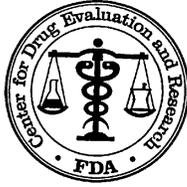


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203312Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

**NDA/BLA Serial
Number:**

203312 (0000)

Drug Name:

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Indication(s):

Parkinson's Disease

Applicant:

Impax

Date(s):

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1 EXECUTIVE SUMMARY

The clinical trial efficacy data provided in this application seems to support the efficacy of IPX066 in Parkinson's disease (PD). In the application there is one placebo controlled study in early Parkinson's, one conversion from IR LD-CD to IPX066 in advanced Parkinson's and, finally, a two-period crossover study involving IPX066 and Carbidopa/Levodopa/Entacapone (CLE) .

2 INTRODUCTION

2.1 Overview

The IND number associated with the development of this drug for this indication is 102,887. IPX066 is a new oral Extended Release (ER) multiparticulate capsule formulation containing Carbidopa-Levodopa (CD-LD), designed to provide fast attainment of therapeutic Levodopa (LD) concentrations, to ensure early onset of effect, and to maintain the desired concentrations for a longer duration than provided by currently approved CD-LD products. The clinical development program includes three randomized, double-blind, active-control Phase 3 studies (one in subjects with early PD [IPX066-B08-05] and two in subjects with advanced PD [IPX066-B09-02 and IPX066-B09-06] to characterize the efficacy and safety of IPX066.

Table 1 Key Efficacy Studies

Study	# of Subjects per Arm	Follow-up Period	Completer N (%)	Primary Efficacy	Study Population
08-05: Parallel Group Study	<u>N</u> Placebo: 92 145 mg: 87 245 mg: 104 390 mg: 98	30 weeks	71 (77%) 72 (83%) 83 (80%) 74 (76%)	Baseline UPDRS II+III: 36.7 Chg. UPDRS II+III: - 0.6 -11.7 vs -0.6 P < 0.0001 -12.9 vs -0.6 P < 0.0001 -14.9 vs -0.6 P < 0.0001	Early PD 36% US
09-02: Dose Conversion Study	<u>N</u> IR LD-CD: 192 IPX066: 201	IR Titration: 3 weeks IPX Conversion: 6 weeks Maintenance: 13 weeks	182 (95%) 186 (93%)	Baseline % Off Time: 5.97 Ending % Off Time: 29.79±15.81 P < 0.0001 23.82±14.91	Adv. PD 52% US
09-06: Two period Two group, Crossover Study	N=91	Conversion period: 6 weeks Double Blind period: 2 weeks treatment/ 1 week washout/ 2 weeks treatment	84 (92%)	Baseline % Off Time: 36.1 Ending % Off Time: IPX: 24.0 P < 0.0001 CLE: 32.5 (first period only p=.0091)	Adv. PD 48% US

CLE= Carbidopa-Levodopa-Entacapone

Studies 08-05 and 09-02 were selected for detailed review after consultation with the medical officer. The third study, which was not reviewed in detail, used a crossover design and involved active control only.

2.2 Data Sources

At the time of review the locations of the primary endpoint data for the two key studies were as follows.

<\\Cdsub1\evsprod\NDA203312\0000\m5\datasets\ipx066-b08-05\analysis\adam\datasets\adqsupd.xpt>

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 08-05

The date of the first patient's enrollment was 13 April 2009 and the date the last patient completed was 5 October 2010. The final protocol (amendment 2) was dated 6 February 2009 and the statistical analysis plan was dated 18 October 2010.

3.2.1.1 Study Design and Statistical Methods

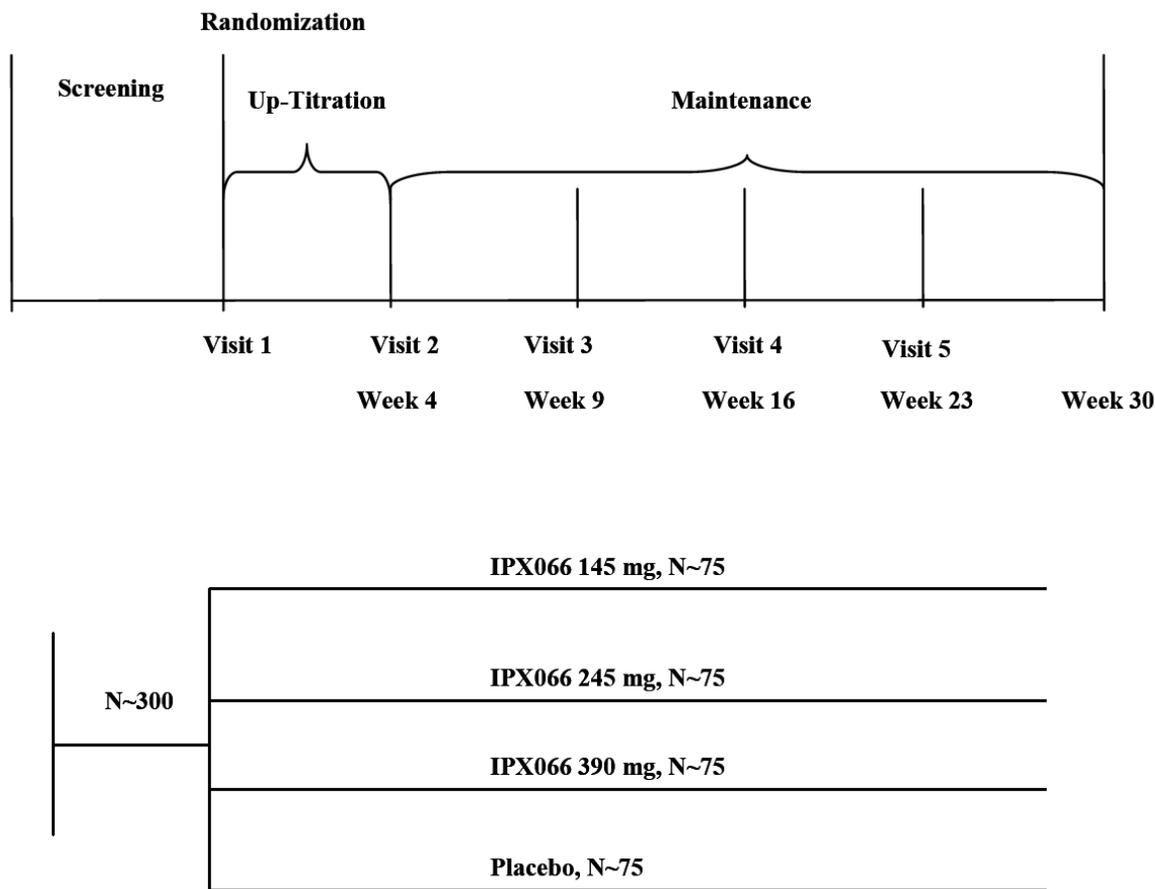
The objective of this study was to evaluate the safety and efficacy of IPX066 in the treatment of subjects with early PD.

This phase 3, randomized, double-blind, placebo-controlled, fixed-dose, parallel-arm study evaluated three doses of IPX066 versus placebo for the treatment of subjects with early PD who were LD-naïve, which was defined as subjects who had not been exposed to LD or LD in combination with catechol-O-methyl transferase (COMT) inhibitors for more than 30 days and the exposure was not within 4 weeks before study enrollment and not treated with dopamine agonists. Subjects were equally randomized into one of four treatment groups of IPX066 145 mg LD, 245 mg LD, 390 mg LD, or placebo and were administered a dose of IPX066 or placebo 3 times per day. This 30-week double-blind study included a Titration period of 4 weeks (up to 3 weeks of dose escalation and 1 week of stabilization), which allowed a safe escalation to the allocated dose, and a 26-week Maintenance treatment period. The primary efficacy variable was the change from Baseline in the sum of the Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activities of Daily Living) and Part III (Motor Examination) scores at the End of Study (EOS; i.e., Week 30 or the last value reported if the subject discontinued the study prematurely).

Subjects enrolled in each of the two strata will be randomized separately:

- Stratum 1 - Subjects who have never taken PD medications
- Stratum 2 - Subjects who have previously, or are currently using non-CD-LD medications for PD

Figure 1 Study 08-05 Schedule



Note: This figure was copied from the sponsor’s statistical analysis plan, page 4.

Sample Size Calculation

This is a randomized, parallel-group, 30-week comparison of IPX066 to placebo in subjects with early PD. In published studies in early PD, effective active agents demonstrated a mean improvement of at least 25% in UPDRS motor symptoms at 6 months. Similarly, Fahn et al. demonstrated a slight worsening of mean UPDRS (Activities of Daily Living plus Motor symptoms) change from Baseline; a sample size of 75 per group at Week 30 has approximately 85% power to detect a mean difference of 6 units between IPX066 and placebo, assuming a standard deviation of 12 units. Assuming no improvement in the placebo group, and a mean baseline score of approximately 25, a mean difference of this magnitude indicates a mean improvement of approximately 25% from Baseline. Separate randomizations were developed for subjects in each of the two strata:

- ☐ Stratum 1 - Subjects who have never taken PD medications
- ☐ Stratum 2 - Subjects who have previously, or are currently using non-CD-LD medications for PD

Efficacy Analysis Set

The Efficacy Analysis Set was to include all treated subjects with at least one efficacy measurement post dosing. Subjects were to be analyzed on an as-treated basis, i.e. each subject was to be associated with the dose to which they were randomized. At the End of Study, the primary endpoint, a Last Observation Carried Forward (LOCF) analysis was to be conducted.

Imputation of Missing Data within a Visit

For each of the questionnaire measures UPDRS and PDQ-39, missing questions within a questionnaire were to be treated as follows:

UPDRS : If a question was not answered in one of the sub parts of the questionnaire (i.e. Parts I, II, III, or IV) the answer to that question from the most recent previously administered questionnaire was to be substituted in calculating both the sub part total and the overall total for that visit.

