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RESEARCH**

APPLICATION NUMBER:

203312Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Resubmission - Class 2
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Division / Office	CDER/ OND / ODE1/ DNP
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	2014 December 19
Established Name	IPX066
(Proposed) Trade Name	Rytary
Therapeutic Class	Anti-Parkinson Drug
Applicant	IMPAX Pharmaceutical
Formulation(s)	Oral extended release capsule
Dosing Regimen	Mg (carbidopa / levodopa) 23.75 / 95 36.25 / 145 48.75 / 195 61.25 / 245
Indication(s)	Parkinson's Disease
Intended Population(s)	Adults with Parkinson's Disease

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarketing Requirements and Commitments	6
2	INTRODUCTION AND REGULATORY BACKGROUND	7
2.1	Product Information	8
2.2	Tables of Currently Available Treatments for Proposed Indications	8
2.3	Availability of Proposed Active Ingredient in the United States	9
2.4	Important Safety Issues With Consideration to Related Drugs.....	9
2.5	Summary of Presubmission Regulatory Activity Related to Submission	9
2.6	Other Relevant Background Information	10
3	ETHICS AND GOOD CLINICAL PRACTICES.....	10
3.1	Submission Quality and Integrity	10
3.2	Compliance with Good Clinical Practices	10
3.3	Financial Disclosures.....	10
5	SOURCES OF CLINICAL DATA.....	11
5.1	Tables of Studies/Clinical Trials (source: sponsor).....	12
5.2	Review Strategy	12
7	REVIEW OF SAFETY.....	13
	Safety Summary	13
7.1	Methods.....	14
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	14
7.1.2	Categorization of Adverse Events.....	16
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	17
7.2	Adequacy of Safety Assessments	17
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	18
7.3	Major Safety Results	21
7.3.1	Deaths.....	22
7.3.2	Nonfatal Serious Adverse Events	22
7.3.3	Dropouts and/or Discontinuations	23
7.3.4	Significant Adverse Events	23
7.3.5	Submission Specific Primary Safety Concerns	23
7.4	Supportive Safety Results	24
7.4.1	Common Adverse Events	24
7.4.2	Laboratory Findings	25
7.4.3	Vital Signs	25

7.4.4	Electrocardiograms (ECGs)	25
7.4.5	Special Safety Studies/Clinical Trials	25
7.4.6	Immunogenicity	25
7.5	Other Safety Explorations.....	25
7.7	Additional Submissions / Safety Issues	25
8	POSTMARKET EXPERIENCE.....	25
9	APPENDICES	26
9.1	Literature Review/References	26
9.2	Labeling Recommendations	26
9.3	Advisory Committee Meeting.....	27

Table of Tables

Table 1 Currently available levodopa preparations (not including generic versions).....	8
Table 2 IPX066 Development Program (source: Sponsor)	12
Table 3 Study IPX066-B12-01 in healthy volunteers (Sponsor's synopsis).....	15
Table 4 Study IPX066-B12-03 in healthy volunteers (Sponsor's synopsis).....	15
Table 5 Study IPX066-B11-01 in patients with advanced PD (Sponsor's synopsis)	16
Table 6 Parts 2 and 3 Cumulative exposure since the First Cycle cut-off date	19
Table 7 Sponsor's schema for initial levodopa dose conversion to IPX066 in Study IPX066-B-11-01	20
Table 8 AEs reported by at least two volunteers in the Phase 1 studies reported in the First and Second Cycle NDA submissions.....	22
Table 9 Serious Adverse Events in Study IPX066-B11-01 not previously reported.	22
Table 10 Treatment emergent adverse events in Study IPX066 –B11-01.....	24
Table 11: Adverse Reactions in Study 1, a Placebo Controlled Trial in Early Stage Parkinson's Disease	26
Table 12: Adverse Reactions in Study 2, an Active Controlled (IR CD-LD) Trial Study 2 in Advanced Stage Parkinson's Disease	27

Table of Figures

Figure 1 Study IPX066-B11-01 Levodopa conversion to IPX066 (source: Sponsor)	19
Figure 2 Study IPX066-B11-01 Disposition of patients (source: Sponsor)	21

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Following assessment of the clinical data, it is the opinion of this reviewer that IPX066 (Rytary®, carbidopa levodopa extended release) is a safe and effective treatment for Parkinson's disease (PD). It has a side effect profile consistent with its pharmacological class and its overall risk to benefit ratio is therapeutically acceptable.

1.2 Risk Benefit Assessment

The IPX066 clinical development program demonstrated that the drug is safe and effective for the treatment of the motor signs and symptoms of early and advanced Parkinson's disease in the first cycle of NDA review. The side effect profile of IPX066 in patients with early and advanced Parkinson's disease is similar to adverse events described in the product information labels for Sinemet® and Sinemet CR®, the Reference Listed Drugs for this 505(b)(2) application.

There is nothing found in this second cycle of NDA review to suggest otherwise.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarketing Requirements and Commitments

This review does not recommend any postmarketing requirements or commitments for clinical studies.

The sponsor has committed to conducting two nonclinical studies as postmarketing requirements:

Six-month oral toxicology study of methacrylic acid copolymer, (b) (4) in rat. The methacrylic acid copolymer, (b) (4), should be the same as the excipient in the to-be-marketed product.

Timetable (submitted October 17, 2014)	
Final Protocol Submission:	04/2015
Study Completion:	10/2016
Final Report Submission:	12/2016

Oral absorption study of radiolabeled methacrylic acid copolymer, (b) (4) in rat. The methacrylic acid copolymer, (b) (4) should be the same as the excipient in the to-be-marketed product.

Timetable (submitted October 17, 2014)
Final Protocol Submission: 07/2015
Study Completion: 08/2016
Final Report Submission: 10/2016

2 Introduction and Regulatory Background

This is the second NDA review cycle for IPX066. In the first NDA cycle, following review of efficacy and safety data, the clinical opinion supported approval. However, due to issues of quality in production, a non-approval letter was issued. The only clinical data in the Complete Response to the non-approval comes from volunteers and patients participating in 3 open trials in progress after the 120 day safety update cut-off date in the first cycle. The submission contains no efficacy data.

Reviewer's comment: The First Cycle primary clinical review and CDTL review are available in DARRTS (AE Constantino and GD Podskalny, respectively, January 18, 2013). This review does not revisit that analysis or the review team's consensus opinion which was based upon comprehensive review of the submission. This review focusses upon new clinical information from the remaining 89 volunteers and patients in the development program participating in open studies since the First Cycle review. The aim of this review is solely to ascertain whether new safety information is discovered that would alter the approvability of the agent or provide evidence to support alteration of safety information contained in the label.

Parkinson's disease is a common degenerative neurological disorder beginning on average in middle age. It results from degeneration of the dopamine neurons in the midbrain, resulting in motor, autonomic and cognitive symptoms. It is a major cause of neurological disability in the US.

Levodopa (LD) is a naturally occurring substance that is converted to dopamine in humans, thereby replacing the missing neurotransmitter responsible for motor symptoms. Because the conversion to dopamine takes place throughout the body via dopa decarboxylase, carbidopa (CD) is administered in combination with levodopa to block the decarboxylation outside of the central nervous system. This carbidopa/levodopa combination product has been marketed in the US as Sinemet® since 1974.

Pharmacological control of motor symptoms diminishes in a characteristic fashion with each passing year of levodopa treatment. Patients develop end-of-dose wearing off of control of motor symptoms. In addition, levodopa induced dyskinesia appears. It is generally thought that these phenomena develop due to the poor pharmacological properties of levodopa (poor absorption, short half-life). As a result, extended release

products have been developed to treat the disease and provide greater patient convenience in dosing. IPX066 is such a product and seeks to employ the 505(b)(2) pathway for regulatory approval of this carbidopa / levodopa extended release product with Sinemet® and Sinemet CR® as the reference listed products. Sinemet® and Sinemet CR® are indicated for the treatment of idiopathic PD, post-encephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide and/or manganese intoxication in early and advanced PD.

2.1 Product Information

IPX066 is a multi-particulate, extended-release capsule formulation of CD-LD designed to provide therapeutic LD plasma concentrations more rapidly and for longer time periods in order to accommodate less frequent dosing. As with the other carbidopa levodopa preparations, it contains carbidopa and levodopa, in a 1:4 ratio.

Rytary® is provided in the following strengths of carbidopa / levodopa (mg) in capsules imprinted with “IPX066” and the milligrams of levodopa in it:

- 23.75 / 95, blue/white capsule
- 36.25 / 145, blue/light blue capsule
- 48.75 / 195, blue/yellow capsule
- 61.25 / 245, blue/blue capsule

2.2 Tables of Currently Available Treatments for Proposed Indications

There are a number of different classes of products approved to treat Parkinson’s disease: dopamine precursor, dopamine agonist, anticholinergic, COMT inhibitors, and MAO-B inhibitors. The table below presents the levodopa containing products currently approved in the US for the treatment of Parkinson’s disease.

Table 1 Currently available levodopa preparations (not including generic versions)

Levodopa Preparations	Available Doses	Initial Dosing
Carbidopa/Levodopa (Sinemet ®)	10/100 mg, 25/100 mg, 25/250mg	25/100 2 to 3x daily
Carbidopa Levodopa controlled release (Sinemet CR ®)	25/100 mg, 50/200 mg	50/200 mg 2x a day
Carbidopa/Levodopa/Entacapone (Stalevo ®)	12.5/50/200 mg, 25/100/200 mg, 18.75/75/200 mg, 31.25/125/200 mg, 37.5/150/200 mg, 50/200/200 mg	12.5/50/200 mg

2.3 Availability of Proposed Active Ingredient in the United States

Carbidopa and levodopa, the active ingredients in IPX066, are currently marketed in the US as listed in Table 1 above.

2.4 Important Safety Issues With Consideration to Related Drugs

Important side effects known to occur during levodopa treatment of PD include: falling asleep and somnolence, hyperpyrexia and confusion, dyskinesia, hallucinations and psychotic behavior, impulse control disorder and compulsive behavior.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Impax submitted a 505(b)(2) New Drug Application (NDA) for a new carbidopa levodopa extended release capsule, IPX066 (Rytary®) in December 2011. The application included results from new efficacy studies to support an indication for patients with early and advanced Parkinson's disease (PD). The application relied upon the approval and information contained in the labels for approved carbidopa and levodopa containing products including Sinemet® and Sinemet CR® (Merck).

The evidentiary support for clinical efficacy and safety for the proposed indication in the application was reviewed and was deemed to be approvable by both the primary clinical neurology reviewer and the Cross Discipline Team Leader. Label discussion was comprehensive, reaching a near-final version of the label, when it was discovered that there were quality and manufacturing concerns that resulted in a complete response for the application in January 2013.

A Type A meeting request outlining the proposed content of the resubmission was submitted to the NDA on March 7, 2014 as S0039, and the meeting was granted for April 7, 2014. On April 4, 2014 the Division sent Impax their written responses to the questions contained in the meeting request. Since only minor additional clarification was needed, Impax cancelled the face-to-face meeting and opted for a teleconference in its place. In accordance with the Division's written responses to Impax's questions and the clarifications provided in the teleconference, Impax is resubmitting the NDA with the content described below.

Resubmission clinical content requested by DNP:

Complete Safety Update as specified in the CR letter and as requested in the Division's April 4, 2014 response to Impax and the April 7, 2014 teleconference. The Safety Update includes all existing safety data for IPX066.

Final clinical study reports for four studies were submitted to the IND but not previously submitted to the NDA:

IPX066-B09-06 Part 2: A Study to Compare IPX066 and CD-LD-Entacapone in Advanced Parkinson's Disease

IPX066-B11-01: An Open-Label Conversion Study of Carbidopa-Levodopa Extended Release (CD-LD ER) Taken Alone or in Combination with Carbidopa-Levodopa Immediate Release (CD-LD IR) to IPX066. (Followed by an Open-Label Extension Safety Study of IPX066 in Subjects with Advanced Parkinson's Disease)

IPX066-B12-01: Assessment of Dissolution Profiles of IPX066

IPX066-B12-03: Comparison of Three Formulations of IPX066

The latter three studies were completed after the cutoff date for the 120 Day Safety Update of the first review cycle (January 23, 2012). Updated datasets using the CDISC SDTM and ADaM standards were submitted for review.

2.6 Other Relevant Background Information

The IPX006 development program has concluded and no clinical or nonclinical studies are underway. The clinical information submitted in this Class II resubmission is, in essence, the final safety update report covering all patients remaining in studies after the NDA 120 Day Safety Update in the first review cycle.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor's submission was in eCTD format using CDISC SDTM and ADaM data standards. It met standards required for filing.

3.2 Compliance with Good Clinical Practices

The Sponsor affirms that the submitted studies adhered to GCP. No evidence arose during review that suggested otherwise. The Sponsor certified that it did not use any debarred investigators. The protocol, informed consent and subject information forms were reviewed and approved by the local Institutional Review Boards or Independent Ethics Committees. No inspections of clinical sites were performed.

3.3 Financial Disclosures

Financial disclosures were appropriately submitted and, upon review, no financial conflicts of interest were evident.

5 Sources of Clinical Data

The first cycle NDA application relied primarily on three controlled clinical trials to support the claim for efficacy and safety as well as the results of a long-term safety study. The clinical information submitted in this Class II covers all patients remaining in studies after the initial NDA 120 Day Safety Update (cutoff date January 23, 2012).

The pivotal trials reviewed in the first cycle:

IPX-B-08-05 was a Phase 3, fixed dose, randomized, double-blind, placebo-controlled, parallel groups study in patients with early PD.

IPX066-B09-02 was a Phase 3, 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 patients with advanced PD.

IPX066-B09-06 was a randomized, double-blind, double-dummy, 2-treatment, two 2-week crossover study of IPX066 versus CLE (Part I) followed by an open-label safety study (Part 2) of IPX066 in Advanced Parkinson's disease.

The application included long-term, open label safety information in the form of an interim report for study IPX066-B09-03. Patients who completed studies IPX066-B08-05 (early PD) an IPX066-B09-02 (advanced PD) were eligible to enroll in study IPX066-B09-03. In addition, patients from study IPX066-B08-11, a randomized, open-label, multicenter, two-period, cross-over pharmacokinetics and pharmacodynamics study of IPX066 versus IR CD-LD in subjects with advanced PD with motor fluctuations contributed to the long-term open-label safety database.

The Sponsor's 120-day safety update primarily included additional information from patients enrolled in IPX066-B09-03.

The clinical information submitted in this Class II resubmission is, in essence, the final safety update report covering all patients remaining in studies after the initial NDA 120 Day Safety Update. This includes any safety information since the January 23, 2012 cutoff date for the first review cycle NDA 120-Day Safety Update. There are no active studies at this time.

This **Resubmission Safety Update** presents the new safety data available since the 120-Day Safety Update on 89 persons (46 human volunteers and 43 patients with advanced PD). These data are from one phase 3, open-label extension study in subjects with advanced PD, Study IPX066-B11-01. In addition, data from three Phase 1 studies (IPX066-B12-01, IPX066-B12-02, and IPX066-B12-03) in healthy subjects are presented. (In the Phase 1 palatability study (Study IPX066-B12-02) there was no drug substance administered.)

A table of all studies in the development program may be found in the next section.

5.1 Tables of Studies/Clinical Trials (source: sponsor)

Table 2 IPX066 Development Program (source: Sponsor)

Study Numbers	Study Title	Status	Number of Subjects	
			Enrolled	Completed
STUDIES IN HEALTHY SUBJECTS				
Phase 1, Pooled Studies				
IPX066-B08-08 ^a	Effect of Food on the Pharmacokinetics of IPX066 (stopped early)	Study stopped	21	None
IPX066-B08-09	Assessment of Dose Proportionality of IPX066	Completed	31	28
IPX066-B08-10	Relative Bioavailability of IPX066 to Carbidopa-Levodopa Formulations	Completed	24	22
IPX066-B09-01	Effect of Food on the Pharmacokinetics of IPX066	Completed	21	19
IPX066-B09-04	Effect of Alcohol on IPX066	Completed	27	18
IPX066-B10-01	Bioequivalence study Between Two Manufacturing Sites	Completed	39	34
IPX066-B12-01	Assessment of Dissolution Profiles of IPX066	Completed	20	17
IPX066-B12-02	Palatability of IPX066	Completed	18	18
IPX066-B12-03	Comparison of Three Formulations of IPX066	Completed	28	27
Total Number of Subjects in Phase 1 Studies			229	183
STUDIES IN SUBJECTS WITH PARKINSON'S DISEASE				
Phase 2, Controlled Study				
IPX066-B08-11	A Study to Compare Pharmacokinetics and Pharmacodynamics of IPX066 to Standard Carbidopa-Levodopa	Completed	27	27
Total Number of Subjects in Phase 2 Study			27	27
Phase 3, Adequate and Well-Controlled Studies				
IPX066-B08-05	A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson's Disease	Completed	381	300
IPX066-B09-02	A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson's Disease	Completed	471	368
IPX066-B09-06 Part 1	A Study to Compare IPX066 and CD-LD-Entacapone in Advanced Parkinson's Disease	Completed	110	84
Total Number of Subjects in Phase 3 Controlled Studies			962	752
Phase 3, Open-Label, Long-Term Safety Extension Studies^b				
IPX066-B09-03 ^b	An Open Label Extension Study of the Safety and Clinical Utility of IPX066 in Subjects with Parkinson's Disease	Completed	617 ^b	567
IPX066-B09-06 Part 2 ^c	A Study to Compare IPX066 and CD-LD-Entacapone in Advanced Parkinson's Disease	Completed	74 ^c	66
IPX066-B11-01	An Open-Label Conversion Study of Carbidopa-Levodopa Extended Release (CD-LD ER) Taken Alone or in Combination with Carbidopa-Levodopa Immediate Release (CD-LD IR) to IPX066 Followed by an Open-Label Extension Safety Study of IPX066 in Subjects with Advanced Parkinson's Disease	Completed	43	33/25/12 ^d
Total Number of Subjects in Long-Term Safety Extension Studies			734	645

5.2 Review Strategy

The adequate and well-controlled trials that contributed to the evidentiary support for this application have been previously reviewed in the first cycle. The clinical data submitted in this complete response do not come from any blinded or controlled trials and provide only unblinded safety information.

No efficacy data is submitted in this Complete Response to the First Cycle review.

This review inspects this **safety update**, focusing on duration of exposure, deaths, dropouts, serious and / or unexpected adverse events. Following this review, it was found that the data submitted in this application does not serve to alter the adverse event tables found in the label that were previously agreed to by the sponsor. For the reader's convenience, the adverse event tables in the proposed label may be found in the Appendix, Section 9.2 Labeling Recommendations.

