CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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:	22-514
Drug Name:	Mirapex (Pramipexole dihydrochloride)
Indication:	Early and Advanced Parkinson's Disease
Applicant:	Boehringer Ingelheim
Date of Submission:	05/21/2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Key Words:	Parkinson's Disease, UPDRS Part II+III, ANCOVA

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on the results of Study 248.525, there is evidence that Mirapex (pramipexole extended release, in daily doses from 0.375 mg to 4.5 mg q.d.) is effective as compared to placebo in L–Dopa+ treated patients with advanced 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 Study Reports for Study 248.525.

Study 248.525 was a multi-centre, multinational, double-blind, double-dummy, placebo-controlled, randomized, three parallel-group efficacy and safety 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. It was conducted in 76 active sites in 14 countries (all were foreign countries) for L-Dopa+ treated patients with advanced Parkinson's Disease. A total of 517 patients were randomized into the trial and treated.

1.3 Statistical Issues and Findings

The objective of Study 248.525 was to determine the efficacy, safety and tolerability of Mirapex (pramipexole extended release, in daily doses from 0.375 mg to 4.5 mg q.d.) compared to PPX IR and placebo in L–Dopa+ treated patients with advanced PD.

The primary endpoint was change from baseline in the UPDRS Part II+III score. It was analyzed by ANCOVA with treatment and pooled country as factors and UPDRS Part II+III score at baseline as covariate on the Full Analysis Set (FAS) (using LOCF). Following meetings between the sponsor and regulatory agencies, 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 advanced PD patients. Therefore, the confirmatory analysis for the superiority hypothesis (pramipexole ER vs. placebo) was performed at Visit 8 (18 weeks), instead of at Visit 11 (33 weeks), as initially planned.

The key secondary endpoint was the change from baseline to week 18 in the percentage off-time during waking hours. It was analyzed using ANCOVA with baseline as covariate and treatment and pooled country as factors.

Regarding multiplicity, superiority of PPX ER versus placebo was tested for the primary endpoint as the first step. If this was significant at the 2-sided 5% level, then in a second step the superiority of PPX ER versus placebo was tested for the key secondary endpoint.

For Study 248.525, the mean of UPDRS Part II+III total score at baseline was 40.0 points in the placebo group, 41.7 points in the PPX ER group and 40.8 points in the PPX IR group. At week 18, the means (calculated with LOCF) were 33.2, 29.5 and 27.2 points, respectively. The difference in improvement in UPDRS Part II+III total score between PPX ER and placebo were statistically significant (ANCOVA, p=0.0001). In both active treatment groups there were small differences in the mean change from baseline to week 33 compared to the mean change from baseline to week 18 (pramipexole ER: +0.8 points; pramipexole IR: 1.5 points). Thus, it appears that maintenance of efficacy at week 33 was shown in both pramipexole groups. The results of the key secondary endpoint show that the difference in improvement in percentage off-time between PPX ER and placebo were statistically significant (ANCOVA, p=0.0122) and it appears that the maintenance of efficacy at week 33 was confirmed.

This reviewer conducted the following additional analyses for Study 248.525. 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.

- **Conduct subgroup analysis by country.** It appears that there is no meaningful difference between countries in change from baseline in UPDRS Part II+III total score.

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\NDA022514\0000 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY 248.525

3.1.1.1 Study Objectives

The general aim of this trial was to determine efficacy (as measured by the change from baseline in the total score for UPDRS Parts II and III combined), safety, and tolerability of pramipexole ER, in daily doses from 0.375mg to 4.5mg qd, in comparison to placebo, in L–Dopa+ treated Parkinson patients with advanced PD and motor fluctuations. In addition, a numerical comparison of the efficacy of pramipexole ER versus pramipexole IR was done. The efficacy of pramipexole IR was also compared to placebo, for assay sensitivity.

3.1.1.2 Study Design

This was a double-blind, double-dummy, placebo-controlled, randomized, three parallel groups efficacy and safety multinational multi-centre study evaluating pramipexole ER (in daily doses from 0.375mg to 4.5mg per day qd) compared with placebo and with pramipexole IR over an up to 26-week maintenance phase.

The study was conducted in L-Dopa+ treated patients with motor fluctuations and with a modified Hoehn and Yahr scale of 2 to 4 at on-time.

After a 1- to 2-week screening phase and a 7-week double-blind flexible up-titration phase, there was an up to 26-week double-blind maintenance phase, followed by a 1-week downtitration

phase (only for those patients not entering the open-label extension study). Therefore, the trial could have lasted for up to 36 weeks, totally.

At the end of the double-blind maintenance treatment phase, patients might have been eligible to enter an open-label extension study with pramipexole ER.

3.1.1.3 Efficacy Measures

Primary efficacy endpoint

- Change from baseline to week 18 in the UPDRS parts II+III score

Key secondary efficacy endpoint was (to be assessed at week 18 and at week 33):

- Percentage off-time during waking hours – diary based (change from baseline)

Other secondary efficacy endpoints were (to be assessed at week 18 and at week 33):

- Proportion of patients with at least a 20% improvement relative to baseline in the percentage off-time during waking hours – diary based;
- Percentage on-time: without dyskinesia; with non-troublesome dyskinesia; without dyskinesia or with non-troublesome dyskinesia (i.e. “good on time”); with troublesome dyskinesia; during waking hours – diary based (change from baseline);
- Responder rate for Clinical Global Impression of Improvement (CGI-I);
- Responder rate for Patient Global Impression of Improvement (PGI-I);
- Responder rate for Patient Global Impression of Improvement (PGI-I) for early morning off-symptoms (was added as secondary endpoint in amendment 1, dated 18 April 2007);
- Proportion of patients with at least a 20% improvement relative to baseline in the UPDRS II+III total score;
- UPDRS I, II, III and IV scores separately (change from baseline);
- Beck’s Depression Inventory (BDI) version IA (change from baseline);
- Parkinson’s Disease Sleep Scale (PDSS) total score (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);
- L-Dopa daily dose (change from baseline);
- Cost-effectiveness analysis will be conducted to compare treatments. Results will be reported separately.