Primary Efficacy Variable

The primary efficacy variable is the change from baseline in the UPDRS II plus UPDRS III score reported at EOS. Study efficacy endpoint was defined as Visit 6 (Week 30), or the last value reported if the subject left the study prematurely. Analysis was to be done assuming a three-factor main effects model with treatment, strata, and center being the main effects. The analysis for UPDRS II plus UPDRS III was to proceed in the following manner. An overall test for treatment effect was to be conducted at EOS. Assuming a significant treatment effect ($P < 0.05$), tests of the three pairwise comparisons of interest (IPX066 145 vs. placebo, IPX066 245 vs. placebo, and IPX066 390 vs. placebo) would then be conducted. Recognizing that with four treatment groups, this is not a closed testing procedure, the final analysis plan stated that a sensitivity analysis was to be conducted using Dunnett's procedure to individually compare the three active treatments to placebo. To further categorize the timing and duration of effect, the same analyses were to be conducted with the available data for the variable at each of Weeks 4, 9, 16, 23, and 30.

A few clarifications and modifications (as compared to the protocol) to this proposed analysis were made in the analysis plan as follows.

1. With 4 treatment arms and 2 strata, each site would need at least 8 subjects for each treatment/stratum combination to have at least one subject. Since over two thirds of the sites (41 of 56) randomized fewer than 8 subjects it is difficult to construct a reasonable model with center as a factor. Therefore, a Region factor has been created with centers broken into two regions, North America, and Europe in place of a center factor.
2. Rather than a strict change from baseline analysis, an Analysis of Covariance (ANCOVA) approach was to be used with the baseline values used as the covariate.
3. Prior to adopting a three factor main effects model, the full three factor interaction model was to be examined.

If the three factor interaction term was significant at the 0.10 significance level, the full model was to be used.

If not, then the two factor interactions involving treatment were to be examined and if either is significant at the 0.10 significance level, then the model was to

include the significant two factor interactions. Additionally the two factor interactions were to be examined to determine if the interaction(s) were due to differences in degree or kind (i.e., are the different treatment effects in the same relative order within each of the other factors, or are the treatment effects in different orders between the factors [qualitative interaction]).

If two factor interactions were not significant, then the analysis was to be conducted on a three factor main effects model.

This approach was to be used for all continuous variables at EOS. The model used at EOS for each variable was to also be utilized at each of the scheduled assessment time points (Weeks 4, 9, 16, 23, and 30).

For categorical variables, a generalized Cochran Mantel Haenszel (CMH) approach was to be used at EOS with the combinations of region/stratum levels as CMH strata. If the Generalized CMH Statistic is significant ($P \leq 0.05$), each of the active treatments was to be compared to placebo also using CMH with the same strata.

Adjustments for Multiple Comparisons

Rather than adjusting significance levels, the issue of multiple comparisons was to be addressed by analyzing efficacy in a hierarchical manner as follows.

1. Primary Efficacy Variable

The primary efficacy variable is the change from baseline in the UPDRS II plus UPDRS III score reported at EOS. The analysis for UPDRS II plus UPDRS III was to proceed in the following manner. An overall test for treatment effect was to be conducted at EOS. Assuming a significant treatment effect ($P < 0.05$), tests of the three pairwise comparisons of interest (IPX066 145 vs. placebo, IPX066 245 vs. placebo, and IPX066 390 vs. placebo) were to be conducted. Recognizing that with four treatment groups, this is not a closed testing procedure, a sensitivity analysis was to be conducted using Dunnett's procedure to individually compare the three active treatments to placebo. To further categorize the timing and duration of effect, the same analyses were to be conducted with the available data for the variable at each of Weeks 4, 9, 16, 23, and 30.

2. Additional Efficacy Variables

The additional efficacy variables to be examined are the PGI, CGI, and change from baseline in various configurations of the UPDRS (Total UPDRS, UPDRS I plus UPDRS Part II plus UPDRS Part III, UPDRS Part I, UPDRS Part II, UPDRS Part III, and UPDRS Part IV). Since, in the literature it is common to report the UPDRS results using Total UPDRS, this analysis will be conducted. Since over 90% of the Total UPDRS score consists of the scores from UPDRS Part II and UPDRS Part III, it is expected that the Total UPDRS results would be similar to those of Parts II and III combined. The individual aspects of the UPDRS (Parts I, II, III, and IV) were to be analyzed individually to further categorize any significant results of the primary efficacy variable. The PGI and CGI provide global assessments of how well the subjects and investigators feel the treatment is

working.

For each of these variables, analyses were to be conducted in the same manner as for the primary measure, i.e., testing for overall difference among the treatments at EOS, and then if results were significant ($P < 0.05$), examining the relevant pairwise comparisons, and lastly, analyzing the results at each of the 5 measurement time points.

3. Quality of Life

Quality of Life was to be measured using the PDQ-39. Analyses were to follow the same approach as used for the additional efficacy endpoints.

3.2.1.2 Patient Disposition

During the study, 427 subjects were screened and 381 were randomized to one of the four treatment groups in a 1:1:1:1 ratio: 87 in the 145 mg LD, 104 in the 245 mg LD, 98 in the 390 mg LD, and 92 in the placebo group.

Overall, approximately one-fifth of the subjects (21.3%) in the study discontinued treatment early, and subjects in the 145 mg LD group had the lowest discontinuation rate among all of the treatment groups (17.2%, 20.2%, 24.5%, and 22.8% in the 145 mg LD, 245 mg LD, 390 mg LD, and placebo groups, respectively). Overall, the primary reason given most often for discontinuation was Adverse Event [AE] (10.2%), with a smaller proportion of subjects in the 145 mg LD and placebo groups discontinuing due to AEs than in the 245 mg LD and 390 mg LD groups (5.7% and 4.3% compared with 14.4% and 15.3%, respectively). In contrast, a notably higher proportion of subjects discontinued due to lack of efficacy in the placebo group (13.0%) than in the 145 mg LD, the 245 mg LD, or the 390 mg LD groups (4.6%, 0, and 1.0%, respectively). Few subjects ($\leq 4.3\%$) withdrew consent, and fewer still ($\leq 2\%$) discontinued as a result of a protocol violation, noncompliance with treatment, lost to follow-up, or other reason. One subject in the 245 mg LD group (Subject 209-006) died during the Titration period, and the cause of death was non-Hodgkin's lymphoma.

3.2.1.3 Baseline Demographics and Disease Characteristics

As shown in Table 2, baseline demographics were reasonably well balanced across the four treatment groups. The average age of subjects ranged between 63.8 and 65.4 years across the groups. Slightly more male than female subjects were randomized in each group (range 54.0% to 56.7%), almost all subjects were white (range 97.8% to 100%), and the vast majority of subjects were not of Hispanic or Latino ethnicity (range 87.5% to 94.6%). Similarly, mean height (range 168.1 to 169.3 cm), weight (range 77.32 to 81.22 kg), and body mass index (27.19 to 28.26 kg/m^2) were comparable across all treatment groups. There were no notable differences across the four treatment groups in the distributions by age, with approximately three-fourths of subjects being between 50 and 75 years of age, or by body mass index (BMI), with approximately 30% of subjects in each treatment group having a BMI of between 18 and 25, approximately 40% having a BMI between 25 and 30, and approximately 25% having a BMI ≥ 30 . North American sites enrolled more male subjects (64.9%) than did European sites (48.1%), and the mean weight and BMI of North American subjects (81.01 kg and 28.14 kg/m^2 ,

respectively) at Baseline were somewhat higher than the mean weight and BMI of the European subjects (76.70 kg and 27.14 kg/m²).

Table 2 Study 08-05 Baseline Demographic Characteristics

Characteristic	Number of Subjects (%)			
	Placebo (N = 92)	IPX066 LD Dose Group		
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)
Age, years				
Mean (SD)	65.4 (9.43)	63.8 (9.81)	65.2 (9.73)	64.8 (9.32)
Median (Range)	66.0 (36–83)	64.0 (37–87)	65.0 (42–85)	66.5 (43–82)
Sex, N (%)				
Male	52 (56.5)	47 (54.0)	59 (56.7)	54 (55.1)
Female	40 (43.5)	40 (46.0)	45 (43.3)	44 (44.9)
Race, N (%)				
White	90 (97.8)	87 (100)	102 (98.1)	96 (98.0)
Black or African American	0	0	2 (1.9)	0
Asian	1 (1.1)	0	0	1 (1.0)
Other	1 (1.1)	0	0	1 (1.0)
Ethnicity, N (%)				
Hispanic or Latino	3 (3.3)	5 (5.7)	7 (6.7)	4 (4.1)
Not Hispanic or Latino	87 (94.6)	78 (89.7)	91 (87.5)	89 (90.8)
Not Reported	2 (2.2)	4 (4.6)	6 (5.8)	5 (5.1)
Height (cm)				
Mean (SD)	168.6 (9.91)	168.6 (9.28)	169.3 (9.39)	168.1 (10.63)
Median (Range)	167.7 (150.0–191.0)	170.0 (148.0–189.0)	169 (148.0–191.0)	166.0 (150.0–197.0)
Weight (kg)				
Mean (SD)	77.92 (15.261)	77.79 (15.239)	81.22 (16.134)	77.32 (15.474)
Median (Range)	78.50 (42.0–138.4)	75.00 (48.9–121.6)	78.50 (53.0–129.4)	77.00 (39.9–113.0)
Body Mass Index (kg/m ²)				
Mean (SD)	27.36 (4.586)	27.19 (4.277)	28.26 (4.647)	27.43 (5.072)
Median (Range)	27.02 (18.2–42.3)	26.04 (19.8–41.1)	27.42 (19.1–43.3)	26.87 (15.5–50.2)

Abbreviations: N = number of subjects; SD = standard deviation.