The sponsor's tables which compare safety information submitted with the original NDA to this Complete Response are reproduced here for the reader's convenience in order to provide continuity with the first cycle review.

7 Review of Safety

Safety Summary

First Cycle Safety Summary (from the primary clinical review, DARRTS 1/18/2013)

- There were 11 deaths in 1098 patients (1.0%) reported from all of the studies submitted to this NDA (including the 120 day safety update). The deaths did not appear to be drug related and were mainly due to cardiopulmonary causes which are the most common cause of death among patients with Parkinson's disease.
- Of 849 patients exposed to at least one dose of the study drug in the submitted clinical trials for this study, there were 38 (4.5%) serious adverse events. Adverse events were more frequent in the advanced PD population. Drug related serious adverse events include nausea/vomiting, acute psychosis and disabling dyskinesias.
- In the early PD (B08-05) study, nausea and vomiting is the most common AE occurring in 61 (16%) of subjects on IPX066 and 11 (2.9%) on patients on placebo. They occurred more frequently during the titration phase (12.6%) than during the Maintenance Phase (4.2%). Nausea and vomiting also was the most common adverse event that led to early withdrawals.
- In the advanced PD study, there were more frequent cases of dyskinesias (2.5% vs. 1%), nausea and vomiting (4.5% vs. 3.6%), orthostatic hypotension (4.5% vs. 2.6%), hallucinations (1.7% vs. 0.7%) and impulse control behavior disorders (1.4% vs. 0) in the IPX066 treated group than in the IR group.
- The adverse events reported in this clinical development program for IPX066 were similar to the type and frequency of adverse events that were seen in early and advanced PD patients enrolled in PD drug studies.

7.1 Methods

This Resubmission Safety Update presents the new safety data available since the 120-Day Safety Update from one phase 3, open-label extension study in subjects with advanced PD, Study IPX066-B11-01. In addition, data from 2 phase 1 studies (IPX066-B12-01 and IPX066-B12-03) in healthy subjects are presented.

This reviewer has reviewed all patients in this safety update, focusing on deaths, dropouts, serious and / or unexpected adverse events.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The IPX066 clinical study safety database includes data for 1218 subjects treated across 15 completed clinical studies, of which 1187 received IPX066: 978 subjects with PD (951 in Phase 3 and 27 in Phase 2) and 209 healthy subjects. The updated safety information in this resubmission comes from studies completed since the first cycle: two Phase 1 studies and two Phase 3 open treatment long term extension study.

Three Phase 1 studies in healthy subjects (Study IPX066-B12-01, Study IPX066-B12-02, and Study IPX066-B12-03) were initiated and completed since the NDA 120-Day Safety Update. For 2 of these studies (Study IPX066-B12-01, Study IPX066-B12-03), 46 subjects were exposed to **single doses** of IPX066. In these multiple arm studies, only one arm in each study received the to-be-marketed formulation of IPX066. The findings from these two single dose studies of IPX066 in human volunteers are presented together.

The third Phase 1 study, Study IPX066-B12-02, was a palatability study in which subjects did not ingest IPX066 drug substance. It is not considered further in this review.

Study IPX066-B11-01 a Phase 3, open-label extension study in subjects with advanced PD, had 43 patients with exposure to IPX066 after the First Cycle review.

Table 3 Study IPX066-B12-01 in healthy volunteers (Sponsor's synopsis)

Study ID, No. of Centers, Location	Study Start Date, Enrollment Status and Date, Total Enrollment/Planned	Design	Study and Control Drugs Dose, Route, Regimen	Study Objective	No. of Subjects by Arm Who Entered/Completed	Duration	M/F Mean Age, yr (range), Race (W/B/AI/A/O) ^a	Diagnosis Inclusion Criteria	Safety Assessments ^b
IPX066-B12-01 1 center United States	Started: 9Nov2012 Completed: 3Dec2012 17/20	Phase 1, randomized, single-center, single-dose, open-label, 5-sequence, 5 treatment crossover study	IPX066, oral capsule, 5 Treatments: A (Fast): one 245 mg LD capsule (C0022) B (Medium): one 245 mg LD capsule (C0018) C: (Slow 1): one 245 mg LD capsule (C0023) D: (Slow 2): one 245 mg LD capsule (C0024) E: (Reference):	To assess PK of IPX066 formulations with different in vitro profiles, in order to develop an in-vitro/in-vivo correlation	Period 1: 20 Period 2: 19 Period 3: 19 Period 4: 18 Period 5: 17	Single dose (6-day washout period between tx)	7M/13F 42.1 (20-65) 15W/5B	Healthy male or female subjects ≥ 18 yr and 65 yr, inclusive. BMI 18–31 kg/m ²	ECGs, clinical lab tests, vital signs (BP, HR, RR, and temp), physical exams, C-SSRS, and concomitant medications.

Table 4 Study IPX066-B12-03 in healthy volunteers (Sponsor's synopsis)

Study ID, No. of Centers, Location	Study Start Date, Enrollment Status and Date, Total Enrollment/Planned	Design	Study and Control Drugs Dose, Route, Regimen	Study Objective	No. of Subjects by Arm Who Entered/Completed	Duration	M/F Mean Age, yr (range), Race (W/B/AI/A/O) ^a	Diagnosis Inclusion Criteria	Safety Assessments ^b
IPX066-B12-03	Started: 16Dec2012 Completed: 28Dec2012 28/36 27 complete ^d (One subject dropped by PI prior to treatment)	Phase 1, randomized, single-center, open-label, 3 treatment, 3 sequence crossover study		To assess bioavailability and PK of three IPX066 formulations	Three treatments: Period 1: 28 Period 2: 27 Period 3: 27	Three treatment periods separated by a 6-day washout period	14M/14F 33.7 (20-60) 13W/15B	Healthy subjects between 18 and 65 years of age, inclusive. No evidence of suicidal ideation within 3 months or suicidal behavior within 6 months based on the Columbia Suicide Severity Rating Scale (C-SSRS)	ECGs, clinical laboratory tests, AEs, vital signs, C-SSRS, physical examinations, and concomitant medications.

Table 5 Study IPX066-B11-01 in patients with advanced PD (Sponsor’s synopsis)

Study ID, No. of Centers, Location	Study Start Date, Enrollment Status and Date, Total Enrollment/Planned	Design	Study and Control Drugs Dose, Route, Regimen	Study Objective	No. of Subjects by Arm Who Entered/Completed	Duration	M/F Mean Age, yr (range), Race (W/B/AI/A/O) ^a	Diagnosis Inclusion Criteria	Safety Assessments ^b
IPX066-B11-01 8 centers: United States	Started: 19Aug2011 Completed 20MAR2013 40/43 subjects	Phase 3, open-label conversion study from CD-LD ER alone or in combination with CD-LD IR products to IPX066	IPX066, oral capsule Part 1 (Dose Conversion) —IPX066 in an open-label manner Additionally, OPDM/PK subset of subjects (Cohort 2) received a fixed dose of CD-LD ER 100 mg x 2 tablets (Visit 0) and IPX066 145 mg x 3 capsules (Visit 1). Part 2— IPX066 in an open-label manner. Part 3— IPX066 in an open-label manner.	Part 1 1. To evaluate the dose conversion from CD-LD ER taken alone or in combination with CD-LD IR to IPX066 in Advanced PD subjects 2. To evaluate the utility of an exploratory computer-based system OPDM is assessing dexterity and mobility in a subset of PD subjects. Part 2: To evaluate the long-term safety and clinical utility of IPX066 under open-label conditions in eligible subjects who success-fully complete Part 1 of the study. Part 3: To evaluate the long-term safety and clinical utility of IPX066 under open-label conditions in eligible subjects who success-fully complete Part 2 of the study.	Part 1: 43/33 Part 2: 32/25 Part 3: 12/12	Part 1: approximately 6 wk Part 2: approximately 6 mo Part 3: Approximately 6 mo	20M/23F 66.4 (47–89) 42W/1A	Advanced PD, currently taking CD-LD ER alone or in combination with CD-LD IR products, requiring ≥ 400 mg LD TDD with a dosing frequency of ≥ 4x/d; ≥ 30 yr old at PD diagnosis, MMSE score ≥ 26, Hoehn & Yahr stage I–IV in “on” state, average ≥ 2.5 h/d “off” time for the last 2 wk. Cohort 2 (OPDM/PK subjects) must be able to tolerate >7 h of clinical evaluation and able to withhold LD-containing drugs from 22:00 onward on evening prior to OPDM assessment.	Vital signs (BP, HR, temp, and RR), physical exam, AEs, clinical lab tests, ECGs, C-SSRS, and concomitant medications

7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Affairs (MedDRA), Version 12.1 was used for adverse event coding. Treatment emergent adverse events (AEs) were defined as AEs that began after the first dose of study treatment was administered up until 72 hours after the last dose of study treatment study was administered. These were classified by System Organ Class (SOC) and Preferred Term. Adverse events were also classified into serious, common and special in its class.

The sponsor’s safety coding for these newly submitted patients was reviewed for preferred and verbatim terms that are commonly reported by patients with Parkinson’s disease.

Reviewer's Comment: The adverse events occurring in these additional patients from the three studies in this submission were compared to the First Cycle safety reviews. No new or unexpected events were reported. To the extent possible in a small population, the rates of common AE's approximated those of the rest of the study population.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A document from the Sponsor entitled Resubmission Safety Update (dated April 8, 2014) was submitted to identify and present their safety findings from these final patients. In addition, these new safety findings are compared and used to update that which was presented in the First Cycle Integrated Summary of Safety. This met agreements made prior to the NDA Complete Response submission.

This document served as a guide for the reviewer to verify the sponsor's findings using the submitted SDTM and ADaM standardized datasets.

7.2 Adequacy of Safety Assessments

IPX066-B12-01 Effect of dissolution profiles on the pharmacokinetics of IPX066

This was a phase 1, single-center, open-label, randomized, **single-dose**, 5- sequence, 5-treatment crossover study in healthy subjects between 18 and 65 years of age, inclusive. Only one of the five treatments represented the to-be-marketed formulation. Up to 20 healthy subjects were to be enrolled. The objective of the study was to assess the PK of IPX066 formulations with different in vitro release profiles in order to develop an in vitro/in vivo correlation for IPX066.

Safety parameters measured during the study included AEs, 12-lead ECGs, physical exams, clinical laboratory test data, vital signs, C-SSRS, and concomitant medications.

IPX066-B12-03 Bioavailability and pharmacokinetics of three IPX066 Formulations

This is a single-center, open-label, randomized, **single-dose**, 3-sequence, 3-treatment crossover study in healthy subjects. A total of 36 subjects were enrolled but only 12 received the to-be-marketed formulation. The objective of the study was to assess the bioavailability (BA) and PK of three IPX066 formulations.

Criteria for safety evaluation included AEs, 12-lead ECGs, physical examinations, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs, C-SSRS, and concomitant medications over the course of the study.

IPX066-B11-01 Open label extension safety study in subjects with advanced Parkinson's disease

This study was a multicenter, open-label, dose-conversion study (Part 1) of extended release CD-LD taken alone or in combination with immediate release CD-LD to IPX066 followed by optional participation in two consecutive open-label extensions (Part 2 and Part 3), each lasting 6 months, in subjects with advanced PD.

Eight US centers enrolled 46 patients with two centers accounting for two thirds of patients.

Safety assessments performed at the start and finish of each six month extension included the following: vital signs (blood pressure [BP], heart rate, temperature, and respiratory rate), physical examination, AEs, clinical laboratory tests (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale scores (C-SSRS), and concomitant medications during study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

IPX066-B12-01 Effect of dissolution profiles on the pharmacokinetics of IPX066

Each volunteer was administered a single treatment followed by 6 days of observation for each of 5 weeks. The treatment arms comparing various formulations of IPX066 61.25 / 245 mg CD / LD were:

A (Fast): one 61.25 / 245 mg CD / LD capsule (C0022)	n=20
B (Medium): one 61.25 / 245 mg CD / LD capsule (C0018)	n=19
C: (Slow 1): one 61.25 / 245 mg CD / LD capsule (C0023)	n=19
D: (Slow 2): one 61.25 / 245 mg CD / LD capsule (C0024)	n=18
E: (Reference): Sinemet, immediate release 25 /100 mg	n=17

Arm B, C0018, is the to-be-marketed formulation.

Twenty patients were enrolled: 7 men, 13 women, mean age 42 (range 20-65).

IPX066-B12-03 Bioavailability and pharmacokinetics of three IPX066 Formulations

Each volunteer was administered a single treatment followed by 6 days of observation for each of 3 weeks. The treatment arms compared two other formulations of IPX066 61.25 / 245 mg CD / LD to the to-be-marketed formulation C0018. Twenty-eight volunteers enrolled, with one dropping out after the first period. The volunteers were equally divided between men and women, with an average age of 34 (range 20 – 60).

IPX066-B11-01 Open label extension safety study in subjects with advanced Parkinson’s disease

Forty three patients with advanced PD entered this study: 33 of the 43 completed the six week dose conversion portion of the study. 32 entered the first long term open extension and 25 completed. 12 entered the second long term extension and all completed.

All but one of the patients were white, average age 66, range 47 -89, M:F 20:23. Most had had PD for 8 years, were in Hoehn – Yahr Stage I, II, or III and had been on levodopa 7 years on average.

This study had begun in August, 2011 before the January 2012 cut-off date and finished March 20, 2013. As a result Part 1, the six week conversion phase, and some data from Part 2 had been reviewed previously in the First Cycle. The safety data in the latter parts represents advanced patients on stable chronic doses of IPX066.

Each patient was converted from their stable pre-study carbidopa levodopa dose to IPX066 using a study algorithm.

Figure 1 Study IPX066-B11-01 Levodopa conversion to IPX066 (source: Sponsor)

Baseline Total Daily LD ^a Dose (mg)	Suggested Initial Total Daily IPX066 Dose (mg)	Suggested Initial IPX066 (LD in mg) (Each Dose Approximately 6 Hours Apart During Waking Hours)
(b) (4)	855	3 capsules x 95 mg TID
(b) (4)	1140	4 capsules x 95 mg TID
(b) (4)	1305	3 capsules x 145 mg TID
(b) (4)	1755	3 capsules x 195 mg TID
(b) (4)	2340	4 capsules x 195 mg TID or 3 capsules x 245 mg TID

^a Abbreviations: LD = levodopa, TID = three times per day

Table 6 Parts 2 and 3 Cumulative exposure since the First Cycle cut-off date

Any Exposure	N = 43
≤ 29 Days	8
30-89 Days	5
90-179 Days	5
180-364 Days	13
≥ 365 Days	12

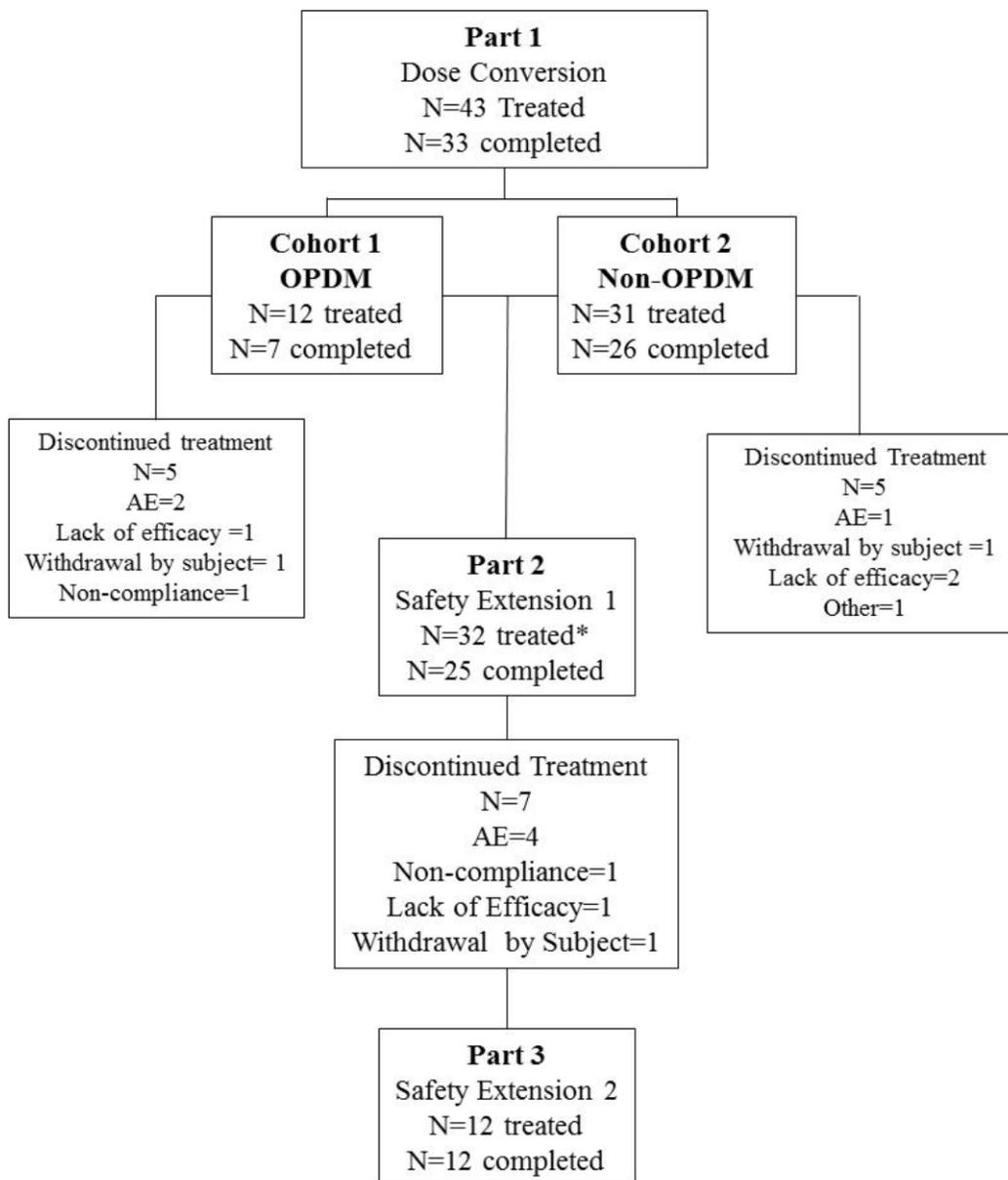
The mean total daily dose was 1393 mg (range 508 – 2925 mg/d; 95% CI: 1186 -1599 mg/d). For reference, this was the Sponsor’s conversion schema:

Table 7 Sponsor's schema for initial levodopa dose conversion to IPX066 in Study IPX066-B-11-01

Baseline Total Daily LD^a Dose (mg)	Suggested Initial Total Daily IPX066 Dose (mg)	Suggested Initial IPX066 (LD in mg) (Each Dose Approximately 6 Hours Apart During Waking Hours)
(b) (4)	855	3 capsules x 95 mg TID
(b) (4)	1140	4 capsules x 95 mg TID
(b) (4)	1305	3 capsules x 145 mg TID
(b) (4)	1755	3 capsules x 195 mg TID
(b) (4)	2340	4 capsules x 195 mg TID or 3 capsules x 245 mg TID

^a Abbreviations: LD = levodopa, TID = three times per day

Figure 2 Study IPX066-B11-01 Disposition of patients (source: Sponsor)



7.3 Major Safety Results

There were no serious adverse events, deaths or early discontinuations due to AEs in either of the two single dose Phase 1 studies. In the two Phase 1 studies, 6 volunteers of 46 (13%) reported an AE. Four of the six were thought to be related to treatment. All had been previously reported except one case of rhinorrhea. None were severe. There were no Phase 1 study discontinuations due to an AE. There were no clinical laboratory abnormalities, electrocardiogram abnormalities or vital sign changes of note.