3.1.1.4 Statistical Analysis Plan

Changes in the Planned Analysis

Following FDA recommendation, a confirmatory statistical analysis was to be done in all patients who were treated for 18 weeks or had discontinued treatment prior to week 18.

Revised Analysis Plan (Final Analysis Plan)

The primary efficacy endpoint was the change from baseline (week 0) to week 18 on the UPDRS Parts II+III score combined. The key secondary endpoint was the change from baseline to week 18 in the percentage off-time during waking hours. For both primary endpoint and key secondary endpoint, the statistical model was an analysis of covariance (ANCOVA) with baseline as covariate and treatment and pooled country as factors.

The key secondary endpoint was the change from baseline to week 18 in the percentage off-time during waking hours. It was analyzed using ANCOVA with baseline as covariate and treatment and pooled country as factors.

Regarding multiple comparison, superiority of PPX ER versus placebo was tested for the primary endpoint as the first step. If this was significant at the 2-sided 5% level, then in a second step the superiority of PPX ER versus placebo was tested for the key secondary endpoint.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

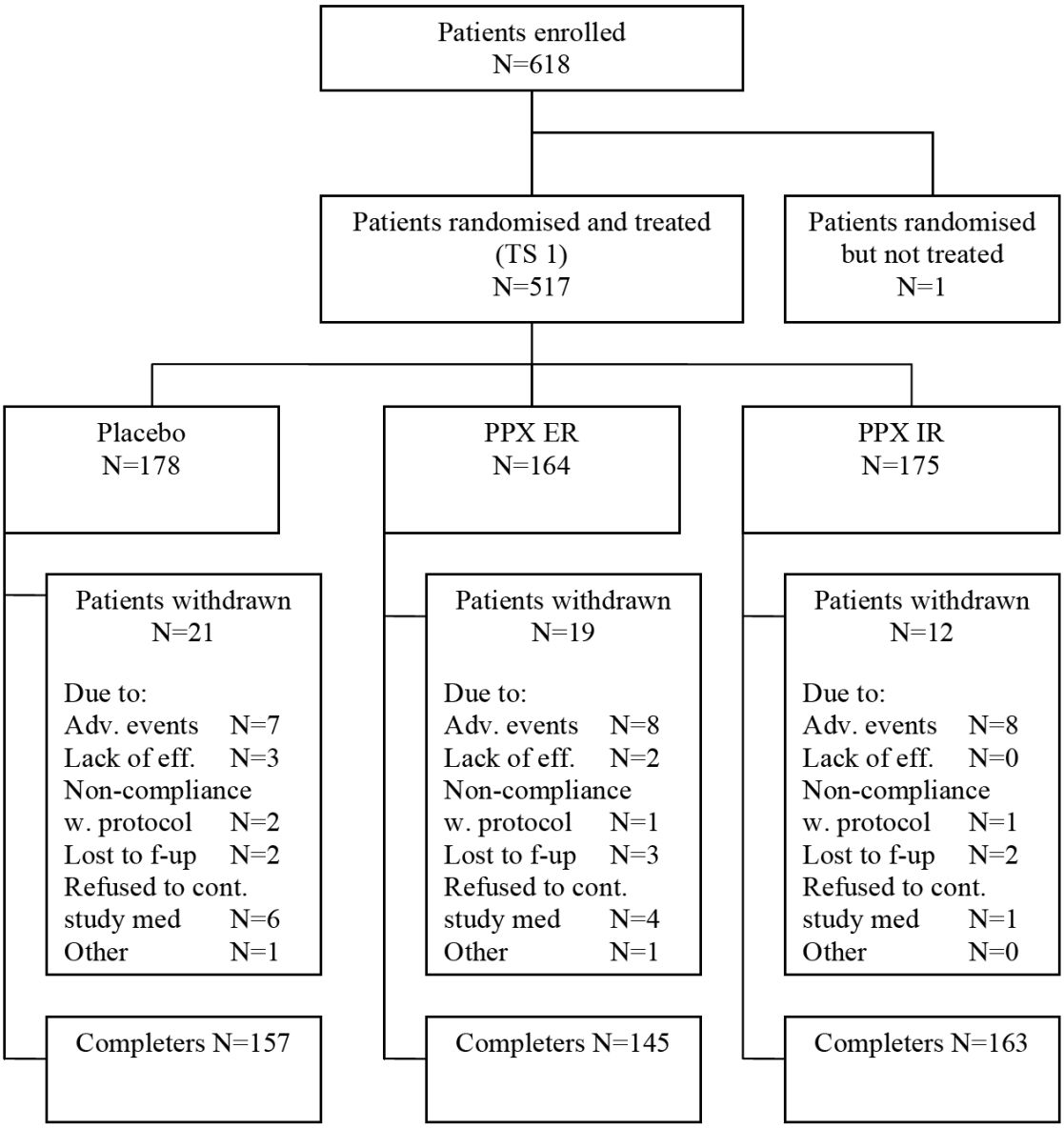
Patient Disposition

A total of 618 patients were enrolled into the trial. Of those 618 patients, 87 patients (14.1%) were screening failures. A total of 518 patients were entered into the trial. The most frequent reasons for not being randomized were violation of an inclusion or exclusion criteria (64 patients) and consent withdrawn (17 patients). The patient disposition is summarized in Figure 1 for Treated set 1 and Table 1 for Treated set 2.