Note: This table was copied from pages 57, 58 of study report

Overall, there were no statistically significant differences at Baseline across the treatment groups in age at PD onset, the PD duration at study entry, MMSE scores, BDI-II scores, or Hoehn and Yahr PD stage. Similarly, the distribution of UPDRS scores was comparable across all treatment

groups for the total UPDRS scores, for scores of Part I plus Part II plus Part III, and for the individual UPDRS scores.

As shown in Table 3, overall the mean age at PD onset was 63 years. As expected in a study of subjects with early PD, the mean duration of PD at study entry was 1.98 years (the median was 1.00 years). The majority of subjects (67.6%) had Stage II disease at Baseline, the UPDRS Part II plus Part III score for most subjects was between 20 to <50 units (79.8%), the mean MMSE score at Baseline was 28.9, and the mean BDI-II Baseline score for all subjects was 12.0 (minimal depression).

Table 3 Study 08-05: Baseline Disease Characteristics

Characteristics	Number of Subjects				Total (N = 381)	P Value
	Placebo (N = 92)	IPX066 LD Dose Group				
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)		
Age at PD Onset (years)						0.4247 ^a
Mean (SD)	63.7 (9.48)	61.7 (10.71)	63.6 (10.43)	63.0 (9.38)	63.0 (10.00)	
Median (Range)	64.5 (36–82)	62.0 (31–84)	63.0 (40–85)	65.0 (42–82)	63.0 (31–85)	
Duration of PD (years)						0.3475 ^a
Mean (SD)	1.8 (2.01)	2.3 (3.08)	1.8 (1.85)	2.0 (2.33)	2.0 (2.34)	
Median (Range)	1.00 (0.5–12.0)	1.00 (0.5–17.0)	1.00 (0.5–9.0)	1.00 (0.5–13.0)	1.00 (0.5–17.0)	
UPDRS Part I Score						0.7693 ^{a, b, c}
Mean (SD)	1.5 (1.49)	1.6 (1.38)	1.7 (1.48)	1.7 (1.55)	1.6 (1.48)	
Median (Range)	1.0 (0–7)	1.0 (0–5)	1.0 (0–6)	1.0 (0–8)	1.0 (0–8)	
UPDRS Part II Score						0.9012 ^{a, b, c}
Mean (SD)	10.2 (4.51)	10.3 (4.51)	10.3 (5.02)	9.9 (4.42)	10.2 (4.62)	
Median (Range)	10.0 (2–29)	10.0 (3–22)	9.0 (2–25)	9.5 (2–24)	9.0 (2–29)	
UPDRS Part III Score						0.5558 ^{a, b, c}
Mean (SD)	26.1 (9.00)	25.9 (10.60)	27.8 (12.24)	26.4 (10.10)	26.6 (10.59)	
Median	24.0 (12–61)	24.0 (3–61)	25.0 (10–76)	24.5 (10–48)	24.0 (3–76)	
UPDRS Part IV Score						0.7425 ^{a, b, c}
Mean (SD)	0.4 (0.86)	0.5 (1.18)	0.4 (1.10)	0.5 (1.18)	0.5 (1.09)	
Median (Range)	0.0 (0–5)	0 (0–7)	0 (0–6)	0 (0–6)	0 (0–7)	
UPDRS Parts II plus III Score						0.6796 ^{a, b, c}
Mean (SD)	36.3 (11.89)	36.1 (13.56)	38.1 (15.63)	36.3 (13.04)	36.7 (13.63)	
Median (Range)	34.0 (20–90)	33.0 (19–78)	36.0 (18–89)	34.5 (18–65)	34.0 (18–90)	

Note: Copied from page 61 of sponsor’s study report

Overall, approximately one-fifth of the subjects (21.3%) in the study discontinued treatment early, and subjects in the 145 mg LD group had the lowest discontinuation rate among all of the treatment groups (17.2%, 20.2%, 24.5%, and 22.8% in the 145 mg LD, 245 mg LD, 390 mg LD, and placebo groups, respectively). Most of the discontinuations occurred within the first 9 weeks of study (8.9% at Baseline, 8.1% at Week 4, 3.4% at Week 9, 1.9% at Week 16, and 0.7% at Week 23).

3.2.1.4 Sponsor’s Results

At the EOS, 361 of the 381 randomized subjects were available for analysis following the rules outlined in the analysis plan (4 subjects had no post-Baseline visits and 16 subjects had the early termination visit more than 3 days after the last dose date and had no other post-Baseline visits). As shown in Table 4, each of the three active treatments was statistically significantly superior to placebo ($P < 0.0001$). With only 15 of the 55 sites enrolling at least 8 subjects, the decision was made to substitute a region effect in place of a center effect. As an additional sensitivity analysis,

the 41 centers with fewer than 8 subjects were grouped geographically into 9 combined centers to create 24 centers with between 8 and 24 subjects. An analysis of variance on the change from Baseline for the UPDRS Part II plus Part III score at EOS was conducted using a three-factor model with treatment, center, and stratum as factors. Since the treatment by stratum interaction was not statistically significant ($P = 0.2916$), a main-effects model was used. With this analysis, the overall treatment effect was statistically significant ($P < 0.0001$) as were the individual pairwise comparisons to placebo (all $P < 0.0001$). An ANCOVA analysis on the UPDRS Part II plus Part III score with the Baseline value as the covariate was also conducted and yielded similar results (all $P < 0.0001$).

The mean improvement from Baseline for each of the three active treatments (IPX066 145 mg LD, 245 mg LD, and 390 mg LD) was 11.7, 12.9, and 14.9 units, respectively, compared with a mean improvement of 0.6 unit for placebo. The results were similarly nominally significant for each of the IPX066 treatment groups compared with placebo at Weeks 4, 9, 16, and 23.

Table 4 Summary of Change from Baseline to End of Study in UPDRS Scores by Treatment Group in Study IPX066-08-05 (Randomized Subjects)

UPDRS Parts	IPX066 LD Dose Group Compared with Placebo (N = 90 Subjects in the Placebo Group)		
	145 mg LD (N = 82)	245 mg LD (N = 99)	390 mg LD (N = 90)
UPDRS II + III - Primary Endpoint			
Mean Change (units)	-11.7 vs -0.6	-12.9 vs -0.6	-14.9 vs -0.6
P-Value	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Total UPDRS			
Mean Change (units)	-12.2 vs -0.3	-12.9 vs -0.3	-14.9 vs -0.3
P-Value	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
UPDRS I + II + III			
Mean Change (units)	-12.1 vs -0.4	-13.2 vs -0.4	-15.2 vs -0.4
P-Value	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
UPDRS I			
Mean Change (units)	-0.4 vs +0.2	-0.3 vs +0.2	-0.3 vs +0.2
P-Value	$P = 0.0110$	$P = 0.0316$	$P = 0.0317$
UPDRS II			
Mean Change (units)	-2.8 vs +0.2	-3.1 vs +0.2	-3.9 vs +0.2
P-Value	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
UPDRS III			
Mean Change (units)	-8.9 vs -0.7	-9.8 vs -0.7	-11.0 vs -0.7
P-Value	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
UPDRS IV			
Mean Change (units)	-0.1 vs +0.1	+0.3 vs +0.1	+0.3 vs +0.1
P-Value	$P = 0.5330$	$P = 0.5498$	$P = 0.5617$

Abbreviations: UPDRS = Unified Parkinson's Disease Rating Score.

Note: Significance test: pairwise comparison using Dunnett's procedure.

Note: This table copied from page 72 of the sponsor's study report

For a sensitivity analysis, a mixed-model repeated measures (MMRM) analysis was conducted for the UPDRS Part II plus Part III. The results from the two approaches are similar, with each of the active treatments statistically significantly superior to placebo for each variable (all $p < 0.0001$, with the exception of UPDRS Part II plus Part III comparison of IPX066 145 mg LD and 245 mg LD versus placebo where the MMRM approach had a significance level of $P = 0.0012$ and $P = 0.0123$, respectively). According to the sponsor's report their 'MMRM' model was based on a model assuming a linear relationship between UPDRS II+III over weeks 0 through 30.

Table 5 Sponsor's p-values for Primary and Sensitivity Analyses of UPDRS II+III

Comparison	-----Significance Level-----		
	ANOVA Change from Baseline LOCF	ANCOVA LOCF	ANOVA MMRM
IPX066 145 mg Vs. Placebo	<0.0001	<0.0001	0.0012
IPX066 245 mg Vs. Placebo	<0.0001	<0.0001	0.0123
IPX066 390 mg Vs. Placebo	<0.0001	<0.0001	<0.0001

Note: This table was copied from page 847 of the sponsor's study report

3.2.1.5 Reviewer's Results

Eight subjects assigned to 390 mg, four to 245 mg, two to 145 mg and two assigned to placebo had an early termination assessment more than 3 days after the last dose of study treatment and no other post-baseline UPDRS assessments, so as indicated in the analysis plan the sponsor excluded them from the primary analysis. This reviewer found that the results were not sensitive to excluding these patients. In particular, if these patients were included using the early termination visit that was more than 3 days after the last dose there was no change in the significance of the comparisons with placebo.

Percentages of randomized patients without a Week 30 visit were 22.8, 18.4, 19.2, and 24.5 for placebo, 145 mg, 245 mg, 390 mg, respectively. An analysis of patients with UPDRS assessments available at the Week 30 visit yielded nominally significant estimated differences in UPDRS II+III from placebo of -10.9, -10.5, and -14.6 for 145 mg, 245 mg, and 390 mg, respectively. These were similar to the comparisons with placebo based on the primary analysis. This reviewer's post hoc sensitivity analysis using a mixed model for repeated measures (MMRM) also supports the sponsor's results for the primary endpoint. This model analyzed all the observed post-baseline UPDRS data simultaneously. The model included adjustments for baseline, region, treatment, visit and treatment by visit interactions and it assumed a general "unstructured" covariance matrix for the measurements from the same subject. At week 30 for the comparisons of placebo vs. IPX066 145mg, 245mg, and 390 mg, the estimated differences based on this MMRM model were as shown in Table 6.