Table 8 AEs reported by at least two volunteers in the Phase 1 studies reported in the First and Second Cycle NDA submissions.

Adverse Event by Preferred Term	Original NDA IPX066 Phase 1 studies (N = 163)	Second Cycle IPX066 Phase 1 Studies (N = 46)
Headache	25 (15%)	1 (2%)
Nausea	24 (15%)	2 (4%)
Vomiting	16 (10%)	0
Dizziness	4 (3%)	0
Pyrexia	3 (2%)	0
Pain	2 (2%)	0
Blood creatinine increased	2 (1%)	0
Cough	2 (1%)	0
Oropharyngeal pain	2 (1%)	0
Asthenia	1 (1%)	1 (2%)

Reviewer's comment: The rest of the findings reported on below in this section are from the Phase 3 open follow-up study in advanced PD. The demographic characteristics of these patients were typical of a usual population of patients with advanced PD.

7.3.1 Deaths

One death occurred in an 85 year old man with symptoms of PD dementia and “failure to thrive.” He was admitted to hospice after he stopped eating and gradually became less responsive. IPX066 was discontinued a week before death “due to complications of PD.”

7.3.2 Nonfatal Serious Adverse Events

Nine subjects reported SAEs: 6 on treatment, 1 at screening and 2 post-treatment (one of these SAE's had previously been reported in the first cycle).

Table 9 Serious Adverse Events in Study IPX066-B11-01 not previously reported.

Adverse Event	Not Previously Reported N = 34
Atrial fibrillation	1 (3%)

Orthostatic hypotension	2 (6%)
Sepsis	1 (3%)
Back pain	1 (3%)
Anxiety	1 (3%)
Parkinson's disease	1 (3%)
Cerebrovascular accident	1 (3%)

No pattern of SAEs was discernable. Orthostatic hypotension occurred in a 63 year old man with a previous history while taking 2340 mg daily. It also required hospitalization and treatment with fludrocortisone despite dose adjustment in a 65 year old woman with other signs of autonomic dysfunction and a REM behavior disorder taking 2720 mg /d. An 81 year old man had atrial fibrillation previously reported in Part 1 of this trial in the first cycle. It reoccurred in Part 2 when he developed sepsis. Both episodes resolved spontaneously while treatment with 1755 mg/d continued. The cerebrovascular accident (lacunar stroke) occurred in a 79 year old man on 1140 mg/d. He had a history of hypertension, hypercholesterolemia, diabetes, with a previous history of angioplasty for coronary artery disease.

7.3.3 Dropouts and/or Discontinuations

Early terminations in this group (N=15) were closely related to lack of efficacy. No one who was much or very much improved dropped out. Fourteen patients never reached a stable conversion dose and 10 of these discontinued during the 6 week Part 1 of the study. Seven subjects reported an AE as reason for discontinuation but the complaints were related to their underlying Parkinsonism. Other adverse events experienced by this group included nausea (3), and 1 each of orthostatic hypotension, hallucination, anxiety, vomiting, dyskinesia, confusional state, and agitation among others.

7.3.4 Significant Adverse Events

Most adverse events were mild. The three adverse events with severity called "serious" were orthostatic hypotension (2) and sepsis.

7.3.5 Submission Specific Primary Safety Concerns

Of note, there were no unexpected cardiovascular events attributed to IPX066. There were no cases of impulse control disorder or somnolence. No changes in suicidality occurred as measured by the C-SSRS.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

No adverse events previously unreported with levodopa were encountered in this study.

Reviewer's comment: Note that the table below differs slightly from the TEAE table that was submitted by the Sponsor in the Resubmission Safety Update of April 8, 2014. The table generated by the reviewer is below and is the same as appears in the Sponsor's final clinical trial report for IPX066-B11-01.

Table 10 Treatment emergent adverse events in Study IPX066 –B11-01

Adverse Event	First Cycle Previously Reported N = 43	Second Cycle Not Previously Reported N = 34	Total Reported N = 43
Urinary tract infection	4 (9%)	4 (12%)	8 (19%)
Nausea	4 (9%)	3 (9%)	7 (16%)
Fall	2 (5%)	4 (12%)	5 (12%)
Anxiety	1 (2%)	4 (12%)	5 (12%)
Viral upper respiratory tract infection	1 (2%)	3 (9%)	4 (9%)
Dyskinesia	4 (9%)	0	4 (9%)
Orthostatic hypotension	0	3 (9%)	3 (7%)
Hallucination	2 (5%)	1 (3%)	3 (7%)
Tremor	0	3 (9%)	3 (7%)
Constipation	2 (5%)	0	2 (5%)
Diarrhea	2 (5%)	0	2 (5%)
Vomiting	2 (5%)	0	2 (5%)
Peripheral oedema	2 (5%)	0	2 (5%)
Ear infection	1 (2%)	1 (5%)	2 (5%)
Rib fracture	0	2 (6%)	2 (5%)
Dizziness	0	2 (6%)	2 (5%)
Dystonia	0	2 (6%)	2 (5%)
Parkinson's disease	0	2 (6%)	2 (5%)
Syncope	0	2 (6%)	2 (5%)
Acute renal failure	0	2 (6%)	2 (5%)
Urinary retention	1 (2%)	2 (6%)	2 (5%)
Hypotension	0	2 (6%)	2 (5%)
Pain in Extremities	0	2 (6%)	2 (5%)

7.4.2 Laboratory Findings

There were no abnormalities of note nor was any pattern of shift discernible in the clinical laboratory results.

7.4.3 Vital Signs

Using measures of central tendency there were no significant changes in vital sign measurements (systolic and diastolic pressures and heart rate). Orthostasis was not measured in this study. However, adverse events related to orthostasis (hypotension, dizziness) did occur. This suggests that IPX066 has the same effect on blood pressure as other carbidopa / levodopa preparations.

7.4.4 Electrocardiograms (ECGs)

There were no abnormalities of note. There was no QT prolongation.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Not investigated.

7.5 Other Safety Explorations

No other investigations of safety were pursued.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

IPX066 is not marketed in any other countries.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

Because the Complete Response decision was taken in the final days of the initial review cycle, extensive label-related discussion had taken place with the Sponsor. The label has since been updated with new language that had been added or changed in the label of the Reference Listed Drug for this 505(b)(2) application .

The proposed Adverse Reactions tables are reproduced here:

Table (b) (4): Adverse Reactions in Study 1 (b) (4)

(b) (4)	Placebo	RYTARY 36.25 mg carbidopa 145 mg Levodopa TID	RYTARY 61.25 mg carbidopa 245 mg Levodopa TID	RYTARY 97.5 mg carbidopa 390 mg Levodopa TID
	(N=92) %	(N=87) %	(N=104) %	(N=98) %
Nausea	9	14	19	20
Dizziness	5	9	19	12
Headache	11	7	13	17
Insomnia	3	2	9	6
Abnormal Dreams	0	2	6	5
Dry Mouth	1	3	2	7
Dyskinesia	0	2	4	5
Anxiety	0	2	3	5
Constipation	1	2	6	2
Vomiting	3	2	2	5
Orthostatic Hypotension	1	1	1	5

(b) (4)

Table (b) (4): Adverse Reactions in Study (b) (4)

Period	RYTARY (N=201)		(b) (4) (N=192)	
	Dose Conversion ^b	Maintenance	Dose Conversion ^b	Maintenance
	%	%	%	%
Nausea	(b) (4)	3	6	2
Headache	5	1	3	2



All patients were converted to RYTARY in the open label Dose Conversion period and then received randomized treatment

It is anticipated that these may change in format but not substance as label negotiations are concluded with the sponsor.

9.3 Advisory Committee Meeting

No advisory committee consideration was sought for this application.

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

/s/

KENNETH J BERGMANN
12/19/2014

GERALD D PODSKALNY
12/22/2014

MEMORANDUM

DATE: January 15, 2013 (b) (4)

FROM: Division Director
Division of Neurology Products/HFD-120

TO: File, NDA 203312

SUBJECT: Action Memo for NDA 203312, for the use of (b) (4) (carbidopa/levodopa Extended release capsules) 23.7/95 mg, 36.25/145 mg, 48.75/195 mg, and 61.25/245 mg in patients with Parkinson's Disease (PD)

NDA 203312, for the use of (b) (4) (carbidopa/levodopa Extended release capsules) 23.7/95 mg, 36.25/145 mg, 48.75/195 mg, and 61.25/245 mg (carbidopa/levodopa dose) in patients with Parkinson's Disease (PD), was submitted by Impax Laboratories, Inc., on 12/21/11. The application was submitted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, referencing NDAs for Sinemet, Lodosyn, Sinemet CR, and Stalevo. This product has been formulated to have both immediate release, as well as controlled release, properties. Currently approved carbidopa/levodopa products are either considered immediate release (e.g., Sinemet) or solely controlled release (e.g., Sinemet CR). The proposed product, by combining both immediate- and extended-release components, is designed to produce immediate post-dosing, as well as sustained, levodopa levels, so as to possibly obviate the need for dosing with individual immediate-and controlled-release products.

The application contains reports of three controlled trials, one in patients with newly diagnosed PD, and two in patients with advanced PD who have not responded adequately to available carbidopa/levodopa products. In addition, the application contains the requisite chemistry and manufacturing controls (CMC), non-clinical toxicology, and clinical pharmacology and biopharmaceutics information.

The application has been reviewed by Dr. Anne Constantino, medical officer, Dr. Tristan Massie, statistician, Dr. Charles Jewell, CMC reviewer, Dr. Sandra Suarez Sharp, biopharmaceutics, Dr. LuAnn McKinney, pharmacology reviewer, Dr. Lois Freed, supervisory pharmacologist, Dr. Jagan Parepally, clinical pharmacology, Dr. Li Zhang, pharmacometrics, Dr. Julie Neshiewat, Division of Medication Error Prevention and Analysis, and Dr. Dave Podskalny, neurology team leader, and Cross-Discipline Team Leader (CDTL). I will very briefly provide a summary of the relevant data, and offer the rationale for the division's action on this application.

Effectiveness

As noted above, the sponsor has submitted reports of three controlled trials in patients with PD. The designs and results are well described by the review team; I will only very briefly describe the results.

Study 05

Study 05 was a double-blind, multi-center, randomized controlled trial in which patients were randomized to either (LD dose) 145 mg, 195 mg, or 245 mg TID or placebo. These patients were essentially naïve to CD/LD treatment. Patients were titrated to their randomized dose over 3 weeks (then held stable for one week), after which they were maintained on their dose for an additional 26 weeks. The primary outcome was the change from baseline at study end in the sum of Part II (activities of daily living) and Part III (motor examination). A total of 381 patients were randomized:

	Placebo	145 mg	245 mg	390 mg
Randomized	92	87	104	98
Discontinued	21	15	21	24

14% (N=15) and 15% (N=15) discontinued due to adverse events from the 145 and 245 mg arms, respectively.

The following chart displays the results of the primary outcome:

Dose	Mean Change from Baseline in UPDRS II + III	P-value
Placebo	-0.6	
145 mg	-11.7	<0.0001
245 mg	-12.9	<0.0001
390 mg	-14.9	<0.0001

Various other analyses of the individual components as well as the total of Parts I, II, and III also showed a similar pattern, with a similar dose response (there were no statistically significant differences from placebo on Part IV, and no dose response for Part I alone). Analyses performed by Dr. Massie evaluating the effects of discontinuations did not change the fundamental outcome or conclusions. In addition, analyses of patient and clinician global ratings showed a similar dose response in the percentage of patients who were reported as Much or Very Much Improved (see, for example, Dr. Constantino's review, page 57).

Study 02

This was a randomized, double-blind, double-dummy multi-national study in patients with advanced PD receiving treatment with IR CD/LD products but who were not well controlled. In this study, patients entered a 3 week phase in which their IR treatment was to be “optimized”, followed by a 6 week period in which they were converted to a dose of (b) (4) (target daily dose determined by their final IR dose), then randomized to either the target dose of (b) (4) or their final IR dose, and followed for 13 weeks. The primary outcome was the baseline adjusted percent of wake time spent in the “off” state at the end of the study (last 3 days averaged before the last visit). This metric was recorded in a patient diary, along with “on without dyskinesia”, “on without troubling dyskinesia”, and “on with troublesome dyskinesia”. The following dosing paradigm was used to convert patients from their IR dose to their (b) (4) dose:

Daily IR LD dose	(b) (4) dosing (TID)
400- <550 mg	285 mg TID
551-750 mg	380 mg TID
751-950 mg	435 mg TID
951-1250 mg	585 mg TID
1251-1650 mg	780 mg TID or 735 mg TID
>1650 mg	980 mg TID

As noted above, in this trial, patients were to have their IR dose optimized in a three week phase prior to conversion to (b) (4). The following Sponsor charts displays patients’ IR doses before and after this 3 week “optimization” phase:

PROTOCOL IPX066-B09-02: FINAL POST TEXT REPORT

TABLE 14.1.3.1 (Page 1 of 1)
Distribution of Total Daily Dose of IR CD-LD Pre Randomization
(All Enrolled Subjects)

Total Daily Dose	Screening (N=471)	Enrollment (V1) (N=471)	End of Dose Adjustment (V2) (N=450)
< 400	0	0	0
400 to < 800	264 (56.1%)	258 (55.0%)	221 (49.3%)
800 to < 1200	134 (28.5%)	136 (29.0%)	146 (32.6%)
>= 1200	73 (15.5%)	75 (16.0%)	81 (18.1%)
Missing	0	2	2
N (%)	471 (100%)	469 (99.6%)	448 (99.6%)
Mean (SD)	789.6 (374.5)	794.3 (364.2)	825.4 (360.4)
Median	750.0	750.0	800.0
(Min, Max)	(400, 3600)	(400, 3000)	(400, 2550)

TABLE 14.1.3.4 (Page 1 of 1)
Distribution of Change in Dosing Frequency of IR CD-LD Pre Randomization
(All Enrolled Subjects)

Change in Dose	Change from Screen to V2 (N=471)	Change from V1 to V2 (N=471)
Decreased	21 (4.5%)	16 (3.4%)
Remained the Same	362 (77.2%)	385 (82.4%)
Increased	86 (18.3%)	66 (14.1%)
Missing	2	4
N (%)	469 (99.6%)	467 (99.2%)
Mean (SD)	0.2 (0.7)	0.1 (0.6)
Median	0.0	0.0
(Min, Max)	(-4, 5)	(-4, 4)

The following chart displays the flow of patients through the study:

Enrolled into IR dose adjustment Phase	471
Discontinued during IR dose adjustment	21
Entered conversion to (b) (4) phase	450
Discontinued during conversion phase	57 (23 due to adverse events; 2 deaths)
Randomized to (b) (4)	201
Completed	186
Randomized to IR CD/LD	192
Completed	182

The following chart displays the results of the primary, as well as other, analyses (taken from Table 9, Dr. Massie’s review, page 24):

	(b) (4)		IR	
	Baseline	EOS	Baseline	EOS
Percent Wake Time In “Off”	36.9	23.8	36	29.8
Hours “Off”	6.1	3.9	5.9	4.9
“On with No or Non-Troublesome Dys” (hours)	10	11.8	10.1	10.9

These comparisons were highly significant (<0.0001, <0.0001, and 0.0002, respectively). The comparisons became significant at the first post-randomization visit, 3 weeks after randomization (see Figure 3, Dr. Massie’s review, page 25). In addition, analyses of the percentage of patients who had decreases in “Off” times of at least 1, 2, and 3 hours showed highly significant results (see Sponsor’s Table 23, as reproduced in Dr. Constantino’s review, page 67). Analyses of various UPDRS scores were also statistically significantly in favor of (b) (4) (see Sponsor’s Table 24, reproduced by Dr. Constantino, page 68 of her review), as were analyses of patient- and clinician-rated global scores (see Dr. Constantino’s review, page 70).

Study 06

This was a two-period (each treatment period 2 weeks) counterbalanced cross-over study in patients receiving a stable dose of carbidopa/levodopa/entacapone (CLE) prior to study who received (b) (4) (and CLE placebo) and CLE (and (b) (4) placebo) during the two treatment periods. The periods were separated by a one-week open label washout. A total of 91 patients were randomized: 48 to (b) (4) CLE (45 completed) and 43 to CLE-(b) (4) (39 completed). The primary outcome was the Percent of Wake Time Spent “Off”. The results were highly statistically significant in favor of (b) (4) as shown below:

Mean Percent of Wake Time Spent “Off”

(b) (4)		CLE		P-value
Baseline	End	Baseline	End	
36.1	22.8	24	32.5	<0.0001

Safety

A total of 1098 patients/subjects received at least one dose of (b) (4). In early PD patients, 265 and 201 patients received at least 6 months and one year of treatment, respectively. For advanced PD patients, 330 and 78 patients were treated for at least 6 months and one year, respectively.

A total of 180 patients received at least 1170 mg of LD/day for 6 months to 1 year, and 132 patients received at least 1170 mg of LD/day for greater than one year.

Deaths

There were a total of 11 deaths in the development program. None were clearly related to treatment. Three deaths occurred in controlled trials. A 73 year old woman in Study 05 who was treated for 16 days, and who died 17 days after drug discontinuation from non-Hodgkin's lymphoma. Two patients died in Study 02: a 70 year old man with a history of aortic stenosis who received 30 days of treatment in the Conversion phase (1365 mg LD/day) who became short of breath with chest pain and collapsed; autopsy confirmed severe aortic stenosis; and a 74 year old woman with chronic pyelonephritis who received 6 days of treatment in the Conversion phase (3920 mg LD/day) who developed aggravated pyelonephritis with elevated creatinine, urea, and urine nitrogen; cause of death was listed as renal insufficiency.