Treated set 1 (TS 1) population was defined as all patients who were dispensed study medication, were documented to have at least one dose of study medication and were treated for 18 weeks (or had discontinued treatment prior to week 18). Data limited to visit 8 (or V11 in case of premature discontinuation before visit 8).

Treated set 2 (TS 2) population was defined as all patients who were dispensed study medication, were documented to have at least one dose of study medication and completed visit 11 (were treated for 33 weeks or had discontinued treatment prior to week 33).

Figure 1: Patient disposition, TS1



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

Table 1: Patient disposition, TS 2

Disposition	Placebo N (%)	PPX ER N (%)	PPX IR N (%)	Total N (%)
Treated (33 weeks)	140 (100.0)	120 (100.0)	135 (100.0)	395 (100.0)
Completed (33 weeks)	111 (79.3)	103 (85.8)	123 (91.1)	337 (85.3)
Prematurely discontinued	29 (20.7)	17 (14.2)	12 (8.9)	58 (14.7)
Adverse event	9 (6.4)	7 (5.8)	7 (5.2)	23 (5.8)
AE study dis. worse	3 (2.1)	1 (0.8)	2 (1.5)	6 (1.5)
AE other dis. worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AE other	6 (4.3)	6 (5.0)	5 (3.7)	17 (4.3)
Lack of efficacy	4 (2.9)	2 (1.7)	0 (0.0)	6 (1.5)
Non compl. protocol	2 (1.4)	1 (0.8)	1 (0.7)	4 (1.0)
Lost to follow-up	4 (2.9)	2 (1.7)	2 (1.5)	8 (2.0)
Refused cont. medication*	9 (6.4)	4 (3.3)	2 (1.5)	15 (3.8)
Other	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.5)

*informed consent withdrawn not due to AE
Source Data: Table 15.1.1.2: 1

Source: Table 10.1:2 of sponsor's Clinical Study Report

Demographic Data and Other Baseline Characteristics

Demographic data and selected PD-related baseline characteristics are presented below for TS1 in Table 2 and Table 3.

Table 2: Demographic data, TS 1

	Placebo	PPX ER	PPX IR	Total
Number of patients	178	164	175	517
Gender [N (%)]				
Male	94 (52.8)	92 (56.1)	98 (56.0)	284 (54.9)
Female	84 (47.2)	72 (43.9)	77 (44.0)	233 (45.1)
Age [years]				
Mean (SD)	60.9 (9.7)	61.6 (9.7)	62.0 (10.3)	61.5 (9.9)
Age classes [N (%)]				
<65 years	104 (58.4)	94 (57.3)	100 (57.1)	298 (57.6)
>=65 years	74 (41.6)	70 (42.7)	75 (42.9)	219 (42.4)
Race [N (%)]				
White	92 (51.7)	81 (49.4)	87 (49.7)	260 (50.3)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	86 (48.3)	83 (50.6)	88 (50.3)	257 (49.7)
BMI [kg/m²]				
Mean (SD)	25.0 (4.6)	24.7 (3.9)	24.5 (4.2)	24.7 (4.3)

Source data: Table 15.1.4.1: 1

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

Table 3: Selected PD-related baseline characteristics, TS 1

		Placebo	PPX ER	PPX IR	Total
PD duration [years]					
Duration mean(SD) or median (IQR)		5.9 (3.8)	6.1 (4.0)	6.6 (4.4)	6.2 (4.1)
PD known since					
0-< 2 [y]	N (%)	1 (0.6)	1 (0.6)	3 (1.7)	5 (1.0)
2-< 5 [y]	N (%)	90 (50.6)	82 (50.0)	76 (43.4)	248 (48.0)
>= 5 [y]	N (%)	87 (48.9)	81 (49.4)	96 (54.9)	264 (51.1)
UPDRS Part II+III total score					
Number of Patients		178	164	174	516
Mean (SD)		39.6 (18.2)	41.7 (17.9)	40.7 (17.6)	40.6 (17.9)
Percentage off-time					
Number of Patients		178	164	175	517
Mean (SD)		38.6 (15.6)	36.0 (15.7)	37.7 (13.2)	37.5 (14.9)
Off-time in hours					
Number of Patients		178	164	175	517
Mean (SD)		6.0 (2.5)	5.8 (2.8)	6.0 (2.2)	5.9 (2.5)
UPDRS Part I total score					
Number of Patients		178	164	175	517
Mean (SD)		1.9 (1.9)	2.1 (1.8)	1.9 (1.7)	1.9 (1.8)
UPDRS Part II total score (average on and off-period)					
Number of Patients		178	164	174	516
Mean (SD)		11.9 (6.1)	12.7 (6.5)	12.3 (5.7)	12.3 (6.1)
UPDRS Part III total score					
Number of Patients		178	164	175	517
Mean (SD)		27.7 (13.6)	29.0 (12.9)	28.3 (13.3)	28.3 (13.2)
PDSS					
Number of Patients		178	164	175	517
Mean (SD)		101.7 (25.3)	96.8 (27.7)	101.1 (26.2)	100.0 (26.4)

Source data: Table 15.1.4.1: 2, 15.1.4.1: 3, 15.1.4.1: 4

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

In general, it seems that the 3 treatment groups were comparable regarding demographic characteristics and baseline characteristics.