Table 6 Reviewer’s MMRM sensitivity analysis of Change in UPDRS II+III at Week 30

IPX066 Dose Group	Estimated Difference from Placebo at Week 30	Std. Error	p-value for Comparison of Drug with Placebo
145	-12.2301	1.6590	p<0.0001
245	-12.4374	1.5864	p<0.0001
390	-14.6632	1.6268	p<0.0001

This model differs from the model denoted MMRM by the sponsor because unlike the sponsor’s model the reviewer’s model assumes a categorical effect of visit instead of forcing a linear slope relationship between UPDRS II+III and Visit and it also incorporates the baseline score as a covariate instead of treating it the same as the post-baseline assessments of the UPDRS II+III, i.e., as part of the dependent variable, which the sponsor’s model did. However, based on these results there is no obvious indication that the primary result is sensitive to the missing Week 30 UPDRS assessment data.

This reviewer also verified the sponsor’s claim about nominal significance of each dose compared to placebo in terms of UPDRS II+III change from baseline at the earlier visits of the study. The sponsor’s reported result for the secondary endpoint, Clinical Global Impression of Change was also verified at the end of study visit.

3.1.2 Study 09-02

The first patient enrolled on 29 Sept 2009 and the last patient completed on 19 January 2011. The final protocol was dated October 27, 2009; the statistical analysis plan (SAP) is dated 04 February 2011.

3.1.2.1 Study Design and Statistical Methods

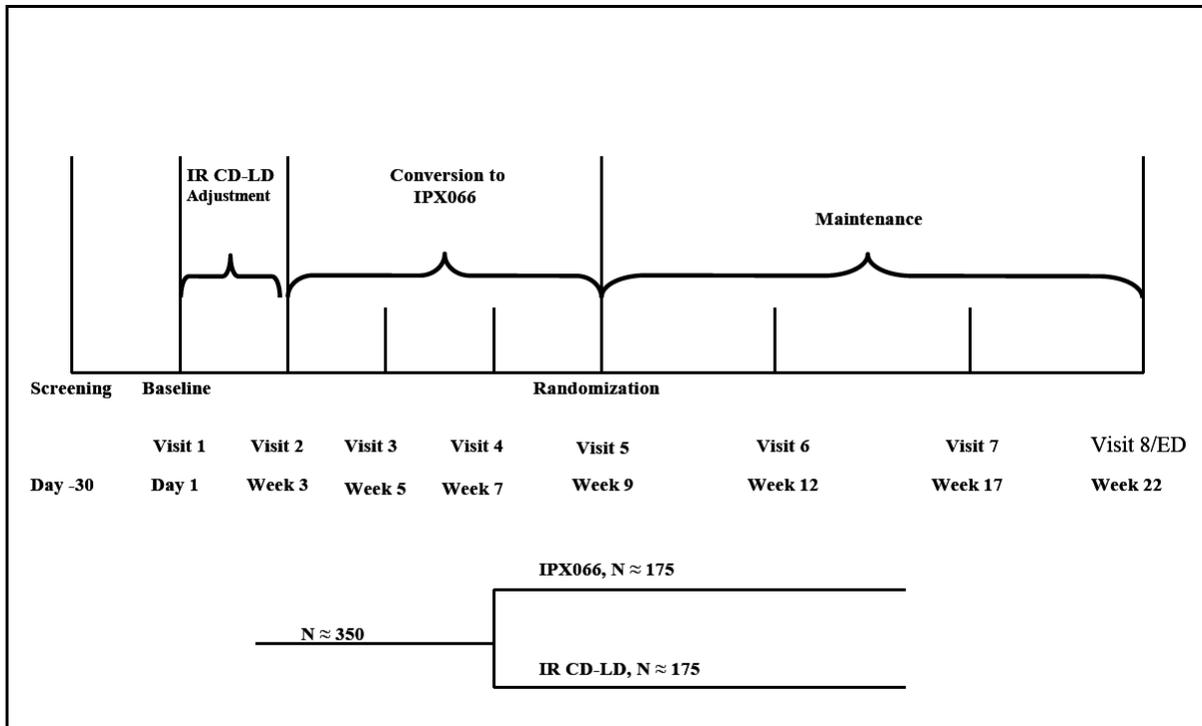
This study was a randomized, double-blind, double-dummy, active-control, parallel-group study planned to compare the efficacy and safety of IPX066 to that of IR CD-LD in subjects with advanced PD with insufficient control of motor symptoms or motor fluctuations. Qualified subjects must have been maintained on a stable standard LD regimen with a total daily LD dose of at least 400 mg and a daily dosing frequency of at least four times, and experiencing at least 2.5 hours of “off” time per day during waking hours. Subjects entered a 3-week IR CD-LD treatment period to allow for dose adjustment of their IR CD-LD regimen, followed by a 6-week dose conversion to IPX066 (under open-label conditions for the conversion period). Subjects were then equally randomized in a blinded fashion into one of two parallel treatment arms of either IPX066 or IR CD-LD. Following randomization, subjects entered a 13-week double-blind treatment period using the dosing regimen established at the end of Week 3 (Visit 2) for IR CD-LD and at the end of Week 9 (Visit 5) for IPX066. Approximately 420 enrolled subjects were planned, to have at least 350 randomized subjects.

The diagram of the study design is presented in Figure 2.

Double-blind Randomization (Maintenance period): At the end of Week 9 (Visit 5, end of IPX066 Dose Conversion), the final dosing strength of IPX066 (95, 145, 195 or 245 mg), the

number of doses taken per day and the number of capsules taken in a day were entered, and the subject was randomized per the IVRS/IWRS instructions. Subjects were randomized in a double-blind manner to either the IPX066 treatment group or the IR CD-LD treatment group.

Figure 2 Study B09-02 Schedule



Abbreviations: IR = immediate release; CD = carbidopa; LD = levodopa; ED = early discontinuation

Note: This table was copied from page 28 of the sponsor’s study report

Efficacy Analysis Set

The Efficacy Analysis Set for the double blind portion of the trial was to include all randomized subjects. Subjects were to be analyzed on an as-treated basis, i.e. each subject was to be associated with the active treatment to which they were randomized. In the event of an error in randomization assignment, they were to be assigned based upon the treatment actually received during maintenance. For the open label portion of the trial, the efficacy analysis set was to be all subjects entering the dose adjustment period of the trial.

Primary Efficacy Measure: Subject Parkinson’s Disease Diary

The primary efficacy measure in this trial was the Parkinson’s Disease Diary developed by Hauser and colleagues in 2000 (Hauser 2000). This home diary contains five different functional states: asleep, “off,” “on” without dyskinesia, “on” with non-troublesome dyskinesia, and “on” with troublesome dyskinesia.

The primary efficacy variable was the baseline-adjusted “off” time as a percentage of waking hours at EOS. Analysis of the primary efficacy measurement was done using a two-factor main effects Analysis of Covariance (ANCOVA) model with treatment and centers as factors and the

percent of “off” time during waking hours at Baseline as a covariate.

“Off” time was derived from the PD Diaries. For each day, “off” time was calculated as the number of half-hour intervals in which “off” was checked, and waking hours were the number of hours in the 24-hour PD Diary which the subject had not marked “asleep.” The percent of “off” time was defined as the total “off” time divided by the total waking time from the PD Diaries completed for the 3 days immediately prior to the visit. In the event that 1 or more days of data in the diaries was missing, the diaries from the available days were used.

At the suggestion of the FDA, sensitivity analyses (ANCOVA) were also conducted using Visit 2 (end of IR CD-LD Dose Adjustment) as the covariate, in addition to the primary analysis using Visit 1 as the covariate.

Randomized subjects who have no valid diaries post randomization were to be assigned a value equal to the average of all diary values at Study Endpoint (i.e., all Week 22 values or last of Week 12 or Week 17 values if subject dropped out early)

Additionally, to assess the sensitivity of the imputation method the following alternative imputation methods were to be assessed for “off” time as a percentage of awake time, “off” time in hours, and UPDRS Part II + Part III:

1. For subjects who are randomized but have no post randomization values, the largest value of the measures collected, from the start of the Dose-Conversion period to the point of randomization was to be imputed for those subjects.
2. Subjects who are randomized but have no post randomization values, were not to be included in the analysis.
3. For subjects with at least one post randomization efficacy measure, the LOCF to Week 22 was to be used.
4. An analysis of all available data at Week 22 with no imputation was to be conducted
5. Mixed Model Repeated Measures (MMRM) analyses using data from Visits 6, 7, 8 and one of Visits 1, 2, or 5 (Detailed Models and sample SAS code are shown in Attachment A).

A few clarifications and modifications to this proposed analysis plan were made in the SAP(dated October 18, 2010):

1. Of the 57 sites with randomized subjects, 16 had fewer than 4 subjects randomized. Of these, 10 were in North America and 6 in Europe. For analysis purposes, the 22 subjects from the 10 centers in North America will be placed in a North America Combined category, and the 13 subjects from the 6 centers in Europe will be placed in a European Combined category.
2. In addition to the Analysis of Covariance (ANCOVA) approach with the baseline values of the measure used as the covariate, described in the protocol, the strict change from baseline analysis will be used for EOS analyses. The ANCOVA approach often proves more flexible and sensitive than the strict change from baseline in assessing statistical significance. From a clinical perspective the change from baseline results often seem more intuitively understandable.
3. Prior to adopting a two factor main effects model, the full two factor interaction model will be examined.
 - If the treatment by center interaction is significant at the 0.10 significance

level, then the full model will be used. Additionally, the treatment by center interaction will be examined to determine if the interaction is due to differences in degree or kind (i.e., are the different treatment effects in the same direction within each of the centers, or are the treatment effects in different directions in the different centers [qualitative interaction]). Additionally, in the case of interaction the effect of region (North America or Europe) will be investigated.