A total of 3 deaths were considered of cardiac causes (MI, CAD, aortic stenosis), 2 respiratory (pneumonia, aspiration pneumonia), and one each due to sudden unexplained death, lymphoma, acute pancreatitis, stroke, renal insufficiency, and immobility and fracture due to PD.

Serious Adverse Events (SAEs)

There were few SAEs.

In Study 05, there were SAEs in 3.8% of (b) (4) treated patients, compared to 3.3% of placebo patients. SAEs were not dose related, and did not appear to be obviously drug-related. In Study 02, 5.5% of (b) (4) treated patients, and 2.6% of placebo-treated patients experienced an SAE during the Maintenance phase; 3.6% of patients experienced an SAE during conversion to (b) (4). In Study 02, specific SAEs typically did not occur more than once or twice, and would not be unexpected for an LD containing product (e.g., nausea, vomiting, acute psychosis).

Discontinuations

In Study 05, a total of 14% and 15% of (b) (4) treated patients discontinued treatment due to adverse events (AEs) in the 245 and 390 mg dose groups, respectively, compared to 4.3% in the placebo group. Most of these occurred in the titration phase, and in the highest dose group; the most common AEs were nausea and vomiting, followed by dizziness. In Study 02, 1.1% of patients discontinued the drug during the conversion phase; the most common event causing discontinuation was Dyskinesia (N=5). In the Maintenance phase of Study 02, an equal number of patients (1.5%) in both groups discontinued due to an AE.

Common Adverse Events

Adverse events were more common in the (b) (4) treated patients compared to the placebo-treated patients.

In Study 05, the most common (in descending order) were nausea, headache, dizziness, insomnia, abnormal dreams, dry mouth, vomiting, constipation, dyskinesia, and orthostatic hypotension. Most of these were dose related (see Sponsor Table 56, reproduced in Dr. Constantino's review, page 112). Nausea and vomiting were more common during the titration phase compared to the Maintenance phase.

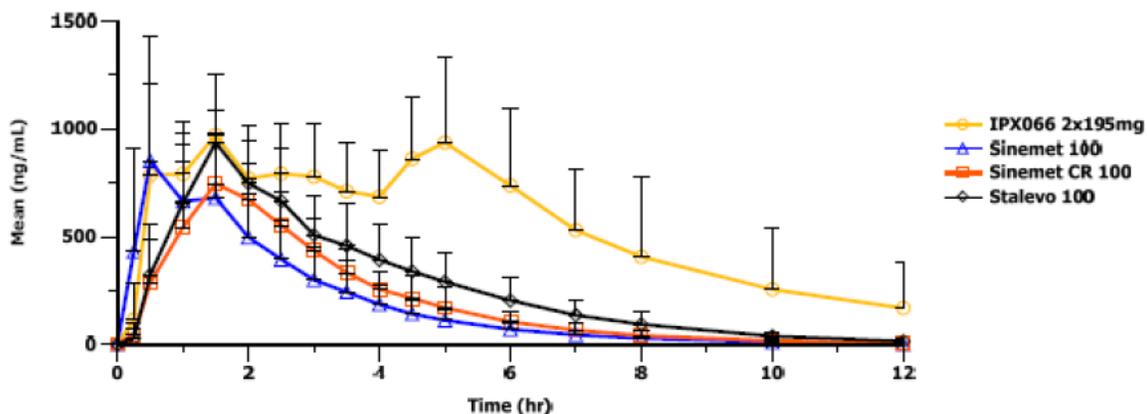
In Study 02, during the Maintenance phase, adverse events that were more common in the (b) (4) treated patients compared to the IR-treated patients were insomnia (most common, at 3.5% compared to 1% in the IR patients), nausea, falls (3% compared to 2.1%), dizziness, dyskinesias, and diarrhea. During the conversion phase, the most common AEs were dyskinesia (5.6%), nausea (5.3%), headache (4.2%), dizziness (3.8%), "On" and "Off" (3.1%), and falls (2.7%).

AEs of Special Interest

Dr. Constantino examined the incidence of several AEs known to be associated with LD-containing products. She reports an incidence of about 2% of hallucinations in both the conversion and maintenance phases of Study 02, as well as 4 cases of Impulse Control Disorder in (b) (4) treated patients (compared to none in the IR-treated patients). Further, there were 4.5% of (b) (4) compared to 1% of IR-treated, patients who were potentially symptomatic of orthostatic hypotension.

Clinical Pharmacology

The relative bioavailability of LD when (b) (4) is given is about 70% of that relative to Sinemet IR in patients with PD. Following multiple dosing, the AUC_{0-12} after a 245 mg dose of (b) (4) was about 13,400 hr.ng/mL, compared to an AUC_{0-12} of about 13,800 hr.ng/mL after a 250 mg dose of IR CD/LD, though the shapes of the curves are different, as seen in the following Sponsor graph, taken from Dr. Parepally's review, page 19 (note that the doses of LD from (b) (4) and the Sinemet formulations are quite different):



The C_{max} of LD from a 245 mg dose of (b) (4) is about 2100 ng/mL, compared to a C_{max} of about 4000 ng/mL from a 250 mg dose of IR CD/LD; the LD % fluctuation was about 1.6 from (b) (4) compared to about 4 from IR CD/LD.

Non-clinical

There is a single non-clinical issue that requires discussion.

The product contains numerous excipients; the one of interest for our purposes is the co-polymer (b) (4). Although the sponsor asserts that the amount of this excipient (and others) does not exceed the maximum amount listed in the Inactive Ingredients Database (IID), these amounts would be exceeded at the maximum proposed dose (15, 61.25/245 mg capsules). This dose would result in a daily dose of (b) (4) or (b) (4) mg. As pointed out by Dr. Freed, on a per capsule basis, the amount of (b) (4) is no greater than that in approved drug products, but, as noted, on a daily dose basis, this would exceed the amount in any approved drug product.

In addition, clear systemic effects (thyroid activation) of (b) (4) were seen in mouse, rat, and rabbit. This is unexpected, given that the bioavailability of this excipient is expected to be quite low (this has been demonstrated for (b) (4) (also contained in this product; (b) (4) differ only in the ratio of the two component monomers, (b) (4), respectively).

As noted by Dr. Freed, the NOAEL for this thyroid finding is 100 mg/kg/day in the mouse, the most sensitive species. The safety margin calculated with mg/kg dosing at the sponsor's maximum recommended dose is about (b) (4). However, given that we believe the thyroid finding is a systemic finding, the more appropriate units with which animal and human exposure should be predicted (and compared) is mg/m²: when this is done, there is no margin between the calculated exposures between the animal NOAEL and that at the proposed maximum human dose. Further, although thyroid activation was not detected at 30 days and 6 weeks in the rat and dog up to 2000 mg/kg/day (the NOAEL in the

rat was determined in a 6 month study), mouse and rabbit were not tested in chronic studies (they were each tested in a single 6 week study), so it is unknown if the NOAEL would remain the same, or decrease, with chronic exposure in these species.

Inspections

The application contained two sites of drug manufacture at the time of the NDA submission: one in Hayward, CA, and one in Taiwan. Previous inspections of general CGMP functions at the Hayward location (12/3-10-1/21/11 and 2/23-3/28/12) revealed numerous significant deficiencies. Based on the results of the first inspection, the inspection was classified as Official Action Indicated (OAI) and the Agency issued a Warning letter on 5/31/11; deficiencies noted in that letter included failure to monitor and validate manufacturing processes, and the firm's failure to adequately investigate batch failures. Subsequent to the issuance of the Warning letter and the second inspection, members of the San Francisco District Office met with representatives of the company on June 12, 2012 to discuss these continuing deficiencies noted by the Agency.

On 12/6/12, the sponsor submitted an amendment stating that they were removing the Hayward site from the NDA. However, the Agency is currently re-inspecting the Hayward site at the time of this writing; this inspection relates to product-specific, as well as general CGMP, issues. Although this inspection is not completed, Agency inspectors have determined that, despite the sponsor's 12/6/12 amendment, considerable analytic work on product manufactured at the Taiwan site is still being performed at the Hayward site. As noted above, serious deficiencies have been noted at this latter site, and these have not yet been documented to have been resolved (preliminary results of the on-going inspection suggest numerous deficiencies still exist at the Hayward site). Based on all the available data, the District Office, and the Office of Compliance have recommended that the application not be approved at this time.

Comments

The sponsor has submitted the results of two adequate and well-controlled clinical trials that provide substantial evidence that (b) (4) is effective in the treatment of early and advanced PD. It should be noted that this application has been submitted as a 505(b)(2) application, referencing numerous CD/LD product NDAs. (These products are approved for numerous indications in addition to PD. Although (b) (4) has not been studied in these other indications, it is reasonable to conclude that, if these other products are effective for these indications, (b) (4) . In addition, the available clinical data have not raised any safety signals that would preclude approval.

There are several issues that need to be addressed.

First, as described above, patients receiving doses at the higher end of the recommended dose range will be exposed to higher levels of (b) (4), for longer durations, than is the case for patients taking other medications that contain this excipient. Also as noted above, animal studies do not provide any margin between the NOAEL for thyroid activation in the most sensitive species and levels of the (b) (4) that we expect humans to be exposed to. However, as Dr. Freed notes in her memo of 1/18/13, given the expectation of minimal bioavailability of the (b) (4) (this has been documented for the related (b) (4)), and the age of the animal studies (1984-1989), it is possible that the thyroid changes seen (in our view, evidence of a systemic effect) were due to an unidentified impurity, and that, therefore, we should require additional non-clinical studies before we definitively conclude that (b) (4) is causing the thyroid changes, and that this can be done in Phase 4 as Post-Marketing Requirements (PMRs). I would also add that another factor that argues for requiring these studies in Phase 4 is that the sponsor has demonstrated that, under at least certain circumstances, (b) (4) is superior to IR CD/LD (this was shown in Study 02; it is worth noting in this regard that the minimal changes in dosing during the 3 weeks of the IR optimization phase in this study suggest that these patients were more or less optimally controlled prior to having been randomized). For these reasons, then, I agree that these non-clinical studies can be performed as PMRs. Indeed, the sponsor and the division have agreed that two non-clinical studies will be done as PMRs: 1) an oral absorption study, and 2) a six-month oral toxicity study in rat.

The final issue that needs to be addressed is the issue of the inspectional results.

As described above, the district office has, in two past general CGMP inspections of the Hayward manufacturing site, found significant deficiencies in critical analytic processes. These deficiencies have led to the issuance of a Warning letter (after the first inspection) and a regulatory meeting with the sponsor (after the second inspection). In the view of the district office and the Office of Compliance, these deficiencies have not been determined to have been resolved. Further, preliminary results of an on-going inspection of the product-specific processes at the Hayward site suggest continued problems, and, although the sponsor submitted an amendment withdrawing the Hayward site from the NDA, they are still doing analytic work on product manufactured in Taiwan. Until and unless the Agency can determine that the Hayward site is satisfactory (presumably unlikely at this time, based on the preliminary results), the application cannot be approved. Further, the inspectional findings may raise significant questions about the acceptability of the product made in Taiwan (since the analyses of this product are performed in Hayward), and, indeed, because much of the CMC data (e.g., stability, methods validation) is brought into question by the (past, and possible current) deficiencies at Hayward, it is not clear at this time whether many of the critical CMC tests will need to be repeated.

In addition, whether any of these findings bring into question the results of the clinical studies remains to be seen.

Recommendation

Although the sponsor has provided substantial evidence of effectiveness of (b) (4) in patients with PD, and no unacceptable clinical safety signals have been noted, there are as yet unresolved manufacturing deficiencies noted on several inspections of the Hayward, CA site that raise critical questions about much of the CMC data submitted in the application. For this reason, then, I will issue the attached Complete Response (CR) letter. Given that another inspection is still on-going, we will not be able to inform the sponsor, at this time, what, if any, deficiencies still exist, and what the ramifications of any such deficiencies will be with regard to any additional requirements; that determination will have to await a final Agency decision about the results of the on-going inspection.

Russell Katz, M.D.

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

/s/

RUSSELL G KATZ
01/18/2013

Cross-Discipline Team Leader Review

Date	1/18/2013
From	Gerald D. Podskalny, DO, MS.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 203312
Supplement#	
Applicant	Impax
Date of Submission	12/21/2011
PDUFA Goal Date	1/21/2013 with extension
Proprietary Name / Established (USAN) names	Rytary/Carbidopa levodopa extended release capsules
Dosage forms / Strength	RYTARY 23.75 mg / 95 mg, RYTARY 36.25 mg / 145 mg RYTARY 48.75 mg / 195 mg, RYTARY 61.25 mg / 245 mg
Proposed Indication(s)	1. Parkinson's disease
Recommended:	<i>Complete Response</i>

1. Introduction

Impax submitted a 505(b)(2) New Drug Application (NDA) for a new carbidopa levodopa extended release capsule, IPX066 (Rytary). The application included results from new efficacy studies to support an indication for patients with early and advanced Parkinson's disease (PD). The sponsor is relying on non-clinical Agency's approval and information contained in the Sinemet, Sinemet CR and Stalevo labels and non-clinical information in published reports. The Sponsor's proposed indication under consideration [redacted] (b) (4) in the approved Sinemet label.

"Rytary (Carbidopa Levodopa extended release) is indicated (b) (4) the treatment of (b) (4) Parkinson's disease (b) (4), postencephalitic parkinsonism and (b) (4) parkinsonism (b) (4) may follow injury to the nervous system by carbon monoxide intoxication (b) (4) or manganese intoxication."

2. Background

Impax submitted a 505(b)(2) NDA for IPX066 for treatment of patients with PD. The application relies on the approval and information contained in the labels for Approved carbidopa and levodopa containing products including Sinemet (Merck), Sinemet CR (Merck) and Stalevo (Novartis). The Application references the Lodosyn (carbidopa) in the application but the reliance on Lodosyn is not appropriate because applicant did not reference information unique to the Lodosyn label. Lodosyn is an adjunctive medication that is used in addition to Sinemet. The Lodosyn label relies largely on information contained in the Sinemet label.

The non-clinical and manufacturing site GMP compliance issues caused the greatest concern during the review of this application. The nonclinical issues centered on [redacted] (b) (4) and [redacted] (b) (4) (methacrylic acid copolymer [redacted] (b) (4)). [redacted] (b) (4)

The copolymers help provide the

(b) (4) properties of IPX066 and they are responsible in part, for the (b) (4) characteristics of IPX066. The amount of (b) (4) present in final product (b) (4) the amounts currently supported by nonclinical studies or by previous human experience at the maximum dose described in the proposed product (15 capsules/day of the 61.26/245 mg capsules).

The sponsor submitted the results from two pivotal controlled clinical trials. The first was study IPX066-B08-05 in patients with Early Parkinson's disease (placebo control) and study IPX066-B09-02 a study to evaluate the safety and efficacy of IPX066 in Advanced Parkinson's disease (active control). Study IPX066-B09-06 enrolled patients who were maintained on a stable non-optimized dose of Carbidopa Levodopa Entacapone (CLE) for 1-month prior to entering the IPX066 Dose Conversion Phase. Next, patients were randomized to either their optimized dose of IPX066 or their non-optimized dose of CLE. The application included long-term, open label safety information in the form of an interim report for study IPX066-B09-03. Patients who completed studies IPX066-B08-05 (early PD) an IPX066-B09-02 (advanced PD) were eligible to enroll in study IPX066-B09-03. In addition, patients from study IPX066-B08-11, a randomized, open-label, multicenter, two-period, crossover pharmacokinetics and pharmacodynamics study of IPX066 versus IR CD-LD in subjects with advanced PD with motor fluctuations, were also invited to enroll in IPX066-B09-03. The Sponsor's 120-day safety update primarily included additional information from patients enrolled in IPX066-B09-03. A small number of additional patients taking open-label IPX066 from trials IPX066-B09-06 Part 2 and IPX066-B11-01 was included in the 120-Day Safety Update.

The application deadline was extended for 3 months due to a late review cycle submission of a Major Amendment from Impax to address the nonclinical findings and the potential relevance to humans.

Late in the review period, The Office of Compliance made the NDA review team aware of possible data integrity problems with the analytical procedures performed at the Impax manufacturing site in Hayward, California. The NDA was submitted with the Hayward site in OAI status following an initial FDA inspection. The Hayward facility was reinspected in July, 2012 (during the NDA review cycle) and the GMP issues were not fully corrected and the OAI status was not lifted. In response, Impax removed their Hayward, California site from the application relying on the Impax, Jhunan Taiwan site for product manufacturing. By removing the Hayward site all cGMP activities for the product would be conducted in Impax, Taiwan. The Taiwan facility was inspected prior to the NDA submission however, access to information for cGMP verification for production methods and validation conducted at the Taiwan facility were not available to the Agency's inspectors. The sponsor referenced the production methods and validation used in the Hayward facility as being the same that were used in the Taiwan facility. However, the product methods and validation in the Hayward facility were found to be deficient by the Agency. These deficiencies were in part, the basis for the Agency's OAI action. By withdrawing the Hayward, California site, the sponsor is no longer able to conduct CGMP related activities related to the manufacture of IPX066 at the site. The Agency is in the process of re-inspecting (unannounced) the Hayward facility late in the review cycle.

1. CMC/Device

Drug Substances

The primary CMC reviewer for this application is Charles F. Jewell Jr., supervisory sign-off was through Ramesh K. Sood. The levodopa drug substance suppliers for IPX066 are (b) (4). The Agency's CMC review staff concluded that DMFs (# (b) (4) and # (b) (4)) referenced for both levodopa drug substance suppliers were adequate for other approved oral drug formulations drug and they considered the DMFs for (b) (4) levodopa drug substances are acceptable.

Levodopa

The CMC reviewer concluded the "stability data supports a retest period of (b) (4) months for (b) (4) material and (b) (4) months for (b) (4) drug substance. Levodopa has a USP monograph and both producer supplied materials meet the limits of the USP specification".

(b) (4) DMF (b) (4) described complete information on impurities for their version of the drug substance. Potential impurities related to the drug substance are degradation products. Inorganic impurities are tested for by USP procedures for heavy metals and residue on ignition. (b) (4) uses only (b) (4) in the manufacture of levodopa and these are controlled below the ICH Q3C guidance limits.

(b) (4) DMF (b) (4) described complete information on impurities for their version of the drug substance. Potential impurities related to the drug substance are degradation products. Inorganic impurities are tested for by USP procedures for heavy metals and residue on ignition. (b) (4) uses only (b) (4) (no organic solvents) in the manufacture of levodopa and this is monitored by using the USP (b) (4).