3.1.1.6 Sponsor's Efficacy Results

Primary Endpoint at week 18 (FAS1, LOCF)

The change from baseline to week 18 (confirmatory analysis) in the primary endpoint UPDRS Parts II+III score was analyzed by Analysis of Covariance (ANCOVA) with treatment and pooled country as factors and with baseline UPDRS Parts II+III score as covariate.

Table 4 displays the results for the confirmatory test for superiority of pramipexole ER versus placebo, for UPDRS Part II+III score at week 18 in the FAS 1 (LOCF) population and Figure 2 displays the adjusted mean change (SE) from baseline in UPDRS Part II+III score in FAS 1 (LOCF) population.

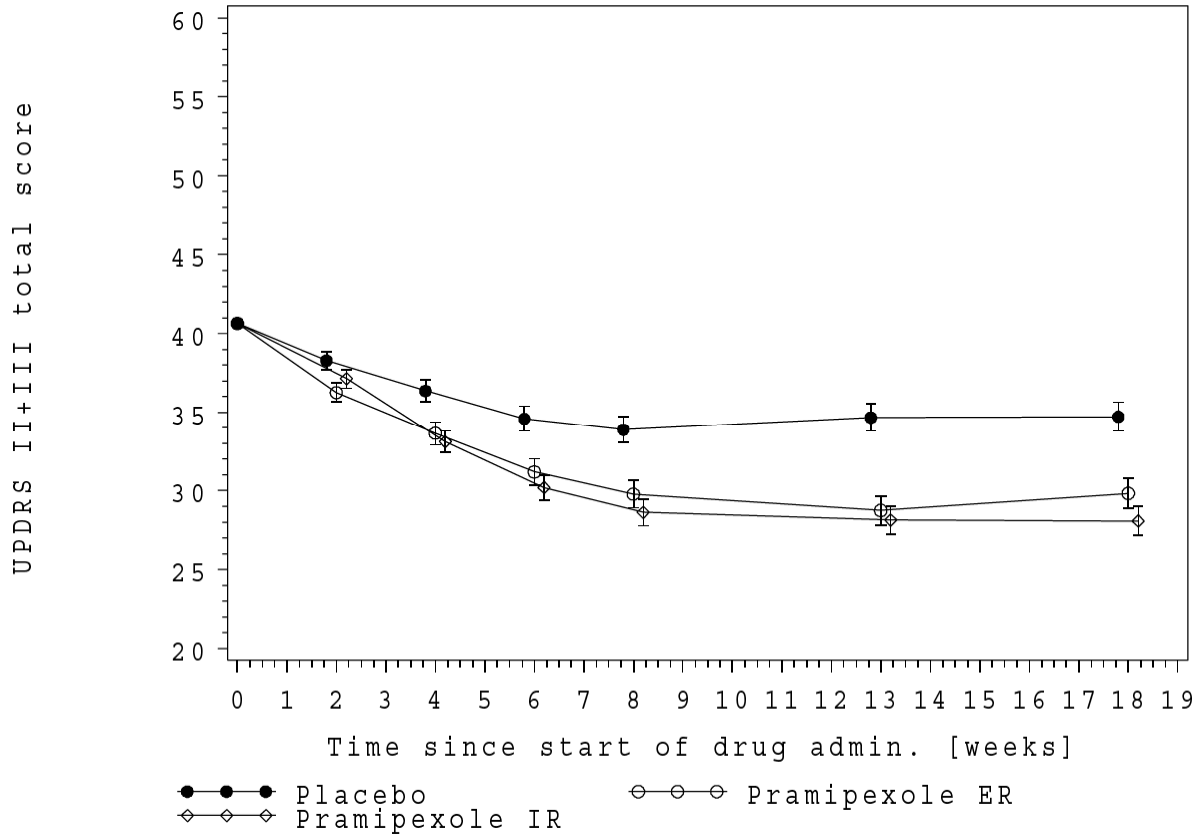
Table 4: UPDRS II+III, 18 weeks treatment, FAS 1 (LOCF)

Primary Endpoint	Placebo	PPX ER	PPX IR	PPX ER vs. placebo
UPDRS Part II&III total score				
Number of Patients	174	161	172	
Mean Baseline (SD)	40.0 (18.1)	41.7 (17.7)	40.8 (17.4)	
Mean week 18 (SD)	33.2 (17.4)	29.5 (17.3)	27.2 (16.4)	
LS Mean Change (SE) – ANCOVA*	-6.1 (0.9)	-11.0 (1.0)	-12.8 (0.9)	**0.0001**
LS Mean Change (SE) – MMRM*	-6.4 (0.8)	-11.4 (0.9)	-12.6 (0.8)	<.0001

*ANCOVA and MMRM with factors treatment and pooled country and covariate baseline
Negative changes imply improvement in UPDRS Part II+III total score
Source data: Table 15.2.1.1: 1

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

Figure 2: Adjusted mean change (SE) from baseline in UPDRS Part II+III score, FAS 1 (LOCF)



Source: Figure 11.4.1.1.1:1 of sponsor's Clinical Study Report

The mean of UPDRS Part II+III total score at baseline was 40.0 points in the placebo group, 41.7 points in the PPX ER group and 40.8 points in the PPX IR group. At week 18, the means (calculated with LOCF) were 33.2, 29.5 and 27.2 points, respectively. The associated adjusted mean changes were -6.1, -11.0 and -12.8 points as calculated by an analysis of covariance (ANCOVA). The difference in improvement in UPDRS Part II+III total score between PPX ER and placebo were statistically significant (ANCOVA, p=0.0001).