□ If the treatment by center interaction is not significant, then the analysis will be conducted on a two factor main effects model.

The primary measure of imputation at EOS for dropouts after randomization was a Last Observation Carried Forward (LOCF) approach for subjects who dropped out after Visit 6 and the substitution of the average EOS value for the two groups combined, for those randomized subjects who dropped out before Visit 6.

Imputation of Missing Data – Dropouts

For randomized subjects with at least one post randomization efficacy value, who drop out prior to Week 22, the primary imputation method for analysis was to be the Last Observation Carried Forward (LOCF). For percentage of “off” time this is defined as the last post randomization observation.

Randomized subjects who have no valid diaries post randomization were to be assigned a value equal to the average of all diary values at Study Endpoint (i.e., all Week 22 values or last of Week 12 or Week 17 values if subject dropped out early)

Additionally, to assess the sensitivity of the imputation method the following alternative imputation methods were to be assessed for “off” time as a percentage of awake time, “off” time in hours, and UPDRS Part II + Part III:

1. For subjects who were randomized but have no post randomization values, the largest value of the measures collected, from the start of the Dose-Conversion period to the point of randomization was to be imputed for those subjects.
2. Subjects who were randomized but have no post randomization values, were not to be included in the analysis.
3. For subjects with at least one post randomization efficacy measure, the LOCF to Week 22 was to be used where necessary.
4. An analysis of all available data at Week 22 with no imputation was to be conducted
5. Mixed Model Repeated Measures (MMRM) analyses using data from Visits 6, 7, 8 and one of Visits 1, 2, or 5 (Detailed Models and sample SAS code are shown in Attachment A).

Adjustments for Multiple Comparisons

Rather than adjusting significance levels, the issue of multiple comparisons was to be addressed by analyzing efficacy in a hierarchical manner.

1. Primary Efficacy Scale and Variable

The primary efficacy scale is the Parkinson’s Disease Diary. The primary efficacy variable is the baseline adjusted mean “off” time as a percentage of awake hours reported at EOS. To further categorize the timing and duration of

effect, the same analyses were to be conducted with the available data for the variable at each of Weeks 12, 17, and 22. Examining the mean numerical baseline adjusted “off” time is another generally accepted way of assessing this endpoint and was to be included in the analysis.

According to the sponsor any improvement in “off” time is assigned less importance unless it is supported by a measurable increase in “on” time with no troublesome dyskinesia, and no significant worsening of “on” time with troublesome dyskinesia. Therefore, these variables were to be examined in the same manner as the primary efficacy measure to assess the degree to which they are supportive of the primary end point.

2. Additional Efficacy Scales and Variables

- PGI at the End of Study was to be analyzed for mean differences in the score, augmented by an examination of percentage of subjects reporting improvement.

- CGI at the End of Study was to be analyzed for mean differences in the score, augmented by an examination of percentage of subjects for whom the investigator reports an improvement.

Various baseline adjusted configurations of the UPDRS (Total UPDRS, UPDRS Parts II plus III, UPDRS Parts I II plus III, UPDRS Part I, UPDRS Part II, UPDRS Part III, and UPDRS Part IV) were to be examined. Since the sum of UPDRS Parts II and III, the sum of UPDRS Parts I through III, and the Total UPDRS (sum of UPDRS Parts I through IV) have been used to demonstrate effectiveness, each was to be analyzed. The sponsor’s assumption is that they would be mutually supportive. The individual aspects of the UPDRS (Parts I, II, III, and IV) were to be analyzed to further categorize any significant results. Analyses of the UPDRS were to be conducted in a similar manner to those of the Parkinson’s Disease Diary measures.

3. Exploratory Efficacy Scales and Variables

- SCOPA-S – There is anecdotal evidence that the use of a longer acting version of CD-LD may have a beneficial effect on sleep and daytime alertness. Therefore the change from baseline in the SCOPA-S domains was to be examined using the same approach as for the primary efficacy variables.

- Use of PDD to compare morning effectiveness. A number of variables were to be explored at EOS to compare the active treatments after morning awakening. Initially, the percentage of subjects “on” immediately after morning awakening, the time from awakening to “on”, and the duration of the first “on” period after morning awakening were to be investigated. Additionally, the “off” time in the morning was to be examined in relation to the “off” time in the afternoon and evening.

4. Quality of Life

Quality of Life was to be measured using the PDQ-39, EQ-5D, MRS, and the SF-36. Analyses of each, and their various domains were to follow the same approaches as used for the other continuous efficacy endpoints.

Reviewer's Comment: This multiplicity adjustment as described in the statistical analysis plan seems a little ambiguous because each of the four steps listed has another layer of multiple comparisons within it (e.g., time of onset of effect analysis). It's not entirely clear if the plan requires winning on all the specified timepoints before moving to the second set of endpoints or if it only requires winning on the primary at endpoint. In the former case if IPX066 wins at some but not all timepoints or possibly if ON time is not significant then formal testing should stop. In the latter case one could question whether it is permissible to make any claims about the onset of effect. In fact, the p-value for on time with troublesome dyskinesia was not significant at the Week 22 (End of Study) Visit, $p=0.6047$ which in the former case would preclude labeling claims involving the CGI and PGI results .

Determination of Sample Size

It was anticipated that the response to IPX066 treatment would be the same order of magnitude as, or better than the response to IR CD-LD plus entacapone. In a 17-center study in North America, a mean difference of 0.9 hours in “off” time was observed between IR CD-LD and IR CD-LD plus entacapone. In terms of percent “off” time during waking hours, this difference represented a drop of 2.0% and 6.7% for IR CD-LD and IR CD-LD plus entacapone, respectively. Using a mean difference of 0.9 hours between the two treatments and standard deviation of 3.0 units, approximately 175 randomized subjects per treatment arm would be required to achieve about 80% power. For this trial, a total of approximately 420 enrolled subjects were planned, to have at least 350 randomized subjects in the two treatment arms.

3.1.2.2 Patient Disposition

Of the 567 patients screened for this study, 471 were enrolled and received at least one dose of study treatment. A total of 393 subjects (83.4%) were randomized at Visit 5 (End of Dose Conversion), and 368 subjects (93.6% of subjects randomized and 78.1% of subjects enrolled) completed the entire 22-week study.

As shown in Table 1, the demographics of the two randomized treatment groups are reasonably similar. In addition, the demographic characteristics of the subgroup of randomized subjects (N = 393) are similar to those of all subjects enrolled (N = 471, Table 14.1.1.3). The mean age of subjects enrolled in the study was 63.5 years, with a range of 40 to 90 years. More males (62.0%) than females (38.0%) were enrolled in the study, reflecting the typical gender profile of PD patients.

Table 7 Summary of Demographics for Randomized Subjects in Study IPX066-B09-02

Characteristic	IPX066 Group (N = 201)	IR CD-LD Group (N = 192)	All Randomized Subjects (N = 393)
Age, years			
Mean (SD)	63.1 (10.0)	63.4 (8.8)	63.2 (9.4)
Sex, N (%)			
Male	129 (64.2%)	125 (65.1%)	254 (64.6%)
Female	72 (35.8%)	67 (34.9%)	139 (35.4%)
Race, N (%)			
White	196 (97.5%)	186 (96.9%)	382 (97.2%)
Height, cm			
Mean (SD)	172.2 (9.5)	170.5 (9.1)	171.4 (9.3)
Weight, kg			
Mean (SD)	80.04 (15.88)	81.53 (16.50)	80.77 (16.18)
Body Mass Index, kg/m ²			
Mean (SD)	26.936 (4.762)	27.992 (5.315)	27.453 (5.062)

Note: This table was copied from page 66 of sponsor's study report

Baseline PD characteristics for randomized subjects are summarized in Table 8. In general, the double-blind IPX066 and IR CD-LD Maintenance groups are comparable to each other in all reported baseline PD characteristics. The baseline PD characteristics of the randomized subjects reflect that most had relatively advanced PD; mean duration of PD at enrollment was 7.42 years, with a range of 0.5 to 29.0 years. Randomized subjects had a mean baseline Total UPDRS score of 39.28±15.50, with a combined Part II + Part III score of 32.37±14.81. Baseline “off” time averaged 5.97±2.12 hours, and mean time “on” with troublesome dyskinesia was 0.36±0.96 hours.

Table 8 Study 09-02: Baseline Disease Characteristics

Baseline Characteristic	IPX066 Group (N = 201)	IR CD-LD Group (N = 192)	All Randomized Subjects (N = 393)
Age at Onset of PD, years			
Mean (SD)	55.5 (10.9)	56.1 (9.4)	55.8 (10.2)
Duration of PD, years			
Mean (SD)	7.54 (4.79)	7.30 (4.15)	7.42 (4.48)
Mini-Mental State Examination (MMSE) Score			
Mean (SD)	29.1 (1.0)	29.0 (1.1)	29.0 (1.1)
Hoehn and Yahr Score			
Mean (SD)	2.5 (0.6)	2.4 (0.6)	2.4 (0.6)
Subject PD Diary (hours), mean (SD)			
“Off”	6.05 (2.26)	5.89 (1.97)	5.97 (2.12)
“On” without Dyskinesia	8.41 (3.31)	8.51 (3.01)	8.46 (3.16)
“On” with Non- troublesome Dyskinesia	1.56 (2.30)	1.59 (2.39)	1.57 (2.34)
“On” with Troublesome Dyskinesia	0.37 (0.93)	0.35 (1.00)	0.36 (0.96)
Asleep	7.61 (1.71)	7.66 (1.47)	7.63 (1.59)
Unified Parkinson’s Disease Rating Scale, mean (SD)			
Parts II + III	32.32 (14.42)	32.41 (15.24)	32.37 (14.81)
Parts I +II + III	34.14 (14.88)	34.26 (15.84)	34.20 (15.34)
Total	39.34 (15.18)	39.22 (15.88)	39.28 (15.50)
Part I	1.82 (1.29)	1.85 (1.44)	1.83 (1.37)
Part II	9.11 (4.75)	8.81 (5.16)	8.96 (4.95)
Part III	23.21 (11.47)	23.60 (11.43)	23.40 (11.43)
Part IV	5.20 (2.15)	4.96 (1.86)	5.08 (2.01)

Abbreviations: IP CD-LD = immediate release carbidopa-levodopa; SD = standard deviation; N/A = results not available.