Carbidopa

The CMC reviewer concluded carbidopa in the form of a mono-hydrate is supplied by (b) (4) and (b) (4). The DMFs (# (b) (4) and # (b) (4) respectively) have been reviewed and are found to be adequate. Carbidopa has a USP monograph and both producer supplied materials meet the limits of the USP specification. Carbidopa has one major degradant, (b) (4) that is adequately controlled in the drug substance. The growth of (b) (4) is a critical consideration for the drug product stability. Stability data supports a retest period of (b) (4) months for the (b) (4) material and the (b) (4) material.

Drug Product

IPX066 is a multi-particulate extended release product. It is designed to release carbidopa and levodopa over a (b) (4) period. Four CD-LD capsules strengths were produced and all are intended for marketing under the NDA. All strengths dose proportional with the fixed ratio of CD/LD being 1:4. Each capsule also contains tartaric acid (TA) (b) (4).

Table 1: Description of Each Capsule Strength (Sponsor's Table)

mg CD/ mg LD	Capsule Size	Capsule Body Color	Capsule Cap Color
23.75/ 95	2	White (b) (4)	Blue (b) (4)
36.25/145	1	Light Blue (b) (4)	Blue
48.75/195	0EL	Yellow (b) (4)	Blue
61.25/245	00	Blue (b) (4)	Blue

There are (b) (4) components to the product:



Beads containing the different drug substances are coated to confer the different release properties (dissolution) and different amounts of each components are loaded into the appropriate size hard gelatin capsule.

Table 2: Summary of Key Attributes of Each Component (Sponsor's Table)

Component ID	Attributes
(b) (4)	

Table 3: Composition of Each Filled Capsule (Sponsor’s Table)

Ingredient	%w/w	IPX066 Fill Weight (mg / Capsule)			
		IPX066 23.75 CD / 95 LD mg	IPX066 36.25 CD / 145 LD mg	IPX066 48.75 CD / 195 LD mg	IPX066 61.25 CD / 245 LD mg
(b) (4)					
Total-Capsule	100.00	261.80	399.58	537.37	675.16
Hard Gelatin Capsule		White (b) (4) Body with Blue (b) (4) Cap, Size 2	Light Blue (b) (4) Body with Blue (b) (4) Cap, Size 1	Yellow (b) (4) Body with Blue (b) (4) Cap, Size 0EL	Blue (b) (4) Body with Blue (b) (4) Cap, Size 00

CMC Reviewer Comments:

Hard gelatin capsules shells used in this drug product are non-compendial. They are manufactured by (b) (4) and reference in DMFs (b) (4). All ingredients in the capsule shells conform to USP/NF standards as well as the Code of Federal Regulations. Certification is provided by the applicant from the supplier (dated August 2011) demonstrating compliance with considerations minimizing the risk (b) (4)

Key Excipients

All excipients used in the IPX066 formulation are USP/NF grade except the capsule shells. The applicant claims that in the final formulation all excipients are present in amounts recognized by the FDA as safe (GRAS) as referenced in the US CFR 21 CFR Part 182, 184 and 186, the FDA Inert Ingredient Guide, and Handbook of Pharmaceutical Excipients, 5th Edition

The CMC reviewer commented that (b) (4) methacrylic acid copolymers (b) (4) and triethyl citrate may be in amounts that lead to unprecedented expose levels to these excipients, it depends on the dose levels of the individual patients.

Release Specifications

The CMC reviewer concluded the applicant has adequately justified the drug product specifications. The Pharmaceutics/toxicology reviewer found the (b) (4) limits adequate and the ONDQA biopharmaceutics reviewer has found the dissolution method justification adequate after discussion with the applicant.

Shelf-life

Dr. Jewell noted that the individual drug product components are manufactured and stored until they are loaded into capsules. Initially, the applicant proposed shelf life period that started (b) (4)

The Agency recommended that expiration dating start with the (b) (4) The applicant agreed but they still recommended marking expiration dating from packaging of drug product (this was used for long-term stability, plus 6 months to cover hold times for components and bulk capsules). The company was informed, that although expiration dating is set by stability studies, (b) (4)

CMC Recommendations regarding Shelf-life

The registration stability data coupled with statistical analysis supports (b) (4) of stability. It is likely that as more long-term storage conditions stability data becomes available, that this will increase.

Drug Product Manufacturers

The application included 2 drug substance manufacturing and analytical facilities. Both facilities were inspected by compliance. The Impax site in Hayward, California was cited for deficiencies (OAI) and upon re-inspection a form 483 was issued for unrelated deficiencies. The Impax site in Taiwan was initially issues a Form 483 following a pre-approval, new facilities cGMP inspection but these issues (VAI) were resolved on follow-up inspection.

Impax Laboratories, Inc., Hayward, CA, USA, has the following responsibilities:

- Manufacture of drug product.
- Release testing of components and drug product to packaging.
- Storage of stability samples and stability testing of the drug product.

Impax Laboratories Taiwan, Inc., Jhunan, Taiwan, has the following responsibilities:

- Manufacture of drug product.
- Release testing of components and drug product to packaging.
- Storage of stability samples and stability testing of the drug product.
- Global Pharmaceuticals, Division of Impax Laboratories, Inc. Philadelphia, USA has the following responsibilities:
- Package and release of drug product to commercial distribution.

Facilities Inspections

The Drug Manufacturing facilities are listed below in a table taken from Dr. Jewell's CMC review.

The Hayward, California manufacturing site was inspected by the Office of Compliance (OC). The initial inspection resulted in an OAI recommendation. The facility was re-inspected July XXX 2012 and a Form 483 was issued for issues unrelated to the OAI problems.

Establishment:

IMPAX LABORATORIES
31153 SAN ANTONIO STREET
HAYWARD, CA 94544

FINISHED DOSAGE MANUFACTURER

OAI Status: Official Action Indicated (OAI) ALERT

Establishment:

IMPAX LABORATORIES (TAIWAN) INC.
NO 1, KE DONG 3RD RD
JHUNAN, MIAO-LI COUNTY, TAIWAN, PROVINCE OF CHINA

FINISHED DOSAGE MANUFACTURER, FINISHED DOSAGE RELEASE TESTER, FINISHED DOSAGE STABILITY TESTER, DRUG PRODUCT MANUFACTURER, LOT, RELEASE TESTING, STABILITY TESTING.

OAI Status: NONE

INSPECTION PERFORMED

NEW PROFILE

This is a comprehensive pre-approval and cGMP Establishment Inspection (EI) of a foreign finished oral dosage pharmaceutical manufacturer relating to FDA review of NDA 203312, IPX066 carbidopa- levodopa extended release capsules (b) (4) submitted by Impax Pharmaceuticals, Inc. (USA). The inspection was initiated through DFI per FACTS assignment # (b) (4). This inspection was conducted in accordance with CPGM 7356.002, Drug Manufacturing Inspections and CPGM 7346.832 Pre-Approval Inspection (PAI). This inspection covered Quality, Facilities and Equipment, Production, Materials, and Laboratory Control systems. Profile Class CTR and TCM were covered. PAC Code covered for this inspection is 46832, 52832, and 56002.

The previous inspection was conducted (b) (4) and classified as VAI. A 7-item FDA-483 for the following: (b) (4)

(b) (4) The current inspection followed up on these items, the firm had corrected these previous deficiencies, and they appeared to be acceptable.

CDTL Comments

As the review of this application progressed the on going re-inspection of the Impax, Hayward, California site found that cGMP activities for the manufacture of IPX066 continues to take place at the site. The recommendation from the Office of Compliance is that at least the method validation and stability data were and still are being conducted at the Hayward facility. The Hayward facility is not compliant and is still in OAI status. The validation methods at the Impax, Taiwan facility are the same as those used in the Hayward facility and are expected to have the same deficiencies. The site in Taiwan was not inspected for changes in validation methods that may have been implemented at the Taiwan facility to correct deficiencies discovered at the Hayward site. The methods validation and stability data included in the CMC section of the NDA was generated at the Hayward facility that remains in OAI status. It is likely that the same noncompliant manufacturing processes were used in the manufacture of the product used in the clinical development program. How this may have affected the ability to rely the CMC information provided in the NDA and the performance of the IPX066 in the pivotal clinical trials can only be determined after the Office of Compliance is able to complete their on going inspection.

CMC Reviewer's Initial Conclusions (Dr. Jewell)

“All reviewed data supports the approvability of this application from the CMC perspective, except the Establishment Evaluation System (EES) recommendation from the Office of Compliance, which is still pending, due to a pending alert at one site (manufacture of drug product in Hayward, CA) and results from inspection at two sites (manufacture of drug product in Taiwan (b)(4)). The CMC reviewer will provide an update review prior to the PDUFA date to indicate an update of status on the pending inspections, and thus the ultimate approvability of the application from the CMC perspective.”

CDTL Comment

There is agreement among the CMC review team members, Office of Compliance and Clinical review team that the findings from the facilities inspections of the Hayward, California site are a significant concern. The Hayward facility remains in OAI status and the initial finding from the on going inspection indicate the facility will remain in OAI status. The manufacturing and validation methods and the product stability data provided in the NDA may be unreliable; therefore, there was no need for alignment of the recommended regulatory action from CMC.

6. Nonclinical Pharmacology/Toxicology

Dr. Luann McKinney DVM completed the primary nonclinical review and Dr. Lois Freed, PhD, provided a nonclinical supervisory memorandum and an addendum. The Sponsor did not submit information from new nonclinical pharmacokinetic or toxicological studies for this 505(b)(2) application. The submission relies on the non-clinical information contained in the labels of the referenced drugs Sinemet, Sinemet CR and Stalevo and information the Sponsor submitted from a review of the published medical literature. The Sponsor concluded there are no new relevant findings regarding the pharmacokinetics of Levodopa or Carbidopa that would influence the IPX066 label.

The sponsor submitted an LOA dated 12/18/2008 referencing information in the Drug Master File (DMF # (b)(4)) held by (b)(4), (b)(4), prepared a report summarizing the

non-clinical information and findings referenced in the (b) (4) DMF supporting the use of (b) (4) in the drug product. Dr. McKinney pointed out in her review, the report by (b) (4) summarized 23 nonclinical studies that Impax referenced to support the use of (b) (4) in IPX066 but it “*did not assess the studies for validity, integrity, or quality of the data. As such, the summary offers only an informed opinion.*”

Triethyl citrate and (b) (4) tartaric acid is recognized as GRAS by the FDA. The amount of triethyl citrate contained in the “To Be Marketed” product at the maximum dose described in the proposed product is within the limits of the GRAS specification. However, the amount of (b) (4) tartaric acid patients may take in a day is far greater than the maximum amount included in the GRAS designation (0.2 g/day). Drs. McKinney and Freed concluded the maximum amount of (b) (4) Tartaric acid in the to be marketed product does not pose a safety concern citing opinions of SCOGS and JECFA based on a 2-year study in rat 2.64-3.2 g/kg/day) and a 150-day study in rabbit (max dose 2.3/gm/kg/day) where the animals far higher doses

Drs. Freed and McKinney conclude, the daily dose of (b) (4) in approved oral drugs is greater than the amount in the daily maximal dose of IPX066 (Rytary) and, in the absence of evidence of absorption or systemic effects from oral administration of the excipient, the levels of (b) (4) in IPX066 (Rytary) are not of toxicologic concern.

However for (b) (4), the nonclinical study results indicated there was dose related changes (activation) in the thyroid gland associated with oral administration of (b) (4) in mice, rats and rabbits. The DMF summary provided by (b) (4) (presented in the NDA) concluded (b) (4) are high molecular weight copolymers that are not absorbed in significant amounts. However, in the Sponsor’s summaries (NDA and (b) (4)) they acknowledge there were dose dependent changes in the thyroid in rodents (mice and rats) and rabbits. The Sponsor’s concludes, “*The dose-response relationship relating to thyroid findings in the rodents and rabbits may not be directly applicable to humans owing to significant species differences in the regulation of thyroid function*”. The presence of these changes in mice, rats and rabbits and findings consistent with dose dependent effects suggest that the method for calculating a NOAEL and the human equivalent dose (HED) is conceptually incorrect. The historical and current method based on calculations in mg/kg is not the correct method, if the change in the thyroid is considered a systemic adverse effects and an approach that uses mg/m² is the correct method for calculating the NOAEL and HED. Calculation of the estimated margin between the nonclinical NOAEL and the highest supported dose in humans should use the mg/m² method. The position is reasonable when the persistent (across species) and dose dependency nature of the thyroid abnormality is considered however, if the mg/m² method is used to calculate the HED there is little if any safety margin. Under these conditions the total daily dose of (b) (4) in the IPX066 (Rytary) exceeds that of approved oral drugs by (b) (4) fold.

Dr. Freed notes in her Supervisory Memorandum, “*the thyroid findings would suggest systemic, not local, effects; therefore, body surface area comparisons appear the more appropriate. In addition, due to the high molecular weight of (b) (4), systemic toxicity is unexpected and would argue for a more thorough assessment of toxicity, e.g., a chronic toxicity study in non-rodent.*”

The (b) (4) (submitted in the major amendment) also described inconsistencies in the reported results of a *“Two 6-month oral toxicity studies were performed with (b) (4). One of these studies with a dose range of 10 – 100 mg/kg/d resulted in a NOAEL of 100 mg/kg/d, as no adverse effects were observed. In the other study (dose range 200 – 1500 mg/kg/d, animals treated with dosages of 200 mg/kg/d and more showed a tendency towards an activation of the thyroidal epithelium. According to the manufacturer of the copolymer and sponsor of this study (b) (4), re-evaluation of findings from the later, high-dose study led to the conclusion that there were documentation deficiencies, which restricted the validity of this study. Details were not provided by the manufacturer.”* A second information request was sent to the sponsor to clarify the inconsistencies in the (b) (4) DMF that were not explained in the materials submitted in the NDA.

Dr. McKinney recommended approval of the application. Dr. Freed, provided a Supervisory Non-clinical Pharmacology/Toxicology memorandum that raised additional concerns regarding the importance of findings in the thyroid suggesting toxicity reported in studies of mouse, rat and rabbit. Dr. Freed and Dr. McKinney expressed concern about the maximum amount of (b) (4) and the finding in the thyroid in multiple animal species.

CDTL Comments

Drs. Freed and McKinney agree that the application may be approved however, as Dr. Freed points out, the non-clinical safety information concerning (b) (4) needed to fully supports and the safe use of the maximum amount that can be taken in IPX066 is lacking. However, there are approved products that contain (b) (4) in amounts that approach those contained in IPX066, at the maximum dose described in the proposed label. The sponsor argues that both (b) (4) are not absorbed and the thyroid changes observed in animals are due to a stress reaction.

The review team met to discuss the issue and agreement was reached of a recommendation for approval. However, postmarketing requirements should be imposed for additional non-clinical studies to study (b) (4) in a relevant species (rat) for a sufficient duration (6-months), at a dose that will support the amount of (b) (4) in IPX066 at the maximum dose (b) (4) of 245 mg IPX066 per day.

The Agency will impose a postmarketing requirement for a non-clinical study to evaluate the potential for systemic absorption of orally administered (b) (4) in animals. A second PMR will be required to evaluate the potential for systemic toxicity in rats given (b) (4) orally for 6-months.

7. Clinical Pharmacology/Biopharmaceutics

The Office of New Drug Quality Assessment (ONDQA) Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer.

Evaluation of the Acceptability of the IVIVC Model

The *in vitro* dissolution data for IPX066 formulations used in the four Phase III studies (IPX066-B08-05, IPX066-B09-02, IPX066-B09-03, and IPX066-B09-06)

Dr. Suarez concluded, the IVIVC model was not acceptable, even though it met criteria for internal and external predictability. *“Several deficiency comments regarding the IVIVC model were sent to*

the Applicant as part of the 74-day letter. The Applicant acknowledged the deficiencies and withdrew the model (refer to communication dated Jul 24, 2012).” The Biopharmaceutical reviewer discussed the IVIVC mode deficiencies with the Sponsor in a teleconference on Aug 7, 2012, and Dr. Suarez provided several recommendations concerning the study design and model development.

The ONDQA-Biopharmaceuticals reviewer noted that Sponsor and Agency agreed on the for Carbidopa+Levodopa fixed dose combination (FDC) extended release (ER) capsules, 23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg (refer to submission dated Aug 24, 2012):

Table 4: Dissolution method and Dissolution Acceptance Criteria

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
Basket/75 rpm	Medium A (Acid phase): SGF (without enzyme) for 120 min then switch to Medium B (Buffer phase): Phosphate buffer 50 mM pH 7.0 for 240 min.	900 mL for all Strength except 500 mL for the Lower strength	Levodopa % Dissolved 30 min: (b) (4) % 120 min: (b) (4) % 180 min: (b) (4) % 360 min: ≥ (b) (4) % Carbidopa % Dissolved 30 min: (b) (4) % 120 min: (b) (4) % 180 min: (b) (4) % 360 min: ≥ (b) (4) % Tartaric Acid % Dissolved 30 min: ≤ (b) (4) % 180 min: (b) (4) % 360 min: ≥ (b) (4) %

Division of Bioequivalence and GLP Compliance (DBGC) Inspection

At the request of the Division of Neurology Products (DNP), the Division of Bioequivalence and GLP Compliance (DBGC) inspected the following BE study:

IPX066-B10-01: “A randomized, single-center, single-dose, open-label, two-sequence, two-treatment crossover study with a 6-day washout between treatment periods in healthy subjects under fasted conditions with an additional treatment after Period 2”

Study IPX066-B10-01 demonstrated the bioequivalence of IPX066 manufactured in Hayward, CA, USA (the manufacturing site for IPX066 supplies used in clinical studies and a planned commercial manufacturing site), and Jhunan, Taiwan (a planned commercial manufacturing site). This study also demonstrated that LD and CD plasma pharmacokinetics from 1 and 2 capsules of IPX066 61.25-245 mg were approximately dose-proportional.

An inspection of (b) (4) was performed on (b) (4). A Form FDA- 483 was issued. The firm’s response was received on August 24, 2012.

The Form FDA-483 observation, (b) (4) response to Form FDA-483 and our evaluation follow:

1. There were inconsistent manual re-integrations of many chromatograms in the method validation (about 142 of 2192 samples) and in study # IPX006-B10-01 (about 387 of 5898 samples), including both quality control and study samples.

In their response to Form FDA-483, (b) (4) provided concentration data obtained from automatic and manual re-integrations, and compared the PK parameters using both data sets. (b) (4) claimed that the use of manual re-integrations had no effect on the validation and study outcomes.

In the opinion of the reviewer, (b) (4) response is adequate.

Conclusion:

The DBGC reviewer recommends that the clinical and analytical data from this study are acceptable for review.

ONDQA-Biopharmaceutics **recommended APPROVAL** of NDA 203-312 for Carbidopa+Levodopa (23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg) fixed dose combination (FDC) extended release (ER) capsules.