In addition, the observed cases (OC) analysis also showed superiority of PPX ER over placebo.

Primary Endpoint at Week 33 (FAS 2)

Maintenance of efficacy was investigated by comparing the mean change in UPDRS Part II+III total score from baseline at week 33 with week 18 data in the completer 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, within each PPX treatment group (i.e. no between group comparisons was done).

The main analysis for the assessment of maintenance of effect was done on FAS 2 (OC). There were 308 completer patients (i.e. patients not prematurely withdrawn before week 33). Results are presented in Table 5.

Table 5: Maintenance of effect in UPDRS Part II+III total score at week 18 and week 33, FAS 2 (OC)

Primary Endpoint (maintenance of effect)		Placebo	PPX ER	PPX IR
UPDRS Part II+III total score				
Number of Patients		100	94	114
Baseline	Mean (SD)	41.3 (18.5)	42.3 (18.9)	41.3 (17.9)
Week 18	Mean (SD)	32.0 (15.9)	27.3 (17.6)	26.4 (17.0)
Change from baseline	Mean (SD)	-9.2 (15.0)	-15.0 (13.2)	-14.9 (12.0)
Week 33	Mean (SD)	31.0 (16.2)	28.1 (19.2)	27.9 (19.1)
Change from baseline	Mean (SD)	-10.3 (14.9)	-14.2 (15.3)	-13.4 (15.8)

Negative changes imply improvement in UPDRS Part II+III total score
Source data: Table 15.2.1.3: 8

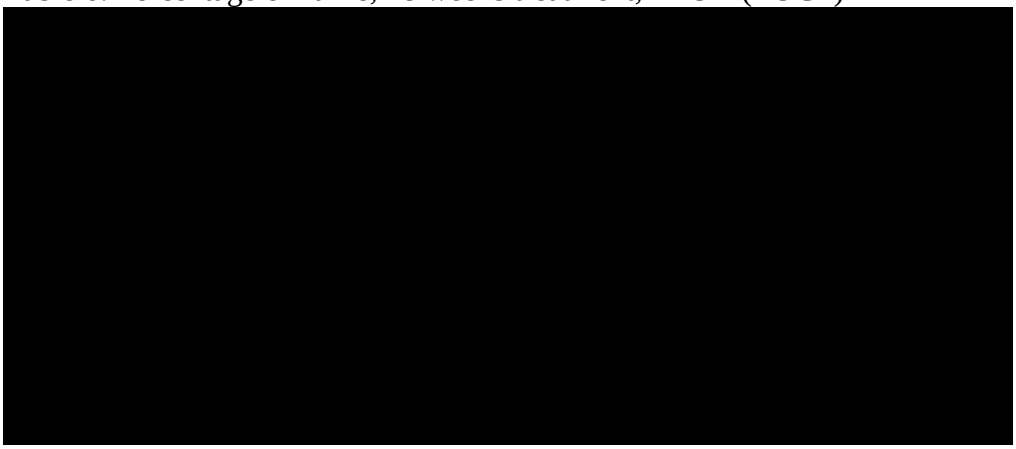
Source: Table 11.4.1.1.4:1 of sponsor's Clinical Study Report

In the PPX ER group, there was a difference in the mean change from baseline to week 33, compared to the mean change from baseline to week 18, of +0.8 points (i.e. 5.3%). In the PPX IR group, there was a difference in the mean change from baseline to week 33, compared to the mean change from baseline to week 18, of +1.5 points (i.e. 10.1%). Therefore, it seems that maintenance of efficacy at week 33 was shown in both pramipexole groups.

Key Secondary Endpoint at Week 18

The change from baseline to week 18 and to week 33 in the percentage off-time was analyzed by Analysis of Covariance (ANCOVA) with treatment and pooled country as factors and with baseline percentage off-time as covariate. Table 6 displays the results for the confirmatory test for superiority of pramipexole ER versus placebo, for percentage off-time at week 18 in the FAS 1 (LOCF).

Table 6: Percentage off-time, 18 weeks treatment, FAS 1 (LOCF)



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

In FAS 1 (LOCF), the mean in percentage off-time during waking hours at baseline was 38.7 points in the placebo group, 36.3 points in the PPX ER group and 37.8 points in the PPX IR group. At week 18, the mean was 29.6 points in the placebo group, 24.1 points in the PPX ER group and 22.3 points in the PPX IR group. The associated adjusted mean changes were -8.8, -13.3 and -15.9 points as calculated by an ANCOVA. The difference in improvement in percentage off-time between PPX ER and placebo were statistically significant (ANCOVA, p=0.0122).

Key Secondary Endpoint at Week 33

For FAS 2 (LOCF), the results are presented in Table 7.