Note: This table was copied from page 67 of sponsor’s study report

3.1.2.3 Sponsor’s Results

The Efficacy Analysis Set for the double-blind Maintenance portion of the trial included all 393 randomized subjects. Subjects were analyzed on an as-treated basis, i.e., each subject was associated with the treatment that they actually received. For the Open Label portion of the trial, the efficacy analysis set included all 471 subjects enrolled.

An End of Study (EOS) measurement was defined in the Statistical Analysis Plan as any

measurement collected at Visit 8 or, if the subject terminated the trial after randomization and there was no Visit 8 measurement, the last blinded measurement collected within 3 days after the last dose.

Results for the primary endpoint, “off” time as a percent of waking hours at EOS, are shown in Table 9. The IPX066 group was significantly superior to the IR CD-LD group ($P < 0.0001$) with Baseline and EOS percentages of 36.88 ± 13.09 and 23.82 ± 14.91 , a relative drop of 13.06 (35.4%), compared with IR CD-LD Baseline and EOS percentages of 35.99 ± 11.40 and 29.79 ± 15.81 , a relative drop of 6.20 (17.2%). These results were also nominally significant at Visits 6, 7, and 8 ($P \leq 0.0004$).

Table 9 Study 09-02: Summary of Parkinson’s Disease Diary Data for Randomized Subjects (Sponsor’s Results)

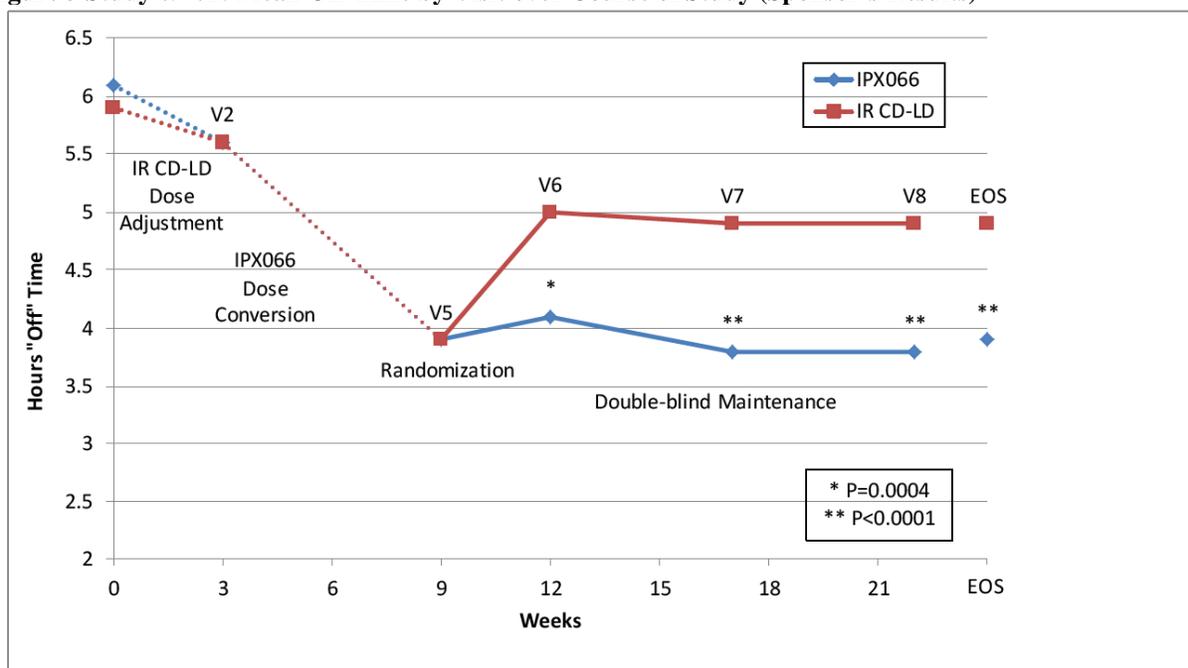
	Mean \pm SD				
	IPX066 (N = 201)		IR CD-LD (N = 192)		P Value ^a
	Baseline (Visit 1)	End of Study	Baseline	End of Study	
“Off” Time as a Percentage of Waking Hours	36.88 \pm 13.09	23.82 \pm 14.91	35.99 \pm 11.40	29.79 \pm 15.81	<0.0001
“Off” Time, hours	6.05 \pm 2.26	3.87 \pm 2.46	5.89 \pm 1.97	4.88 \pm 2.71	<0.0001
“On” Time with No or Non-troublesome Dyskinesia, hours	9.96 \pm 2.43	11.84 \pm 2.96	10.10 \pm 2.29	10.91 \pm 2.82	0.0002
“On” Time with Troublesome Dyskinesia, hours	0.37 \pm 0.93	0.52 \pm 1.37	0.35 \pm 1.00	0.45 \pm 1.44	0.6047
Time Asleep, hours	7.61 \pm 1.71	7.77 \pm 1.60	7.66 \pm 1.47	7.76 \pm 1.42	0.9818

^a Baseline-adjusted analysis of covariance

Note: Copied from sponsor’s study report, page 72.

Figure 3 is a figure created by the sponsor summarizing their results for the analyses of Mean % of Wake Time in Off status at the various scheduled visits in the trial.

Figure 3 Study 09-02: Mean Off Time by Visit over Course of Study (Sponsor's Results)



Abbreviations: IR CD-LD = immediate-release carbidopa-levodopa; V = Visit; EOS = End of Study.
 N values (IPX066/IR CD-LD): V1, V2, V5 = 201/192; V6 = 188/186, V7 = 188/183, V8 = 185/181, EOS = 201/192

Note: This figure was copied from page 73 of the sponsor's study report

Alternative methods as discussed in the protocol and in the Statistical Analysis Plan were also conducted for the "off" time, "off" time as a percent of waking hours, "on" time without troublesome dyskinesia, and UPDRS Part II + Part III. The alternative methods applied were as follows:

- Use a LOCF approach as described above, but use the Visit 5 value for subjects who dropout between Visit 5 and Visit 6 (i.e. for these subjects carry forward the value at the end of dose conversion to IPX066)
- Use a LOCF approach as described above, but use the worse of the Visit 1 or Visit 2 values for subjects who dropout between Visit 5 and Visit 6 (i.e. for these subjects carry forward the worse value for Visit 1 or Visit 2)
- Use a Mixed Model Repeated Measures (MMRM) approach. In this approach analyses were conducted, using information from Visits 1, 6, 7 and 8, from Visits 2, 6, 7 and V8, and from Visits 5, 6, 7, 8

According to the sponsor, in a trial of this type with a large number of sites that randomized a small number of subjects, it is not unusual to see a center by treatment interaction. One approach to assess this type of interaction is to group the centers into larger units and examine the interaction effects. Two approaches were used to further examine this:

- To group centers into two regions, North America and Europe.
- To group centers by country. Since the United States enrollment was so large, United

States centers were grouped by time zone, and since France only had three subjects, France was grouped with Germany.

Using these categorizations in the models, there were no statistically significant interactions of treatment by country or treatment by region. Additionally, each of these two-factor main effects models demonstrated that IPX066 was significantly superior to IR CD-LD.

Table 10 Sponsor’s MMRM sensitivity analyses

Variable	-----Time points used in MMRM-----		
	V1, V6, V7, V8	V2, V6, V7, V8	V5, V6, V7, V8
"Off" Time as a Percent of Walking Hours	0.0005	0.0002	0.0006
"Off" Time in Hours	0.0007	0.0002	0.0015
"ON" with No/ Non-Troublesome Dyskinesia	0.0048	0.0022	0.0060
"ON" with Troublesome Dyskinesia	0.5297	0.4949	0.2013
UPDRS Parts II+III	0.0347	0.0302	0.0181

Note: This table was copied from page 291 of the sponsor’s study report.

3.2.1.6 Reviewer’s Results

This reviewer confirmed that at visit 5, the assessment just before randomization and after conversion/IPX066 titration, there was no group difference in mean percent of wake time in OFF status: 23.81 and 23.81, as expected because of randomization.

At the last assessment (LOCF) mean % off time was 30.0 and 23.7 for IPX-066 and IR LD-CD, respectively. In the primary analysis the sponsor imputed the overall average mean off time at last assessment in the maintenance period for 12 patients who had no post-randomization assessments (7 assigned to IPX066 and 3 to IR). This reviewer’s modified LOCF analysis excluding patients with no post-baseline maintenance period assessments instead of imputing with the overall average mean yielded an estimated difference of -6.08 +/-1.42, p <.0001.

This reviewer found 185 (92%) IPX066 patients and 181 (94%) IR CD-LD patients had assessments at the Week 22 (final) visit(sponsor reported a couple less: 368 completed). Analysis of observed cases at the last visit gave a difference estimate of 6.68 (1.46 SE), p<0.0001.

An MMRM model of observed cases for all maintenance visits gave an estimated difference in %of wake time in off status at Week 22 of -5.67 +/- 1.27 (S.E.), p<0.0001. Thus, in summary, the results of sensitivity analyses suggest relative insensitivity of the primary analysis result to the missing data.