Clinical Pharmacology

Jagan Mohan Parepally, Ph.D. completed the Primary Review for the Office of Clinical Pharmacology (OCP). Dr. Li Zhang, PhD completed the Pharmacometrics Review (OPM). Team Leader concurrence was given by Drs. Men (OCP), Wu (OCP) and Bhattaram (OPM).

Pharmacokinetics

The Sponsor's Description of Absorption, Distribution, Metabolism and Excretion of Levodopa from IPX066

Absorption

The absorption of LD occurs through the saturable neutral L-amino acid transport system is nearly complete with less than 2% of the orally administered drug appearing in the feces

Distribution

LD crosses the blood-brain barrier by stereospecific, saturable, facilitated diffusion via the large neutral amino acid (LNAA) transport carrier system. The apparent volume of distribution (V/F) of LD for IPX066 estimated from population pharmacokinetic analysis was 114 L. LD is not bound to plasma proteins to a significant degree therefore; drug interactions due to displacement of protein bound LD is not expected.

Metabolism

LD is the metabolic precursor for dopamine that does not cross the blood-brain barrier. LD undergoes metabolism via four pathways:

- decarboxylation by aromatic amino acid decarboxylase (AAAD),
- 3-O-methylation by catechol-O-methyltransferase (COMT),

- transamination by tyrosine aminotransferase,
- oxidation by tyrosinase or other oxidants.

Approximately 95% of orally administered LD is decarboxylated peripherally (converted to dopamine peripherally) with only 1% of the LD dose available to enter the brain. The initial product of decarboxylation is dopamine dihydroxyphenylacetic acid (DOPAC) that may be further metabolized to form 3,4-, homovanillic acid (HVA), and to a lesser extent, norepinephrine and vanillinemandelic acid.

Excretion

After an oral dose of 50-200 mg Sinemet or Sinemet CR, only $7.2 \pm 2.4\%$ and $3.0 \pm 1.4\%$ of the LD dose was excreted in the urine as unchanged drug. LD in Sinemet CR is less bioavailable compared to Sinemet. The Sponsor cited references from published reports stating the apparent renal clearance of LD averaged 44 ± 19 and 73 ± 29 mL/min in healthy young and elderly subjects, respectively, after a single 50-200 mg dose of Sinemet CR under fasting conditions. Apparent clearance (CL/F) estimated using a population pharmacokinetic analysis for IPX066 was 56.8 L/h (population pharmacokinetic report) and similar to that reported in the literature accounting for differences in relative bioavailability.

The plasma half-life of LD is about 50 minutes however; CD increases the half-life to approximately 1.5 hours.

Carbidopa

The bioavailability of LD is increased 2 to 3 times in the presence of decarboxylase inhibitors such as carbidopa and benserazide.

Carbidopa inhibits aromatic amino acid decarboxylation. When 100 mg ^{14}C -LD was administered with a single 100 mg CD dose or after 100 mg CD t.i.d. for 7 days as compared to 100 mg ^{14}C -LD given alone, the majority of LD (~90%) was converted to 3-OMD by COMT in the peripheral tissues, peak plasma LD levels increased from non-detectable to 0.7 and 1.2 $\mu\text{g/mL}$, 2-hour dopamine levels decreased from 0.3 $\mu\text{g/mL}$ to non-detectable, and peak HVA levels decreased 80% (Bianchine 1972, Bartholini and Pletscher 1975; Dingemanse 2000).

PK Parameters

Table 5: Summary of Carbidopa Pharmacokinetic Parameters for Completed Subjects in Study IPX066-B08-09, Mean ± SD, (N=28) Sponsor’s Table)

PK Parameter	IPX066 95mg	IPX066 145mg	IPX066 195mg	IPX066 245mg
T _{max} (h) ^a	3.50 (1.00 - 6.00)	4.00 (1.50 - 6.00)	3.50 (1.50 - 6.00)	3.50 (2.00 - 6.00)
C _{max} (ng/mL)	39.74 ± 20.02	59.34 ± 30.31	77.30 ± 31.92	94.99 ± 40.03
AUC _{0-t} (ng·h/mL)	175.38 ± 80.93	268.73 ± 125.97	364.81 ± 147.10	432.07 ± 140.51
AUC _{inf} (ng·h/mL)	182.73 ± 81.52	277.87 ± 128.10	374.49 ± 149.72	447.16 ± 146.08
t _{1/2} (h)	1.66 ± 0.32	1.79 ± 0.32	1.69 ± 0.27	1.88 ± 0.47
Dose Proportionality^b				
C _{max}	0.9739 (0.8322-1.1397)			
AUC _t	1.0283 (0.9077-1.1649)			
AUC _{inf}	1.0075 (0.8933-1.1363)			

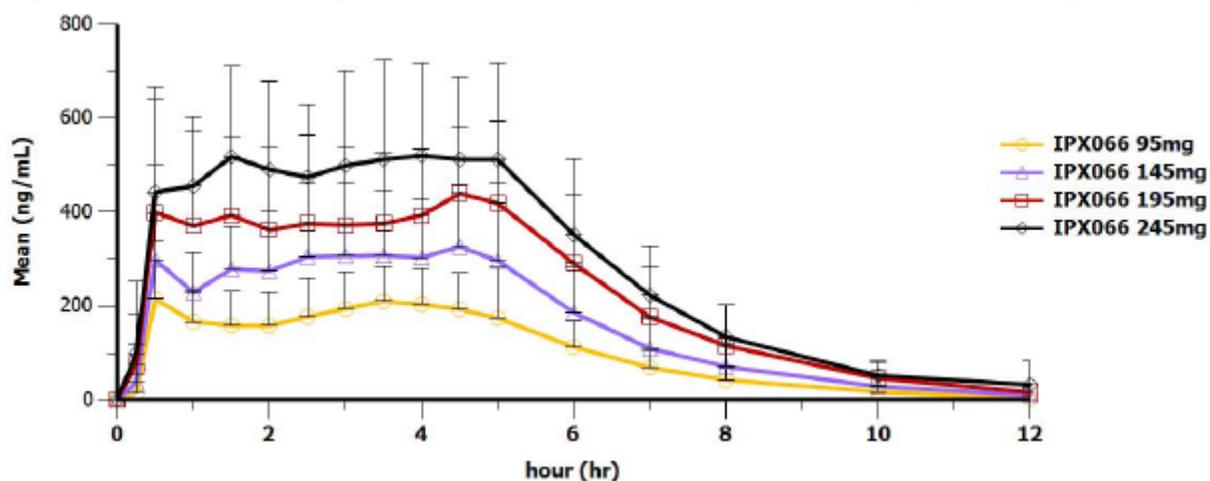
^a Median (range)

^b Power Model. Data reported are β and 90% CI. The acceptance criterion is 0.7645 to 1.2355

Abbreviations: AUC_{inf} = area under the concentration-time curve from time zero to infinity, AUC_t = area under the concentration-time curve from time zero to time t, C_{max} = maximum observed plasma concentration, PK = pharmacokinetic; t_{1/2} = half-life; T_{max} = time to maximum observed plasma concentration.

Source: Study IPX066-B08-09 CSR Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4, 14.2.5.1

Fig 1: Mean (SD) Levodopa Plasma Concentration-Time Profiles (Sponsor’s Figure)



The Sponsor assessed dose proportionality of LD PK parameters following administration of IPX066 was the C_{max} and AUC appear to be proportional across the 4 tablet strengths of IPX066 submitted for approval.

CDTL Comment

As noted in the primary review LD from IPX066 is rapidly absorbed with less fluctuation of the plasma concentrations compared to IR CD-LD (fluctuation of 1.51 ± 0.41 and 3.23 ± 1.26 for IPX066 and IR CD-LD, respectively). Tablet strengths of IPX066 were approximately dose proportional with respect to C_{max} and AUC_{inf} for both CD and LD.

A Comparison of PK Parameters of IR CD-LD and IPX066

The tables below compares the PK characteristics of IR CD-LD to IPX066 for both the LD and CD components.

Table 6: Summary of Levodopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate-Release CD-LD (From OCP Review)

Treatment/ First AM Dose (mg)	Number of Subjects	T _{max} hrs ^a	C _{max} ng/mL ^b	AUC ₀₋₁₂ hr.ng/mL ^b	Accum Index ^{b,c}	Invariance ^b	Fluct % ^{b,c}
IPX066	27	3.0 (0.5 - 11.0)	NA	NA	1.42 ± 0.85	1.15 ± 0.66	1.51 ± 0.41
1 capsule x 245	3	6.0 (1.5 - 9.0)	2107 ± 937	13400.00 ± 6887.88	0.65 ± 0.15	0.52 ± 0.07	1.60 ± 0.19
2 capsules x 245	7	3.0 (0.5 - 9.0)	3227 ± 1089	19481.86 ± 6213.81	1.30 ± 0.40	1.11 ± 0.34	1.66 ± 0.36
3 capsules x 195	3	1.5 (1.5 - 3.0)	3927 ± 306	26976.75 ± 8150.06	2.90 ± 1.26	2.28 ± 1.03	1.48 ± 0.64
3 capsules x 245	11	8.0 (0.5 - 11.0)	4166 ± 1787	27792.03 ± 9329.93	1.33 ± 0.76	1.05 ± 0.56	1.36 ± 0.45
4 capsules x 245	3	2.0 (0.5 - 2.0)	5423 ± 678	35715.92 ± 6124.04	1.28 ± 0.28	1.10 ± 0.20	1.62 ± 0.34
IR CD-LD	27	1.0 (0 - 12.0)	NA	NA	1.11 ± 0.34	0.90 ± 0.31	3.23 ± 1.26
1 tablet x 100	11	0.5 (0 - 12.0)	2209 ± 744	8889.96 ± 2441.67	1.05 ± 0.35	0.85 ± 0.23	3.03 ± 1.05
1.5 tablets x 100	2	3.75 (0.5 - 7.0)	2195 ± 714	6533.59 ± 351.21	1.09 ± 0.25	0.97 ± 0.13	3.94 ± 1.04
2 tablets x 100	9	1.5 (0.5 - 12.0)	3057 ± 1108	11633.64 ± 4602.62	1.12 ± 0.25	0.88 ± 0.32	3.29 ± 1.00
2.5 tablets x 100	3	1.0 (0.5 - 4.0)	3963 ± 186	13783.06 ± 6091.66	0.89 ± 0.19	0.78 ± 0.26	4.17 ± 2.62
3 tablets x 100	2	1.25 (1.0 - 1.5)	3240 ± 806	18648.75 ± 6676.50	1.67 ± 0.62	1.36 ± 0.72	1.88 ± 0.11

^a Data reported as median (range)

^b Data reported as mean and standard deviation

^c Accumulation index was calculated as AUC_{0-τ} on Day 8/AUC_{0-τ} on Day 1 and fluctuation was calculated as (C_{max} - C_{min})/C_{avg} (maximum [peak] drug concentration minus minimum drug concentration divided by average drug concentration), C_{avg} = average drug concentration.

Table 7: Summary of Carbidopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate-Release CD-LD (From OCP Review)

Treatment/First AM Dose (mg)	Number of Subjects	T _{max} hrs ^a	C _{max} ng/mL ^b	AUC ₀₋₁₂ hr.ng/mL ^b	Accum Index ^{b,c}	Invariance ^b	Fluct % ^{b,c}
IPX066	27	3.0 (1.5 - 12.0)	NA	NA	1.63 ± 1.12	1.20 ± 0.84	1.19 ± 0.49
1 capsule x 245	3	1.5 (1.5 - 6.0)	188 ± 58	1312.99 ± 592.30	1.06 ± 0.53	0.72 ± 0.27	1.38 ± 0.39
2 capsules x 245	7	3.0 (1.5 - 12.0)	263 ± 103	1925.39 ± 950.20	1.38 ± 0.60	1.02 ± 0.40	1.18 ± 0.45
3 capsules x 195	3	3.0 (3.0 - 5.0)	363 ± 92	2633.68 ± 794.25	3.01 ± 1.90	2.13 ± 1.64	0.84 ± 0.59
3 capsules x 245	11	3.0 (3.0 - 10.0)	315 ± 192	2303.13 ± 1236.58	1.57 ± 1.18	1.19 ± 0.89	1.16 ± 0.47
4 capsules x 245	3	3.0 (1.5 - 3.0)	498 ± 226	3501.51 ± 1959.32	1.64 ± 0.82	1.25 ± 0.52	1.44 ± 0.75
IR CD-LD	27	4.0 (1.5 - 12.0)	NA	NA	1.22 ± 0.74	0.80 ± 0.63	1.54 ± 0.45
1 tablet x 100	11	4.0 (2.0 - 12.0)	156 ± 38	1137.24 ± 360.99	1.28 ± 0.87	0.73 ± 0.59	1.48 ± 0.34
1.5 tablet x 100	2	5.0 (2.0 - 8.0)	144 ± 42	783.93 ± 211.67	1.13 ± 0.59	0.71 ± 0.16	1.95 ± 0.01
2 tablets x 100	9	3.0 (2.0 - 11.0)	165 ± 48	1219.73 ± 414.41	1.16 ± 0.62	0.85 ± 0.69	1.47 ± 0.42
2.5 tablets x 100	3	3.0 (1.5 - 5.0)	164 ± 68	952.25 ± 285.05	0.85 ± 0.52	0.65 ± 0.60	1.95 ± 0.84
3 tablets x 100	2	6.5 (3.0 - 10.0)	272 ± 6	1949.17 ± 252.53	1.87 ± 1.24	1.22 ± 1.36	1.20 ± 0.32

^a Data reported as median (range)

^b Data reported as mean and standard deviation

^c Accumulation index was calculated as AUC₀₋₁₂ on Day 8/AUC₀₋₁₂ on Day 1 and fluctuation was calculated as (C_{max} - C_{min})/C_{avg} (maximum [peak] drug concentration minus minimum drug concentration divided by average drug concentration). C_{avg} = average drug concentration.

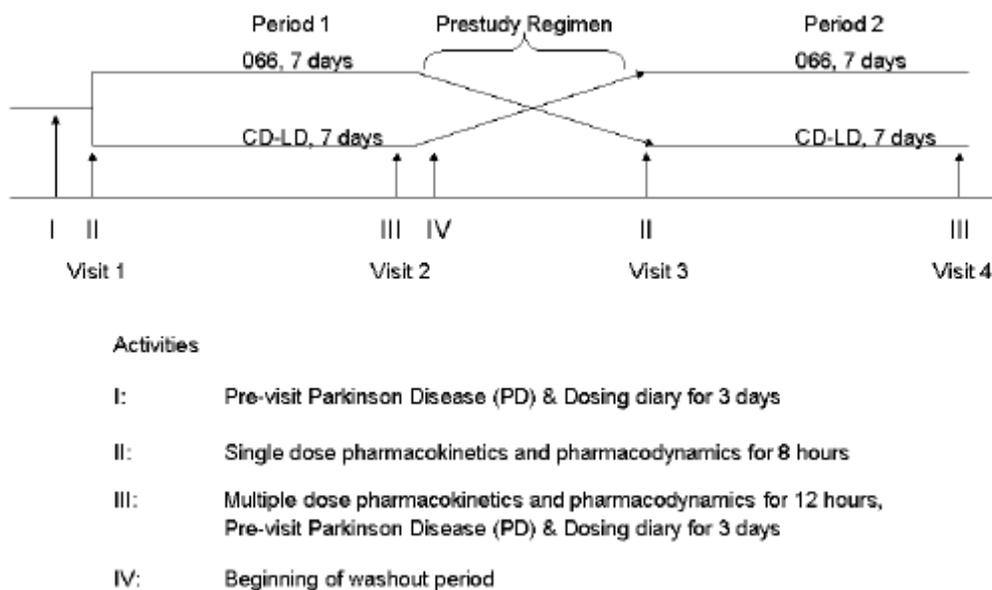
CDTL Comment

As expected, the T_{max} occurred later for IPX066 that contains immediate release, intermediate and delayed release CD-LD components. The Sponsor attempts to demonstrate that the delay in T_{max} does not impact functional onset of action using analyses from a population PK/PD model for Tapping rates and UPDRS Part III scores from study IPX066-B08-11. In addition, the model predicts a prolonged duration of action based on the modeled tapping rates and UPDRS III scores (see the table below).

Study IPX066-B08-11 A STUDY TO COMPARE THE PHARMACOKINETICS AND PHARMACODYNAMICS OF IPX066 TO STANDARD CARBIDOPA-LEVODOPA

This was a randomized, multicenter, open-label, single and multiple oral dose, two-treatment, two-period, crossover study in LD-experienced subjects with PD. Subjects (N=27) received 7 days of one treatment (IPX066 or IR CD-LD) followed by an approximate 7-day washout period followed by 7 days of the other treatment (IR CD-LD or IPX066).

Fig 2: Design of Study IPX066-B08-11



The following efficacy/pharmacodynamic parameters were collected:

- Tapping: the number of times the subject could alternatively tap two counter keys 20 cm apart in 1 minute with the most affected arm assessed every 30 minutes beginning 1 hour before dosing and for 8 hours on Day 1 and hourly for 12 hours on Day 8 of each treatment period. Tapping speed is considered a surrogate measure of bradykinesia.
- Walk Time: the time to rise from a chair, walk 6 meters, turn, return to the chair, and sit down, assessed every 30 minutes beginning 1 hour before dosing and for 8 hours on Day 1 and hourly for 12 hours on Day 8 of each treatment period.
- Patient PD diary: recording “On,” “Off,” and state of dyskinesia, every 30 minutes on 3 days immediately prior to the first treatment and immediately prior to the end of each treatment period.
- Investigator-rated dyskinesia: Assessment of “On,” “Off,” and state of dyskinesia every hour by the Investigator or qualified site personnel on Days 1 and 8 of each treatment period.
- UPDRS Part III score every hour determined by qualified site personnel on Days 1 and 8 of each treatment period.

Model Validation

A nonparametric bootstrap analysis was performed to validate the exposure response model of the continuous PD endpoints, tapping, and UPDRS Part III score. Parameters from 500 replicate trials were calculated by re-sampling the dataset. Median values with 95% confidence intervals (CIs) of the bootstrap parameters were compared with the estimated values and 95% CIs of the final model.

In addition, a visual predictive check was performed to determine if the final model and the parameter estimates adequately described the observed data. One thousand replicate trials were simulated using the final parameter estimates. The similarity between the actual observed data and the simulated data was examined by comparing the 95% prediction interval of the simulated data and the observed data.

Table 8: Comparison of Duration of Effect and Onset of Effect Using Tapping Rate and UPDRS Part III in Study IPX066-B08-11

Treatment	Tapping	UPDRS Part III
	Duration of Effect (hours) on Day 1^a	
IPX066	7.6	7.4
IR CD-LD	5.6	4.5
	Time to Onset of Effect (hours) on Day 1^a	
IPX066	0.39	0.61
IR CD-LD	0.36	0.46

^a Change of more than 15% from baseline value.