Table 7: Percentage off time during waking hours, 33 weeks, FAS 2 (LOCF)

Secondary Endpoint	Placebo	Pramipexole ER	Pramipexole IR
% off time during waking hours			
Number of patients	136	116	131
Baseline, Mean (SD)	39.1 (16.1)	37.3 (16.5)	38.8 (13.3)
Week 33, Mean (SD)	29.9 (18.8)	26.0 (19.2)	21.7 (14.7)
Change from Baseline, Mean [95% CI]	-9.2 [-12.4, -6.0]	-11.3 [-14.9, -7.7]	-17.1 [-19.8,-14.4]
LS Mean Change [95% CI] - ANCOVA*	-8.9 [-11.7, -6.1]	-11.8 [-14.9, -8.7]	-17.0 [-19.9,-14.1]
LS Mean Change [95% CI] - MMRM**	-8.7 [-11.1, -6.3]	-12.7 [-15.3,-10.1]	-16.1 [-18.5,-13.7]

Negative change implies improvement
* ANCOVA with factors treatment and pooled country and covariate baseline
** LS means per treatment group over visits 6 7 and 8 (maintenance)

Source: Excerpt from Table 15.2.2.1.3:1 of sponsor's Clinical Study report

In the PPX ER group, there was a difference in the mean change from baseline to week 33, compared to the mean change from baseline to week 18, of +0.9 points (i.e. -6.3%). In the PPX IR group, there was a difference in the mean change from baseline to week 33, compared to the mean change from baseline to week 18, of -0.9 points (i.e. 5.2%). Therefore, it appears that maintenance of efficacy at week 33 was confirmed in both pramipexole groups. In the placebo group, there was a difference in the mean change from baseline to week 33, compared to the mean change from baseline to week 18, of -0.7 points (i.e. 7.2%).

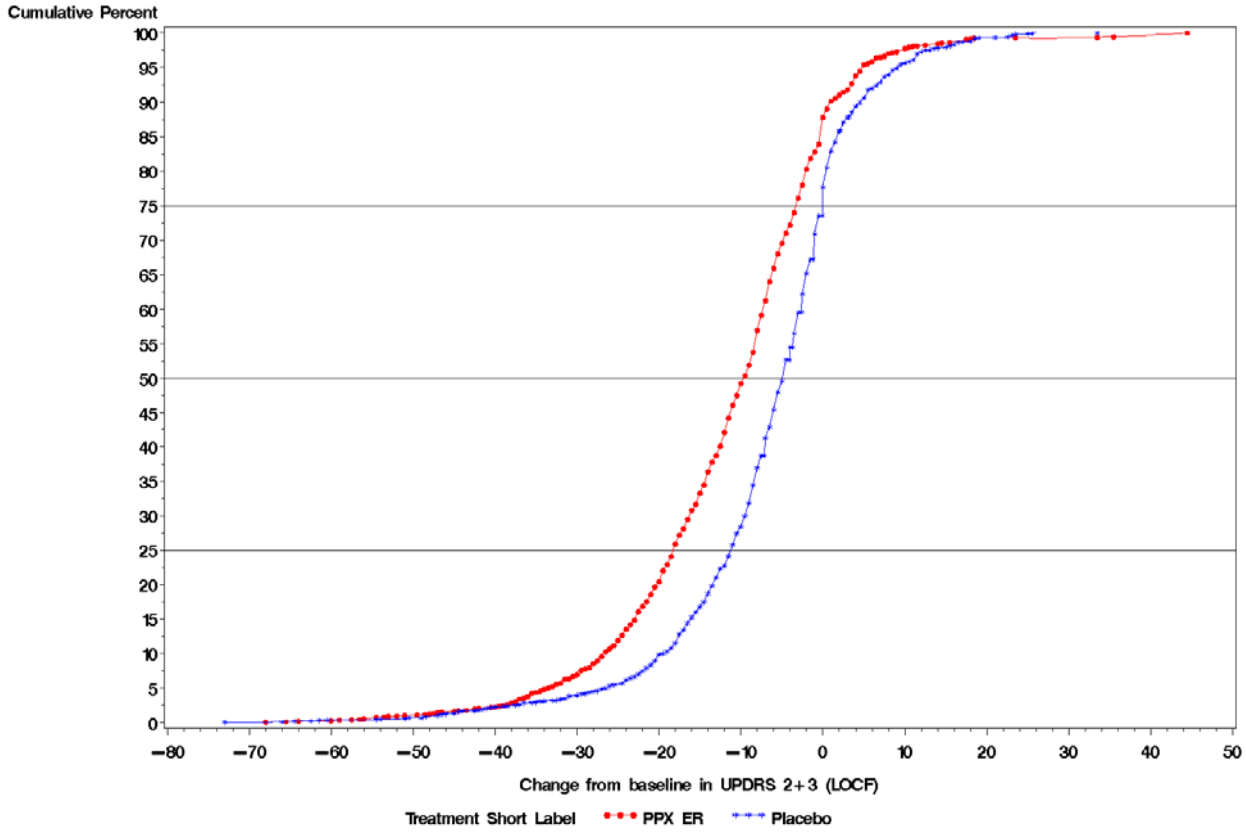
3.1.2 REVIEWER'S ANALYSIS

This reviewer verified the sponsor's efficacy analyses presented in this review. In addition, this reviewer conducted the following analyses for Study 248.525.

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 3for Study 248.525. 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 3: CDF for change from baseline in UPDRS Part II+III at Week 18, FAS1 (LOCF)