Overall, dropouts were reasonably limited and the analysis result for % of wake time in the Off state does not seem sensitive to missing data. Table 11 shows Mean % of wake time in the Off state by Time of Patient’s Last available assessment. The number of patients last assessed at week 12 or 17 is too small to permit making any reliable comparisons between dropouts and completers and, therefore, it seems unlikely that the dropouts had much impact on the outcome of the primary analysis.

Table 11 Study 09-02: Mean %Off by Time of Patient’s Last Available assessment

		Description of Planned Arm											
		IPX066						IR CD-LD					
		Baseline % Wake Time in OFF			% Wake Time in OFF at Endpoint			Baseline % Wake Time in OFF			% Wake Time in OFF at Endpoint		
Last Week	Week	N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std
12	12	6	31.5	15.5	7	34.7	23.1	4	38.3	10.4	4	38.6	17.5
17	12	3	41.7	22.7	3	20.7	13.7	4	35.0	11.7	4	25.4	24.3
22	17	3	41.7	22.7	3	29.6	27.5	3	35.7	14.3	4	16.6	11.0
	12	184	36.7	12.7	184	25.2	15.8	179	36.1	11.5	179	30.5	15.5
	17	185	36.8	12.8	185	23.2	14.2	181	36.1	11.5	181	29.9	15.7
	22	185	36.8	12.8	185	23.2	14.5	181	36.1	11.5	181	30.1	15.7

The sponsor’s reported nominally significant results for the secondary endpoints, Clinical Global Impression of Change and Patient Global Impression of Change were also verified at the end of study visit.

3.1.3 Study 09-06

This study (09-06) is summarized here but was not reviewed with the same level of detail as the other studies because the other two studies both seem to support the efficacy of the drug and they had a more typical design (parallel group) for a confirmatory clinical trial than this crossover designed study. Between treatment Period 1 and treatment Period 2, subjects were to receive open-label IPX066 at the same dosage that was established during Dose Conversion (Part 1-Visit 4, Week 6).

Of the 91 subjects who were randomized, 7 subjects (4 males and 3 females) discontinued the study early. Most enrolled subjects were white (98.2%) and male (69.1%). The mean age of the subjects was 64.6 ± 9.1 years. The 83 subjects who completed both treatment periods had similar demographics to the 110 subjects who were enrolled and the 91 subjects who were randomized.

The primary efficacy parameter for Part 1 of the study (the double-blind part) was the percent “Off” time during waking hours, based on subject PD diaries for the last 3 days collected at the end of each double-blind treatment period. For each day, the percent “Off” time was to be calculated as the number of half-hour intervals in which “Off” was checked in the subject’s PD diary. The percent “Off” time was defined as the total “Off” time divided by the total time not “asleep” (i.e., waking hours) from the subject PD diaries completed for the 3 days immediately prior to the visit. In the event that one or more days of data in the PD diaries were missing, the diaries from the available days were to be used. The difference between the percent “Off” time between treatments was to be analyzed using a standard mixed-model analysis of variance at a 0.05 level of significance (Littell 1996; Fleiss 1986). The model was to include the fixed-effect factors of treatment, sequence and period and the random-effect inter- and intra-subject factors. Since the secondary endpoints are intended to explore differing aspects of the drug effects, no adjustments were to be made in the level of significance for multiple testing among endpoints.

The primary efficacy parameter in Part 1 of the study IPX066-B09-06 was the percent “Off” time during waking hours and was based on 83 subjects who completed Parkinson’s Disease Diary for both Periods 1 and 2. Subjects had on the average a significantly lower percentage of “Off” time during waking hours during IPX066 treatment compared to during CLE treatment with an overall mean (SD) of 23.98% ± 16.24% during IPX066 treatment and a mean of 32.48% ± 21.92% during CLE treatment (P<0.0001). A first period only sensitivity analysis performed by this reviewer yielded an estimated treatment difference, IPX066 minus CLE, of -10.89, p=0.0091, thus providing support for the primary analysis.

3.2 Evaluation of Safety

Safety is not reviewed in this document. Please see the medical officer’s review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study 08-05

In study 08-05 ages ranged from 36 to 87 and the mean as well as the median age was 65. Overall 57.6% were Male and 98.6% were White.

There was no compelling evidence of a differential effect by Gender (interaction p=0.6953) when the region*treatment interaction was in the model. However, when siteid was used instead of region (and for which there was no interaction with treatment) there was some suggestion of an interaction between gender and treatment (p=0.0755). The pattern of this interaction suggests that while in Males it appears that there may be more effect at the high dose than the low or middle doses, in females the effects of the three

doses compared to placebo were much more similar (with the high dose estimate actually slightly numerically worse than low and middle dose estimates). This interaction involving the dose response may be a chance observation and, in any case, in both males and females all drug groups appear superior to placebo in terms of efficacy as measured by the primary endpoint.

Table 12 Study 08-05: Change from baseline to endpoint in UPDRS II+III by Gender

	Sex					
	F			M		
	UPDRS II+III Change			UPDRS II+III Change		
	N	Mean	Std.Err.	N	Mean	Std.Err.
Description of Planned Arm						
IPX066 145 mg	39	-11.7	1.5	45	-11.9	1.8
IPX066 245 mg	44	-13.6	1.6	59	-11.2	1.5
IPX066 390 mg	44	-12.8	1.9	54	-14.9	1.5
PLACEBO	40	-2.0	1.9	52	0.7	1.2
All	167	-10.2	0.9	210	-9.4	0.9

Under 2% of the randomized population was non-white so there is not enough data in other races to say anything reliable about efficacy in other races or comparability of efficacy between races.

There was no compelling evidence (interaction $p=0.6431$) that the treatment effect differed significantly by Age group (>65 vs. ≤ 65). This was supported by the fact that if it was assumed the Change from baseline in UPDRS (part II+III) depended on age linearly across the range of ages and this reviewer tested for a differential slope of age by treatment group then it was found that the slope by treatment group interaction test was not significant ($p=0.9910$).

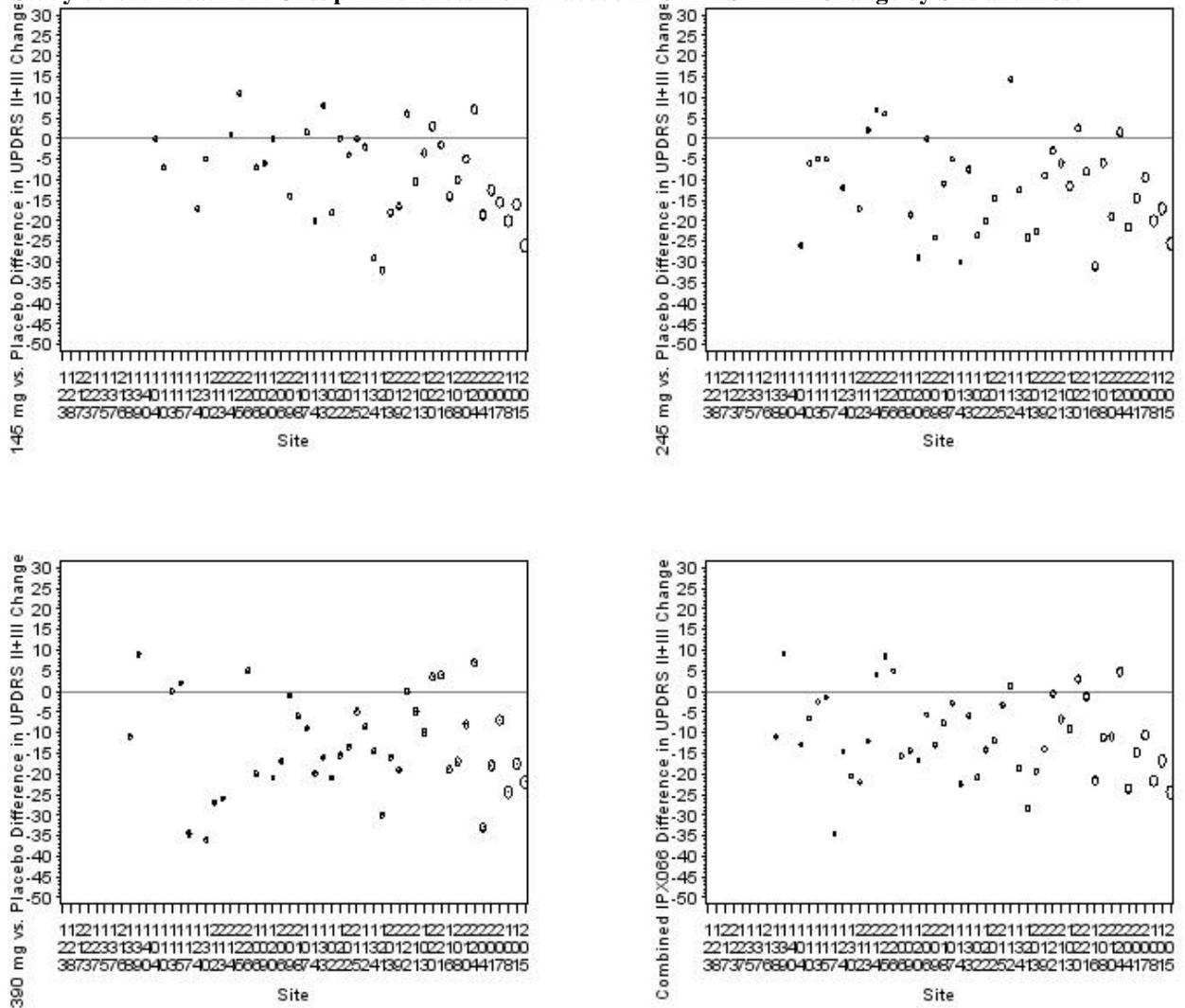
Table 13 Study 08-05: Change from baseline in UPDRS II+III by Age Group

Description of Planned Arm	Age \geq 65?					
	No			Yes		
	Change in UPDRS II+III			Change in UPDRS II+III		
	N	Mean	StdErr	N	Mean	StdErr
IPX066 145 mg	43	-11.1	1.6	41	-12.6	1.8
IPX066 245 mg	51	-13.4	1.6	52	-11.1	1.6
IPX066 390 mg	40	-13.0	1.4	58	-14.7	1.8
PLACEBO	41	-0.4	1.1	51	-0.5	1.7
All Groups	175	-9.7	0.8	202	-9.7	0.9

About 45% of randomized patients were randomized in North America. The significant interaction between treatment group and region (North America vs. Europe) reported by the sponsor seems not to suggest any of the groups are not superior to placebo in terms of the UPDRS II+III, primary endpoint, but rather that there is an increase in effect with increasing dose seen in Europe but not in the US. So this interaction seems to relate to comparisons between the three IPX066 groups rather than involving drug and placebo. In fact, all three doses appeared nominally significant compared to placebo in both regions (-13.2,-14.6,-17.8 in NA; -9.9, -8.3,-9.7 in EU).