Abbreviations: CD-LD = carbidopa-levodopa; IR = immediate release; UPDRS = Unified Parkinson's Disease Rating Scale.

Source: Population Pharmacodynamics Report Table 5

CDTL Comment

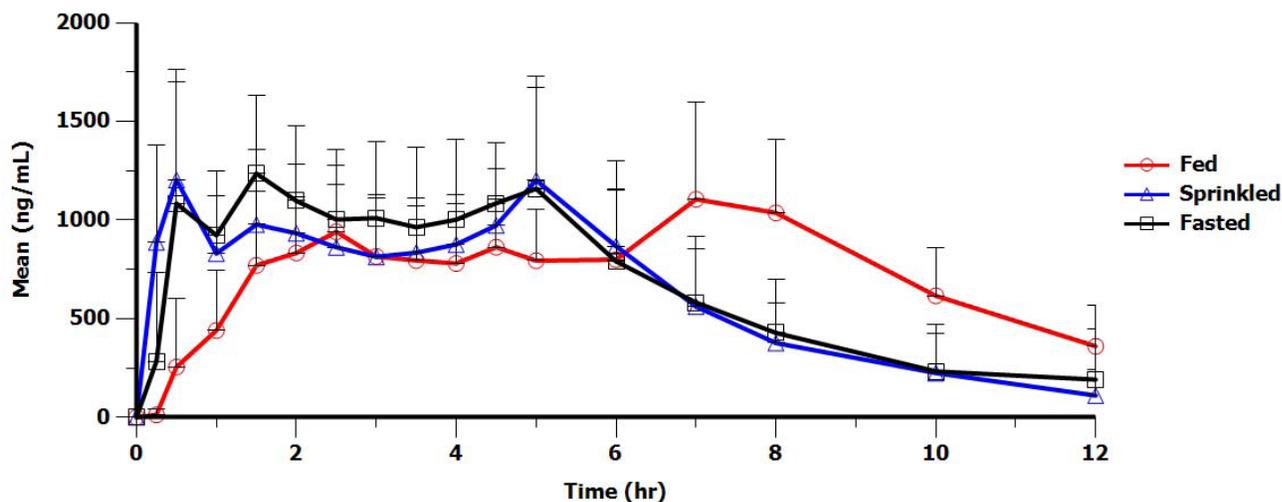
Although the assessments are reasonable (Tapping and UPDRS III) there are several problems with the study design and analysis that detract from the validity of the information or the ability to accept that the information is generalizable to a larger population of patients with Parkinson's disease. The trial specified dosing times but the Methods section did not mention whether dosing was design in a manner that avoided the potential interaction with meals. The scenario of avoiding dosing in close proximity to meals seems more likely in the PK/PD study however, patients in the pivotal efficacy trials and the recommendations in labeling are to dose without regards to meals. The models used by Sponsor are not generally accepted as being able to predict functional response in patients with PD. There was a limited number of "qualified LD-experienced PD subjects" enrolled and participants were not chosen with regard to a baseline level of impairment for the motor tasks evaluated, or dyskinesia. Patients were not screened for other rheumatologic disease that could limit tasks such as tapping. The study lacks assay sensitivity because it compared two similar drugs, without a placebo limb or an accepted active comparator having a well-defined treatment effect on tapping or UPDRS III scores. The non-parametric boot strapping procedure may increase the precision of the models estimates but it does not enhance the accuracy or utility of the information provided by the model.

Food Effects

The OCP reviewer notes that: "following administration of IPX066 capsules (2 x 61.25–245 mg CD-LD, the highest strength) to healthy subjects in fed state (high-fat, high-calorie food) there was a 13% increase in the extent of absorption of LD (AUC_{inf}). There was a delay in LD absorption to reach the secondary peak plasma concentration (T_{max}) by 5.5 hours (from 1.5 hours to 7 hours) and a decrease in LD C_{max} by approximately 21%. There was a delay in LD absorption to reach the initial peak plasma concentration by approximately 2.5 hours (from 1.5 hours to 4 hours). Sprinkling the IPX066 capsule contents on applesauce did not affect the overall LD concentration-

time profile compared to the intact capsule under fasted condition. The delay in LD absorption when administered with high-fat and high calorie meal, compared to when administered in the fasted condition or when sprinkling contents on applesauce.”

Figure 3: Mean (SD) Levodopa Plasma Concentration-Time Profiles



The carbidopa AUC and Cmax values decreased by 40% and 50%, with a delay in reaching Cmax of approximately 1 hour in the presence of high fat and high calorie food compared to the plasma concentrations measured in the fasted state. The OCP reviewer noted that the observed decrease in CD exposure by food is not likely to have adverse impact on availability of LD to the site of action because the peripheral dopa decarboxylase is saturated by carbidopa at approximately 70~100 mg a day.

CDTL Comment

The delay in Tmax (5.5 hours) may be less noticeable by patients because curves indicate IPX066 has plasma levels in the fed state are still near the plasma concentrations observed in the fasted state after 2-3 hours. Increasing the dose of IPX066 may overcome a decline in clinical response due decreased plasma concentrations caused by dosing near a meal.

Although food may interfere with the absorption of IPX066, patients enrolled in the Phase 3 clinical studies were instructed to take IPX066 without regards to meals and mean. The results of these studies demonstrated improved “off” time (Advanced PD) and UPDRS scores (Early PD) despite potential food effects. The proposed label includes a statement warning prescribers about a possible 1-2 hour delay in LD absorption when IPX066 is administered with food. In addition, there is a statement that is similar to statements in other CD-LD product labels recommending that patients should be cautioned about taking IPX066 with proteins rich foods in or amino acids because they may interfere with the oral absorption and pharmacological effects of LD. The effect of delayed “on” caused by dosing near meals may be more prominent with the first dose of IPX066 in the morning.

Because LD containing products are taken often throughout the day (3-5 times) it may not be practical to ask patients to avoid dosing IPX066 near meals since it is likely dosing near mealtime will be unavoidable.

Effects of Alcohol on IPX066 Release

The effects of co-administration ethanol on bioavailability of CD and LD from IPX066 (97.5–390 mg CD-LD dose) was evaluated in a single-dose, open label, randomized, three-sequence, three-treatment (0%, 5%, and 20% (v/v) alcohol) crossover study followed by a fixed treatment (40% (v/v) alcohol) in Period 4 (study IPX066-B09-04) in healthy subjects. The concentration-time profiles of LD in the presence of alcohol are presented in the table below.

The OCP reviewer's conclusions regarding the in vivo study of the effects of ethanol on PK parameters of IPX066.

- *“Alcohol resulted in about 15% increase in LD Cmax and about 23% increase in LD AUC_{0-∞} compared to the 0% alcohol treatment.*
- *Concomitant administration of alcohol decreased CD Cmax by 16% and the mean AUC_{0-∞} was unchanged.*
- *Overall, the changes in PK profile of LD or CD with alcohol coadministration was relatively less.”*

Table 9: Summary of Carbidopa Pharmacokinetic Parameters in Study IPX066-B09-04, Mean ± SD, (N = 15)

PK Parameters	0% Alcohol	5% Alcohol	20% Alcohol	40% Alcohol
Tmax (h) ^a	4.00 (1.50 - 6.00)	4.00 (2.00 - 6.00)	4.00 (1.50 - 6.00)	5.00 (2.00 - 8.0)
Cmax (ng/mL)	125.49 ± 52.58	100.93 ± 29.36	115.01 ± 60.53	109.95 ± 56.97
AUC ₀₋₄ (ng.h/mL)	259.95 ± 90.23	223.91 ± 81.56	252.75 ± 103.25	197.00 ± 88.33
AUC _{0-t} (ng.h/mL)	650.69 ± 303.22	568.72 ± 210.01	689.20 ± 342.65	658.56 ± 318.82
AUC _{0-∞} (ng.h/mL)	660.58 ± 305.49	577.34 ± 211.14	705.90 ± 341.09	684.72 ± 319.39
t _{1/2} (h)	2.14 ± 0.42	2.15 ± 0.27	2.75 ± 1.02	3.35 ± 2.37

a. Median (range)

CDTL Comment

In general, patients with PD should not consume ethanol. PD is associated impairment of balance and coordination and patients with more advanced disease have a substantially greater risk for cognitive impairment. The diseases related impairments are very likely to worsen under the temporary effects of ethanol. The increased levodopa Cmax may result in a temporary increase in peak dose dyskinesia and psychiatric adverse events. Instructions in the label that patients should

avoid taking IPX066 in the presence of ethanol will avoid the potential for an increase in adverse events related to higher plasma concentrations and not cause hardship for patients.

Intrinsic Factors

Age, body weight, gender, and subjects' status (healthy volunteer versus PD patient) had no significant effect on the model parameters. Population PK analysis was conducted by the sponsor using data from two studies in healthy volunteers (IPX066-B08-10, IPX066-B09-01) and one study in subjects with advanced Parkinson's Disease (IPX066-B08-11). The OCP reviewer did not recommend dose adjustments or labeling specific to patient age, gender or weight. The sponsor did not enroll a sufficient number of non-caucasian PD patients to make reliable inference for patients in different racial or ethnic subgroups. This is often the case in clinical trial of PD where Caucasian males are the more likely to have PD.

Extrinsic Factors

No new drug-drug interaction studies were conducted with IPX066 for the current application. Information pertaining to drug-drug interaction related to carbidopa or levodopa is available in the approved labeling for Sinemet CR tablets (see Clinical Pharmacology of the Sinemet CR label).

IPX066-B08-10: RELATIVE BIOAVAILABILITY OF IPX066 TO CARBIDOPA-LEVODOPA FORMULATIONS

The study was a single-center, single-dose, open-label, randomized, four sequence, four-treatment crossover study in healthy volunteers with at least a 6-day washout between treatment periods.

Table 10: Summary of Levodopa Pharmacokinetics Following a Single Dose of IPX066 97.5-390 mg CD-LD, Sinemet® 25-100 mg CD-LD, Sinemet® CR 25-100 mg CD-LD or Stalevo® 25-100-200 mg CD-LD-entacapone in Study IPX066-B08-10, Mean ± SD, (N = 22).

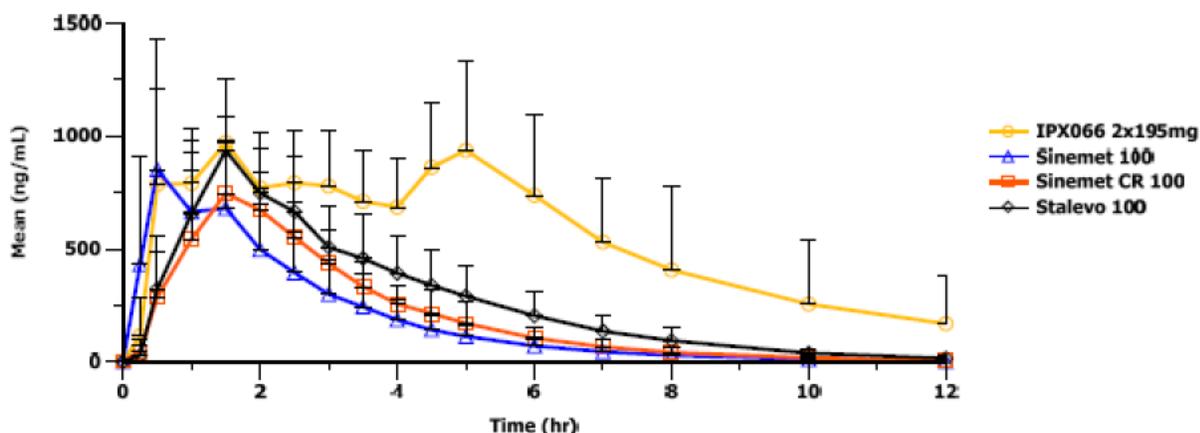
PK Parameters	Treatment/Total Dose CD-LD or CD-LD-entacapone mg			
	IPX066 97.5-390	Sinemet® 25-100	Sinemet® CR 25-100	Stalevo® 25-100-200
T _{max} (h) ^a	4.50 (0.5 - 8.0)	1.00 (0.50 - 2.00)	1.50 (1.00 - 2.00)	1.50 (1.00 - 2.00)
C _{max} (ng/mL)	1325.64 ± 267.88	1094.36 ± 401.14	854.96 ± 299.28	1026.77 ± 284.29
AUC _{0-t} (ng.hr/mL)	6752.81 ± 2086.16	2215.35 ± 665.20	2372.43 ± 682.29	3250.82 ± 1135.40
AUC _{0-∞} (ng.hr/mL)	7243.98 ± 2553.23	2250.63 ± 664.36	2403.06 ± 679.99	3290.75 ± 1149.47
t _{1/2} (h)	1.91 ± 0.66	1.55 ± 0.17	1.55 ± 0.20	1.57 ± 0.19
Time LD Above 50% C _{max} (hours)	4.88 ± 2.36	1.45 ± 0.71	2.11 ± 0.96	2.13 ± 0.96

CDTL Comment:

T_{max} is significantly later for IPX066 compared to Sinemet with a much greater potential for variability. The C_{max} and AUC_{0-t} are also significantly greater compared to other CD LD

containing products. The longer time to T max may not translate clinically to a delayed “on” time or it may be overcome by taking a dose or IR CD LD in the morning. The higher Cmax and AUC0-t may be associated with a greater risk for troublesome dyskinesia but this was not observed in the clinical trial in patients with advanced PD.

Figure 4: Mean Levodopa Plasma Concentration-Time Profiles Comparing the different CD LD Containing Products



Dose Conversion Guidelines

Table 11: Guidelines for Initial Conversion from IR Levodopa Product to IPX066 in Patients with Advanced Parkinson’s Disease.

Total Daily Dose of Immediate Release Levodopa (mg)	Suggested Initial Dose of [TRADE NAME] t.i.d. (Levodopa in mg) ¹	
	Dosage Strength	Capsules per Dose
(b) (4)	[TRADE NAME] 95	3 capsules
	[TRADE NAME] 95	4 capsules
	[TRADE NAME] 145	3 capsules
	[TRADE NAME] 195	3 capsules
	[TRADE NAME] 195	4 capsules
	[TRADE NAME] 245	3 capsules

¹ Bioavailability is 70% relative to immediate release levodopa product in Parkinson’s disease patients (12.3)

The protocol allowed approximately 3 days between each dose adjustment. Adjustments that are more frequent were permitted during the initial phase of the IPX066 Dose- Conversion period, at the Investigator’s discretion.

At the end of dose conversion, the median daily dose of IPX066 was 1365 mg (mean 1622 mg) in Study IPX066-B09-02, which is approximately double of the IR CD-LD dose. After dosing for 5 months in the open-label long-term extension Study IPX066-B09-03, the median daily dose of IPX066 was 1450 mg (mean 1597 mg), which is similar to the doses used in Study IPX066- B09-02.

Dr. Constantino, noted in her review that a substantial number of patients (n=57 or 15% of all randomized subjects) withdrew from IPX066-B-09-02 during the Dose Conversion Phase suggesting

a large number of patients required significant dose adjustment following conversion from IR CD-LD.

The Clinical Pharmacology reviewer simulated two typical scenarios with different IR LD daily dosing and IPX066 daily dosing.

Scenario 1: IR LD was given 4 times per day (time 0 hour, 6 hour, 12 hour and 18 hour) for 7 days followed by IPX066 3 times per day (time 0 hour, 6 hour and 12 hour) for 7 days.

Scenario 2: IR LD was given 4 times per day (time 0 hour, 6 hour, 12 hour and 18 hour) for 7 days followed by IPX066 3 times per day (time 0 hour, 8 hour and 16 hour) for 7 days.

Table 12: Comparison of Cmax, AUC of LD at Steady State Under Scenario 1.

IR LD Daily Dose (mg)	Cmax	AUC(Daily)	IPX066 LD Daily Dose (mg)	Cmax	↑%Cmax	AUC(Daily)	↑%AUC
400	790	7779	855	1032	30.63	14877	91.25
475	938	9238			10.02		61.04
550	1086	10696			-4.97		39.09
550	1086	10696	1140	1376	26.7	19836	85.45
650	1283	12641			7.25		56.92
750	1481	14586			-7.09		35.99
750	1481	14586	1305	1575	6.35	22707	55.68
850	1678	16531			-6.14		37.36
950	1875	18475			-16		22.90
950	1875	18475	1755	2119	13.01	30537	65.29
1100	2172	21393			-2.44		42.74
1250	2468	24310			-14.14		25.61
1250	2468	24310	2205	2662	7.86	38367	57.82
1600	3159	31116			-15.73		23.30

Source: FDA Reviewer’s analysis

Table 13: Comparison of Cmax, AUC of LD at Steady State Under Scenario 2.

IR LD Daily Dose (mg)	Cmax	AUC(Daily)	IPX066 LD Daily Dose (mg)	Cmax	↑%Cmax	AUC(Daily)	↑%AUC
400	790	7779	855	874	10.63	15091	94.00
475	938	9238			-6.82		63.36
550	1086	10696			-19.52		41.09
550	1086	10696	1140	1165	7.27	20122	88.13
650	1283	12641			-9.2		59.18
750	1481	14586			-21.34		37.95
750	1481	14586	1305	1334	-9.93	23034	57.92
850	1678	16531			-20.5		39.34
950	1875	18475			-28.85		24.68
950	1875	18475	1755	1793	-4.37	30977	67.67
1100	2172	21393			-17.45		44.80
1250	2468	24310			-27.35		27.42
1250	2468	24310	2205	2253	-8.71	38919	60.09
1600	3159	31116			-28.68		25.08

Source: FDA Clinical Pharmacology Reviewer’s Analysis

CDTL Comment

The OCP reviewer believes the conversion scheme reasonable. Even though the PK parameters only approximates the Cmax, Tmax and AUC over a range of doses. The PK parameters that are generated by both of the OCP scenarios convert a range of IR CD-LD dosages to a single dose of IPX066. The conversion is not expected to result in a similar Cmax for LD, at all of the IR CD-LD doses in each dose range. To address this issue, sponsor proposed allowing patients to take an additional IPX 066 dose during bedtime if symptoms are not controlled. The pivotal efficacy in patients with advanced PD used this guideline as an initial dose conversion with dose adjustments permitted (up or down). Although, there the reason to believe the dose conversion guideline based on PK parameters is not a close match for a substantial number of patients, it provides a reasonable estimate (likely resulting under-dosing). Close follow-up is needed to successfully convert patients to IPX066 and other levodopa products perhaps closer than the every 3 days (minimum interval) allowed between dose adjustments during the study.

Other Dose Conversion Schemes from CD-LD-Entacapone and from Sinemet CR.