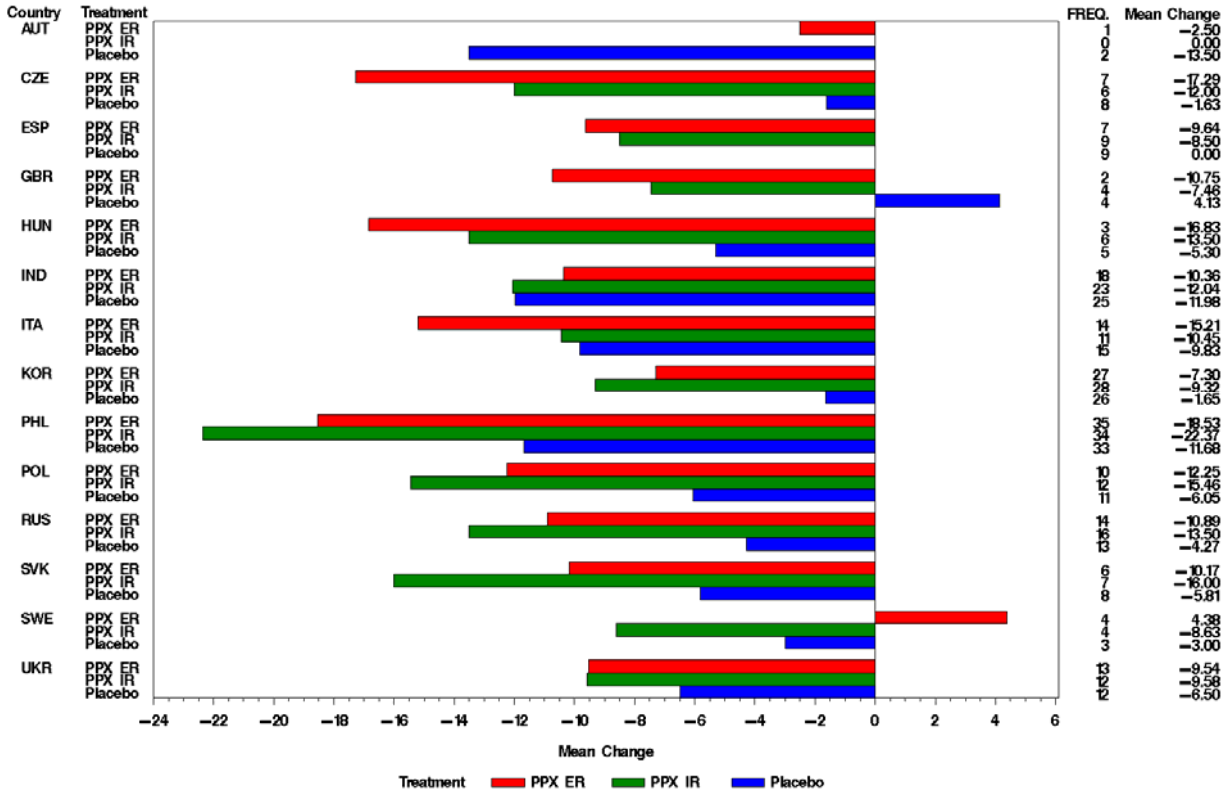


Source: Reviewer's Analysis

3.1.2.2 Subgroup Analysis by Country

Figure 4 displays FAS1 LOCF analysis for change in UPDRS Part II+III total score by country and treatment at week 18 for Study 248.525. It appears that that the point estimates of treatment effect are in the same direction as the overall patients except for Austria, Sweden and India, in which the treatment effect for placebo group is numerically larger than that for PPX ER group. However, for Australia and Sweden, the number of patients in placebo group is very small (2 in Austria and 3 in Sweden); for India, mean change for PPX ER group and Placebo group are very close (-10.36 for PPX ER and -11.98 for Placebo group).

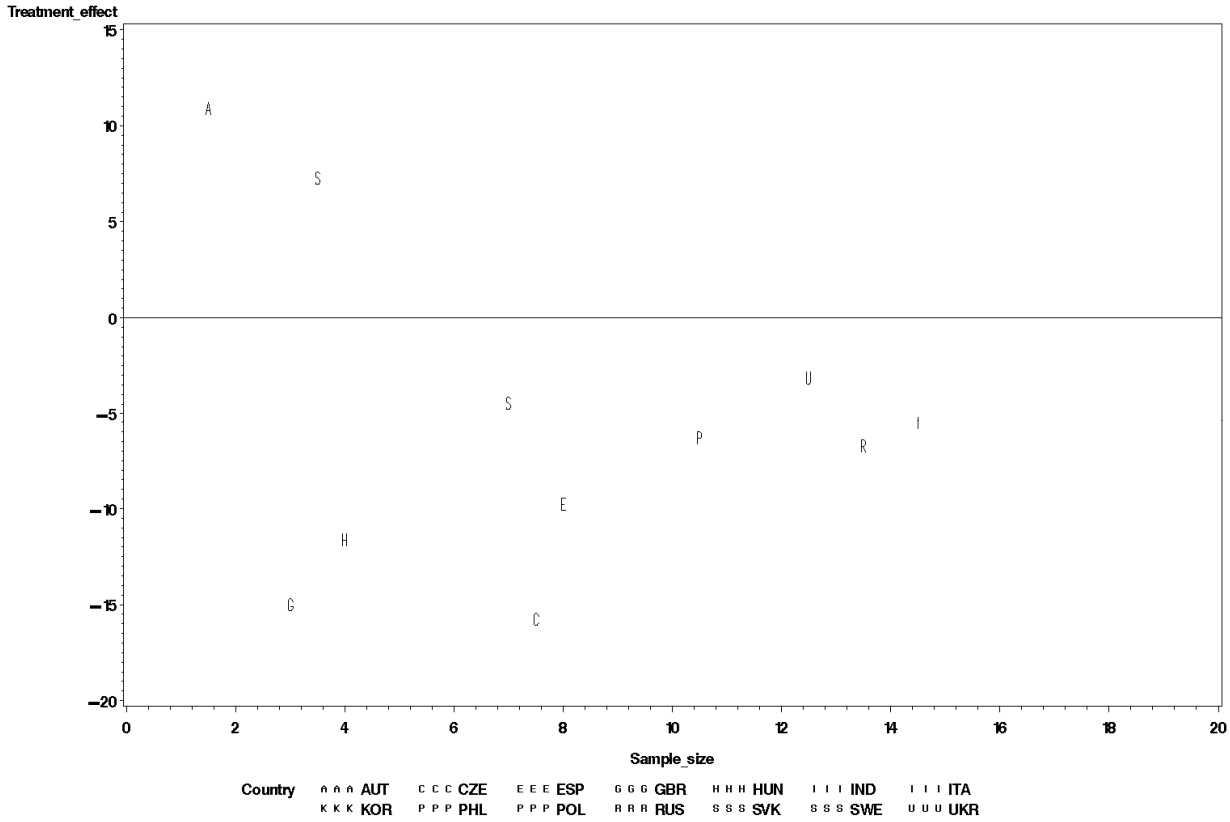
Figure 4: Change in UPDRS Part II+II total score by country and treatment, at week 18, FAS1 (LOCF)