Figure 4 shows observed mean treatment group differences from placebo by individual sites. There is one subfigure for each dose as well as a comparison between all doses combined and placebo (in the bottom right subfigure). The size of the plotting symbol is proportional to the number of patients randomized in the site and the number increases as one moves to the right along the x-axis. Negative differences favor the IPX-066 group.

Figure 4 Study 08-05: Treatment Group Differences from Placebo in UPDRS II+III Change by Site and Dose



4.1.2 Study 09-02

About 64% of the randomized population was Male. There was no compelling evidence of a differential effect by Gender (interaction $p=0.1874$). Table 14 shows summary statistics for percent of wake time in the off state by Gender Subgroup.

Table 14 Study 09-02: Summary Statistics for %Wake Time in OFF by Gender Subgroup

Group	Gender	N	Basel i ne Mean %WAKE i n OFF	%WAKE IN OFF WEEK 22/LOCF	
				MEAN	STD. DEV.
IPX066	Femal e	72	35. 28	23. 81	13. 85
IR CD-LD	Femal e	67	35. 16	27. 47	14. 37
IPX066	Mal e	129	37. 77	23. 83	15. 52
IR CD-LD	Mal e	125	36. 44	31. 03	16. 45

Only about 2% of the randomized population was non-white so there is not enough data in other races to say anything reliable about efficacy in other races.

The mean as well as the median age were about 63. There was no compelling evidence of a differential effect by Age. In particular, if it was assumed that the proportion of off time depended on age linearly, a test for a differential slope of age by treatment group was not significant (p=0.3262).

Table 15 shows summary statistics for percent of wake time in the off state by Age subgroup (Age <65 and Age ≥ 65). The group difference is fairly consistent across these subgroups.

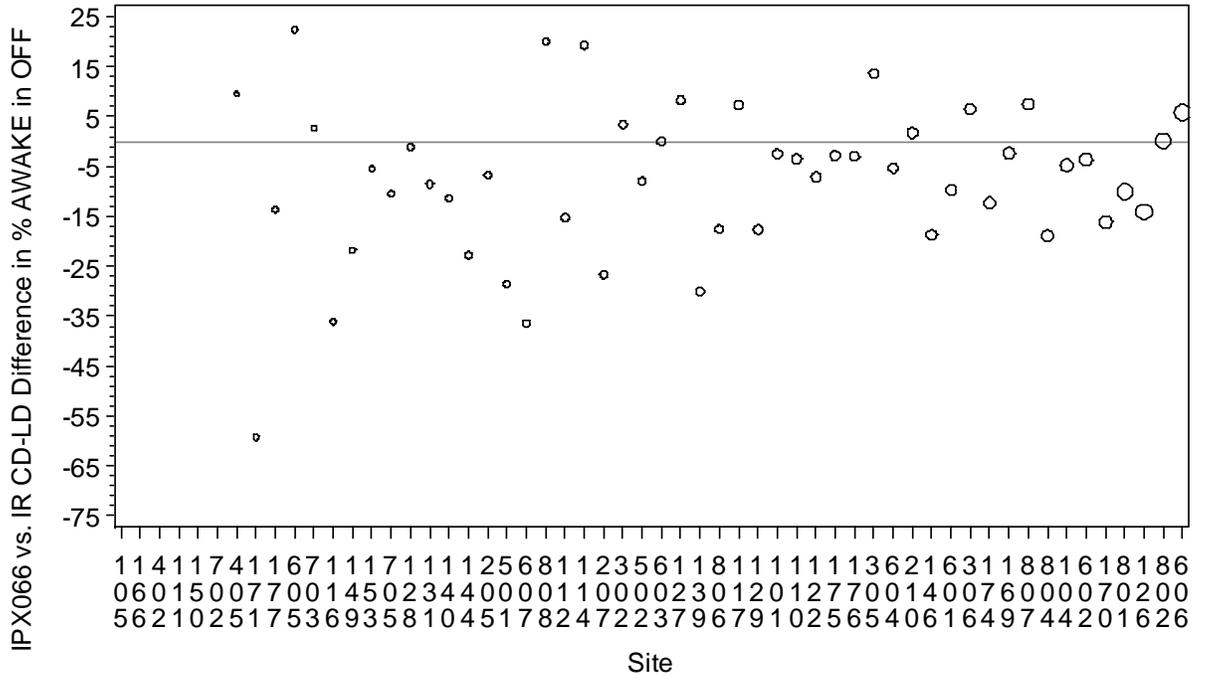
Table 15 Study 09-02: Summary Statistics for %Wake Time in OFF by Age Subgroup

AGE ≥ 65 ?	Randomi zed Group	N	Basel i ne Mean %WAKE i n OFF	% OF WAKE TIME IN OFF WEEK 22/LOCF	
				MEAN	STD. DEV.
NO	IPX066	114	37. 38	24. 14	14. 81
NO	IR CD-LD	100	36. 12	30. 89	15. 34
YES	IPX066	87	36. 22	23. 41	15. 11
YES	IR CD-LD	92	35. 85	28. 58	16. 30

About 53% of study 09-02 randomized patients were randomized in North America. The estimated difference within the North American subgroup was -8.4 +/- 2.0 S.E., which was nominally significant.

Figure 5 shows observed mean treatment group differences from placebo within individual study sites. The size of the plotting symbol is proportional to the number of patients randomized in the site. Negative differences favor the IPX-066 group.

Figure 5 Study 09-02: Treatment Group Difference in Percent OFF while Awake by Site



4.2 Other Special/Subgroup Populations

Prior Use of PD Medication in Early Parkinson's Study 08-05

The randomization in study 08-05 had two strata: Stratum 1--subjects who never received medications for PD; Stratum 2—subjects who previously used or were currently using non-CD-LD medications for PD. About 38% of those randomized fell into the PD medication naïve stratum.

There was no compelling evidence that treatment effects compared to placebo varied significantly according to naïve or non-naïve prior PD medication subgroup classification (interaction test $p=0.6717$).

Table 16 Study 08-05 Change from baseline to endpoint in UPDRS II+III by Prior PD Medication Use Status

Prior PD Med. Use?	Level of ARM	N	Baseline UPDRS II+III		Change	
			Mean	Std Dev	Mean	Std Dev
No	IPX066 145 mg	35	36.54	14.23	-11.43	11.34
No	IPX066 245 mg	40	33.38	13.60	-11.40	9.88
No	IPX066 390 mg	36	33.75	11.76	-13.67	12.17
No	PLACEBO	31	34.26	7.83	-1.81	12.45
Yes	IPX066 145 mg	49	35.88	13.26	-12.12	10.69
Yes	IPX066 245 mg	63	41.02	16.32	-12.76	12.16
Yes	IPX066 390 mg	62	37.82	13.60	-14.13	11.79
Yes	PLACEBO	61	37.28	13.44	0.23	8.92

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study 08-05's UPDRS data seem to provide support for the efficacy of IPX066 in early PD and study 09-02's percent of wake time in off status patient diary data seem to support the efficacy of IPX066 in Advanced PD. Although reviewed in less detail because of its active control and crossover rather than parallel group design, Study 09-06's percent of wake time in off status patient diary data also seem to support efficacy of IPX066 in Advanced PD. Dropouts in the studies seem to be reasonably low and there did not seem to be sensitivity of the primary results to assumptions about the limited missing primary endpoint data. The sponsor imputed the endpoint for those with no post-baseline data with the overall mean change in study 08-05. Single value imputations such as this, particularly those imputing the same value for all affected subjects, are likely to cause bias. As discussed in the National Academy of Science's Report and Prevention and Treatment of Missing Data statistical techniques such as Multiple Imputation or a Missing at Random assumption (which requires no imputation) for the missing data may better reflect the uncertainty surrounding the missing data and be less biased than single value imputation methods. However, in this case, the sponsor's single value imputation approach and a sensitivity analysis assuming missing data was missing at random did not differ substantially.

In the conversion from IR CD-LD to IPX066 study (09-02) subjects had 3 weeks on IR CD-LD followed by 6 weeks for conversion to IPX066. This was then followed by randomization to IR CD-LD or IPX066 and the subsequent 13 weeks of double blind treatment as randomized. It seems to this reviewer that this study design could be susceptible to unblinding of subjects and/or investigators since all subjects experienced both study treatments before randomization. However, this reviewer is not aware of any actual evidence of unblinding in this study.

5.2 Conclusions and Recommendations

In the application there is one placebo controlled study in early Parkinson's, one conversion from IR LD-CD to IPX066 in advanced Parkinson's and, finally, a two-period crossover study involving IPX066 and Carbidopa/Levodopa/Entacapone (CLE). The clinical trial efficacy data provided in this application seems to support the efficacy of IPX066 in Parkinson's disease (PD).

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/s/

TRISTAN S MASSIE
08/13/2012

KUN JIN
08/13/2012
I concur with the review.

HSIEN MING J HUNG
08/13/2012