be used for efficacy claim or can only be used with great caution.**

## 5.2 Conclusions and Recommendations

Based on the results of the first interim analysis, there is evidence that Mirapex (pramipexole extended release) is effective as compared to placebo in the treatment of early Parkinson's Disease (PD), as assessed by the primary endpoint, change from baseline at week 18 in the UPDRS Part II+III total score.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22421	----- ORIG 1	----- BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	----- PRAMIPEXOLE DIHYDROCHLORIDE

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/s/

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JINGYU J LUAN  
07/29/2009

KUN JIN  
07/30/2009

HSIEN MING J J HUNG  
07/30/2009