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.

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

Reviewer's notes:

Since confirmatory tests were conducted on the efficacy endpoints at week 18 for Study 248.525, the subgroups analyses also focus on efficacy data at week 18. Table 8 presents results of the subgroup analyses for the primary endpoint (UPDRS Part II+III total score) at week 18.

Table 8: Summary of subgroup analyses for UPDRS Part II+III total score, 18 weeks treatments, FAS 1 (LOCF)

Subgroup	Placebo			PPX ER			PPX IR		
	N	Baseline	Change*	N	Baseline	Change*	N	Baseline	Change*
Age group									
< 65 year	102	37.3	-7.0	92	40.9	-12.7	97	40.7	-15.3
≥ 65 years	72	43.8	-6.5	69	42.9	-11.6	75	41.0	-11.3
Race									
Asian	83	39.0	-8.6	80	41.9	-13.1	85	39.9	-15.3
White	91	41.0	-5.1	81	41.6	-11.3	87	41.7	-11.9
Sex									
Female	81	38.7	-7.6	70	40.9	-10.3	77	40.3	-12.6
Male	93	41.1	-6.1	91	42.4	-13.6	95	41.2	-14.4

Source: Excerpt from Table 11.4.3:1 of sponsor's Clinical Study Report

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

4.2 Subgroup Analysis by Country

This reviewer conducted descriptive statistical analyses for the primary endpoint (change from baseline in UPDRS Part II+III totals score) by country and treatment.

Based on the subgroup analyses by country presented in Section 3.1.2.2, 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 3.1.2.2 for details.

4.3 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The objective of Study 248.525 was to determine the efficacy, safety and tolerability of Mirapex (pramipexole extended release, in daily doses from 0.375 mg to 4.5 mg q.d.) compared to PPX IR and placebo in L–Dopa+ treated patients with advanced PD.

The primary endpoint was change from baseline in the UPDRS Part II+III score. It was analyzed by ANCOVA with treatment and pooled country as factors and UPDRS Part II+III score at baseline as covariate on the Full Analysis Set (FAS) (using LOCF). Following meetings between the sponsor and regulatory agencies, 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 advanced PD patients. Therefore, the confirmatory analysis for the superiority hypothesis (pramipexole ER vs. placebo) was performed at Visit 8 (18 weeks), instead of at Visit 11 (33 weeks), as initially planned.

The key secondary endpoint was the change from baseline to week 18 in the percentage off-time during waking hours. It was analyzed using ANCOVA with baseline as covariate and treatment and pooled country as factors.

Regarding multiplicity, superiority of PPX ER versus placebo was tested for the primary endpoint as the first step. If this was significant at the 2-sided 5% level, then in a second step the superiority of PPX ER versus placebo was tested for the key secondary endpoint.

For Study 248.525, the mean of UPDRS Part II+III total score at baseline was 40.0 points in the placebo group, 41.7 points in the PPX ER group and 40.8 points in the PPX IR group. At week 18, the means (calculated with LOCF) were 33.2, 29.5 and 27.2 points, respectively. The difference in improvement in UPDRS Part II+III total score between PPX ER and placebo were statistically significant (ANCOVA, p=0.0001). In both active treatment groups there were small differences in the mean change from baseline to week 33 compared to the mean change from baseline to week 18 (pramipexole ER: +0.8 points; pramipexole IR: 1.5 points). Thus, it appears that maintenance of efficacy at week 33 was shown in both pramipexole groups. The results of the key secondary endpoint show that the difference in improvement in percentage off-time between PPX ER and placebo were statistically significant (ANCOVA, p=0.0122) and it appears that the maintenance of efficacy at week 33 was confirmed.

This reviewer conducted the following additional analyses for Study 248.525. 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.

- **Conduct subgroup analysis by country.** It appears that there is no meaningful difference between countries in change from baseline in UPDRS Part II+III total score.

5.2 Conclusions and Recommendations

Based on the results of Study 248.525, there is evidence that Mirapex (pramipexole extended release, in daily doses from 0.375 mg to 4.5 mg q.d.) is effective as compared to placebo in L–Dopa+ treated patients with advanced Parkinson's Disease (PD), as assessed by the primary endpoint, change from baseline at week 18 in the UPDRS Part II+III total score.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22514	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	TBD (PRAMIPEXOLE DIHYDROCHLORIDE)ER TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JINGYU J LUAN
01/28/2010

KUN JIN
01/28/2010

KOOROS MAHJOOB
01/28/2010
I have discussed the results with the primary reviewer and my views are incorporated in her review. I concure with her views presented in this review.