The sponsor proposed additional guidelines for conversion from CLE to IPX066 and conversion from Sinemet CR (marketed CD-LD extended release) to IPX066. The first was a conversion from CLE to IPX066. The sponsor proposed increasing the total daily dose by 30% for patients converting from CLE to IPX066. Patients converting from CD-LD extended release to IPX066 should decrease their total daily levodopa dose of Sinemet CR by 30%. In either case the dose will likely require adjustment based on clinical response to the converted dose of IPX066.

8. Clinical Microbiology

The Sponsor's Justification for Microbial Limits not being included in the NDA are that all development data demonstrated that the drug product is not a growth promoting media. Microbial limits were adequately tested during drug product development.

9. Clinical/Statistical- Efficacy

The application relied primarily on three controlled clinical trials to support the claim for efficacy and safety. The results of a long-term safety study. The first study was IPX-B-08-05 in patients with early Parkinson's disease. The trial was a Phase 3, fixed dose, randomized, double-blind, placebo-controlled, parallel groups study. IPX066-B09-02 was a Phase 3, 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 patients with advanced PD. IPX066-B09-06 was a randomized, double-blind, double-dummy, 2-treatment, two 2-week crossover study of IPX066 versus CLE (Part I) followed by an open-label safety study (Part 2) of IPX066 in Advanced Parkinson's disease. The application included long-term, open label safety information in the form of an interim report for study IPX066-B09-03. Patients who completed studies IPX066-B08-05 (early PD) an IPX066-B09-02 (advanced PD) were eligible to enroll in study IPX066-B09-03. In addition, patients from study IPX066-B08-11, a randomized, open-label, multicenter, two-period, crossover pharmacokinetics and pharmacodynamics study of IPX066 versus IR CD-LD in subjects with advanced PD with motor fluctuations contributed to the long-term. open-label safety database. The Sponsor's 120-day safety update primarily included additional information from patients enrolled in IPX066-B09-03. A small

amount of additional safety information from patients continuing in open-label trials IPX066-B09-06 Part 2 and IPX066-B11-01 was included in the 120-Day Safety Update.

Table 14: Pivotal Efficacy and Safety Trials Included in the NDA (Sponsor's Table)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
STUDIES IN PATIENTS									
Phase 3	IPX066-B08-05 (APEX-PD): A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson's Disease	M5.3.5.1	<ul style="list-style-type: none"> To evaluate the safety and efficacy of IPX066 in the treatment of subjects with early PD. To evaluate the impact of IPX066 on the quality of life in subjects with early PD. 	Randomized, double-blind, placebo-controlled, fixed-dose, parallel-arm study	<p><u>IPX066:</u> 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD) Placebo equivalent</p> <p><u>IPX066 or Placebo:</u> 36.25-145 mg (CD-LD) TID 61.25-245 mg (CD-LD) TID 97.5-390 mg (2 x 48.75-195 mg) (CD-LD) TID</p> <p>Oral</p>	427 patients screened 381 patients randomized	Early LD-Naïve PD patients (Hoehn & Yahr Stage I-III)	30 weeks	Complete Full report
Phase 3	IPX066-B09-02 (ADVANCE-PD): A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson's Disease	M5.3.5.1	To evaluate the safety and efficacy of IPX066 in the treatment of advanced PD subjects in comparison to IR CD LD.	Randomized, double-blind, double-dummy, active-control, parallel-group 13-week comparison study	<p><u>IPX066:</u> 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD) <u>Sinemet®:</u> 25-100 mg (CD-LD)</p> <p>Doses individually titrated during open label, then fixed for double blind phase</p> <p><u>Dose Evaluated:</u> IR CD-LD: 400 – 2550 mg/day IPX066: 855 – 2940 mg/day</p> <p>Oral</p>	471 patients enrolled 393 patients randomized	Advanced PD patients (Hoehn & Yahr Stage I-IV)	22 weeks: (3-week dose adjustment, 6-week dose conversion, 13-week double-blind)	Complete Full report
Phase 3	IPX066-B09-03: An Open Label Extension Study of the Safety and Clinical Utility of IPX066 in Subjects with Parkinson's Disease	M5.3.5.2	To evaluate the long-term safety and clinical utility of IPX066 in subjects with Parkinson's disease (PD).	Multicenter, open-label safety extension study	<p><u>IPX066:</u> 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD)</p> <p>Individualized dosing</p> <p><u>Dose Evaluated:</u> 285 – 2940 mg/day</p> <p>Oral</p>	617 patients enrolled	Early and Advanced PD patients (268 patients with early disease; 349 patients with advanced disease)	9 months	Complete Interim report

Table 14 Continued: Active Comparator to Carbidopa/Levodopa/Entacapone (CLE).

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3	IPX066-B09-06 (ASCEND-PD): A Study to Compare IPX066 and Carbidopa/Levodopa/Entacapone (CLE) Followed by an Open-Label Safety Study of IPX066 in Advanced Parkinson's Disease	M5.3.5.1	<p>Part 1:</p> <ul style="list-style-type: none"> To compare the efficacy of IPX066 and CLE in subjects with advanced Parkinson's disease. To assess the pharmacokinetics and pharmacodynamics of IPX066 and CLE in subjects with advanced Parkinson's disease. <p>Part 2:</p> <ul style="list-style-type: none"> To evaluate the long-term safety and clinical utility of IPX066 in subjects who successfully complete Part 1 of this study under open label conditions. 	<p>Part 1:</p> <p>Open-label, dose conversion followed by randomized, double-blind, double-dummy, 2-treatment, 2-period (separated by 2-week open-label), crossover study</p> <p>Part 2:</p> <p>6-month open-label extension</p>	<p>IPX066:</p> <p>23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD)</p> <p>CLE:</p> <p>Sinemet®: 25-100 mg (CD-LD)</p> <p>Comtan®: 200 mg (CD)</p> <p>Individualized dosing. CLE fixed at entry IPX066 fixed after dose conversion</p> <p>Oral</p>	<p>110 patients enrolled</p> <p>91 patients randomized</p> <p>84 patients completed</p>	Advanced PD patients (Hoehn & Yahr Stage I-IV)	<p>Part 1:</p> <p>11 weeks</p> <p>Part 2:</p> <p>6 months</p>	<p>Complete</p> <p>Part 1:</p> <p>Full report</p>

Individual Trial Efficacy Results

IPX-B-08-05 In Patients with Early Parkinson's disease

The goal of IPX-B08-05 was to demonstrate superiority of 3 strengths of IPX066 compared to placebo. The 23.75/95 mg tablet strength was included in the trial as a titration dose but it was not part of the efficacy comparison. Three hundred and eighty one patients were randomized from 56 sites in the U.S., Canada and Europe (Ukraine, Romania, Lithuania, Latvia, Estonia). The trial design was a double-blind, placebo-controlled, fixed-dose, parallel-arm study evaluated three doses of IPX066 versus placebo in the treatment of subjects with early PD. Patients could not previously been treated with levodopa (LD) or catechol-O-methyl transferase (COMT) inhibitors for more than 30 days and not within 4 weeks before study enrollment (subjects who were considered LD naïve for purposes of enrollment) and were not treated with dopamine agonists. Patients were randomized to 1 of 4 treatment arms or placebo.

- IPX066 36.25–145 mg CD–LD (referred to as 145 mg LD) dosed 3 time a day
- IPX066 61.25-245 mg CD–LD (referred to as 245 mg LD) dosed 3 time a day
- IPX066 97.50–390 mg CD–LD (referred to as 390 mg LD) dosed 3 time a day
- Matching placebo dosed 3 time a day

The trial lasted 30-week study included a Titration period of 4 weeks (up to 3 weeks of dose escalation and 1 week of stabilization), which allowed escalation to the assigned dose, and a 26-week Maintenance treatment period.

Primary endpoint:

Change from Baseline in the UPDRS Questionnaire Part II plus Part III score at the End of Study (i.e., the value obtained at Week 30 or the last post-baseline value reported if the subject discontinued the study prematurely).

Secondary efficacy:

- Sum of individual UPDRS Parts, sum of UPDRS Parts I through III, and sum of UPDRS Parts I through IV collected at Visits 2, 3, 4, 5, and 6 and End of Study and sum of UPDRS Parts II and III collected at Visits 2, 3, 4, 5, and 6.
- Patient Global Impression (PGI) score at End of Study and at Visits 2, 3, 4, 5, and 6 (Weeks 4, 9, 16, 23, and 30).
- Clinical Global Impression (CGI) score at End of Study and at Visits 2, 3, 4, 5, and 6 (Weeks 4, 9, 16, 23, and 30).

The protocol did not specify key secondary endpoints and there was no pre-specified plan to adjust for multiplicity. The sponsor did not plan to describe secondary endpoints in product labeling.

Analysis of the Primary Efficacy Variable

Rather than adjusting significance levels, the issue of multiple comparisons of the treatment arms was addressed by analyzing efficacy the treatment arms in a decreasing hierarchy starting with a comparison of the high dose to placebo. Assuming a significant treatment effect ($P < 0.05$), tests of the three pair-wise comparisons of interest (IPX066 145 vs. placebo, IPX066 245 vs. placebo, and IPX066 390 vs. placebo) were conducted. A sensitivity analysis was also conducted using Dunnett's procedure to individually compare the three active treatments to placebo.

Table 15: Disposition of Subjects in Study IPX066-B08-05 (Randomized Subjects) (Sponsor's Table)

All Treated Subjects	Number of Subjects (%)				
	Placebo (N = 92)	IPX066 LD Dose Group			Total (N = 381)
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)	
Received Study Treatment	92 (100)	87 (100)	104 (100)	98 (100)	381 (100)
Discontinued Study Treatment	21 (22.8)	15 (17.2)	21 (20.2)	24 (24.5)	81 (21.3)
Primary Reasons for Early Discontinuation					
Adverse Event	4 (4.3)	5 (5.7)	15 (14.4)	15 (15.3)	39 (10.2)
Lack of Efficacy	12 (13.0)	4 (4.6)	0	1 (1.0)	17 (4.5)
Withdrawal by Subject	4 (4.3)	3 (3.4)	1 (1.0)	3 (3.1)	11 (2.9)
Protocol Violation	0	1 (1.1)	0	2 (2.0)	3 (0.8)
Noncompliance	0	0	1 (1.0)	1 (1.0)	2 (0.5)
Lost to Follow-Up	0	1 (1.1)	1 (1.0)	0	2 (0.5)
Death	0	0	1 (1.0)	0	1 (0.3)
Other ^a	1 (1.1)	1 (1.1)	2 (1.9)	2 (2.0)	6 (1.6)

^a Six subjects at Site 202 were removed from the study by the Sponsor because the UPDRS ratings performed at this site indicated that the procedures differed significantly from both the Sponsor's expectations of how these ratings were to be performed and how these ratings were performed at other sites participating in the study.

Source: Table 14.1.1.1.

Of the 381 patients (N=171 U.S. sites and N=210 European sites) randomized and who received at least one dose of study medication, 300 completed the trial. Eighty-one subjects discontinued prematurely. The most common reason for early withdrawal in the IPX066 treated patients was due to adverse events in all of the 3 dose arms. The most common reason for early withdrawal in the placebo treated patients was for “lack of efficacy” in patients assigned to placebo. The Sponsor excluded all 6 patients from a single non-U.S. site post-randomization because of suspected data fabrication. The sponsor submitted a review of their site inspection and I agree with the Sponsor’s action removing the site and the data. The efficacy results were calculated after excluding the results from the site in question. Four additional 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 therefore, the Sponsor excluded their efficacy data from the primary analysis. Dr. Massie (FDA Biostatistics Reviewer) found that the efficacy data was not sensitive to the effects of these missing data from the patients who discontinued prematurely or were removed post-randomization.

Baseline Demographic and Parkinson’s Disease Severity.

There were no significant differences in the baseline demographic and Parkinson’s disease related factors (UPDRS Parts II, III, duration of PD).

Efficacy Results

Table 16: Study IPX066-B08-05 Primary Efficacy Endpoint Results (Sponsor’s Table)

TABLE 14.2.4.2-2 (Page 1 of 1)
Analysis of Change from Baseline in End of Study UPDRS Part II plus UPDRS Part III by Treatment (Randomized Subjects)

UPDRS Part II + III	IPX066 145 mg (N=82)	IPX066 245 mg (N=99)	IPX066 390 mg (N=90)	Placebo (N=90)	Total (N=361)
N (%)	82 (100%)	99 (100%)	90 (100%)	90 (100%)	361 (100%)
Mean (SD)	-11.7 (10.97)	-12.9 (11.42)	-14.9 (11.85)	-0.6 (10.37)	-10.1 (12.46)
Median	-11.5	-13.0	-14.0	0.0	-9.0
LS Mean (Min, Max)	-11.6 (-45, 7)	-13.0 (-52, 26)	-15.1 (-51, 6)	-0.3 (-38, 24)	-9.0 (-52, 26)
Significance Test		Dunnett	Fisher		
Overall Treatment Significance			<0.0001		
IPX066 145 mg vs. Placebo		<0.0001	<0.0001		
IPX066 245 mg vs. Placebo		<0.0001	<0.0001		
IPX066 390 mg vs. Placebo		<0.0001	<0.0001		

NOTE: Three Factor ANOVA Model with Main Effects and Treatment By Region Interaction

The results of the secondary outcome variables were generally all in a positive direction with a p-value < 0.05 with the exception of the UPDRS, Part 4 (complication of therapy). Patients with early PD typically have not yet experienced motor complications (i.e., dyskinesia, “off” periods).

CDTL Comment:

The results of the trial indicate a persuasive effect on treating the motor symptoms in patients with early PD. Although the results of 18 patients (and 4 did not have post baseline assessment) were excluded from the efficacy analysis post-randomization, the results were not changed by the missing data. The results for the protocol specified secondary outcome measures in general supported the

positive effect, demonstrating internal consistency of the trial results. The sponsor’s sensitivity analyses ANCOVA using LOCF and MMRM to replace missing data for the primary endpoint plus the additional sensitivity analysis performed by Dr. Massie, ANCOVA using MMRM statistically, support a finding of clinical efficacy.

Advanced Parkinson’s Disease

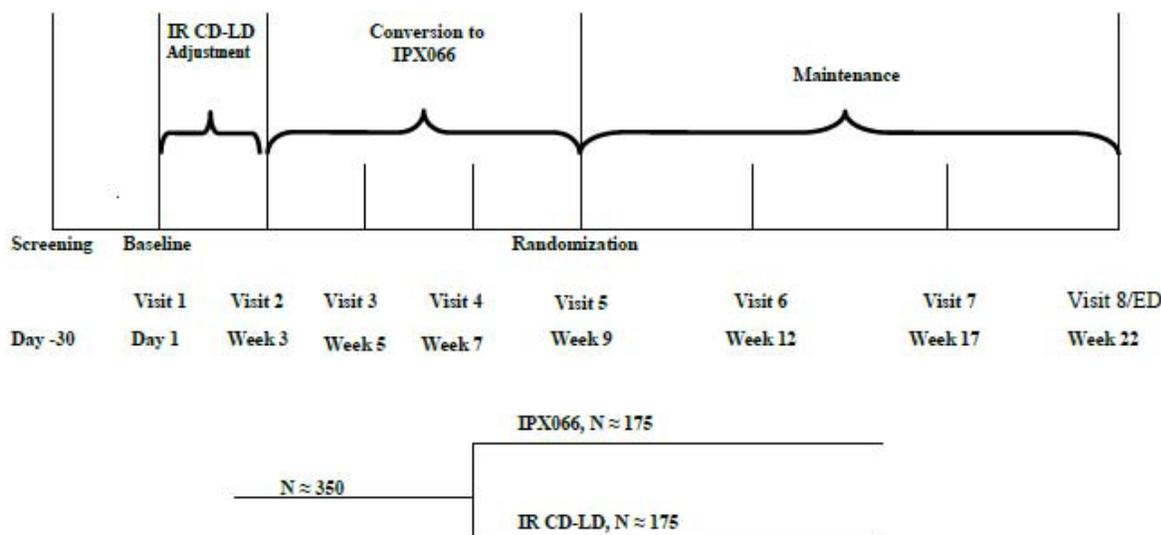
IPX066-B09-02 A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson’s Disease

The trial was a Phase 3, 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 patients with advanced PD. Patients w a total daily LD dose of at least 400 mg at least four times daily and they must experience at least 2.5 hours of “off” time per day.

The first phase of the trial was a 3-week IR CD-LD Dose Adjustment treatment period to allow for dose optimization of the patient’s individual IR CD-LD regimen. This was followed by a 6-week dose conversion to IPX066 according to a pre-specified conversion scheme. Patients randomized in a blinded fashion 1:1 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.

Fig 5: IPX066-B09-02 Trial Design Diagram (Sponsor’s Figure)



Key inclusion criteria included:

- Idiopathic PD per United Kingdom Parkinson’s Disease Society Brain Bank Diagnostic Criteria;
- Hoehn and Yahr Staging I-IV in the “on” state; ≥30 years old at PD diagnosis,
- Current treatment with stable a levodopa (LD) regimen (LD ≥400 mg LD/day, dosed ≥ 4 times/day and stable for ≥4 weeks at Screening);
- The patients is able to differentiate “on” state from “off” state with 75% concordance rate during training;

- Patients experiencing an average of ≥ 2.5 hours “off” time at Visits 1 and ≥ 1 hour “off” each day based on 3 days of diary; able to properly complete diary, had predictable “off” periods (“yes” to Question #36 on the Unified Parkinson’s Disease Rating Scale [UPDRS]).

Subjects randomized to IPX066 during the double-blind Maintenance period received IPX066 (plus placebo matching IR CD-LD). IPX066 was provided in 4 dosing strengths.

- IPX066 23.75–95 mg CD-LD capsules (IPX066 95 mg)
- IPX066 36.25–145 mg CD-LD capsules (IPX066 145 mg)
- IPX066 48.75–195 mg CD-LD capsules (IPX066 195 mg)
- IPX066 61.25–245 mg CD-LD capsules (IPX066 245 mg):

Placebo capsules were provided during the double-blind period for the 4 dosing strengths of IPX066

Duration of treatment:

Each patient could participate for a maximum of 22-week in the trial over three treatment periods:

- Open label IR CD-LD Dose Adjustment (3 weeks)
- Open label IPX06 Dose Conversion (6 weeks)
- Double-blind IPX066 or IR CD-LD Maintenance (13 weeks).

Primary efficacy:

Baseline-adjusted “off” time (derived from the PD Diary) as a percentage of waking hours at the end of study (EOS).

Secondary efficacy:

- Responder analysis: Proportion of subjects with at least 1 hour improvement in “off” time from Baseline (primary responder analysis), as well as 0.5, 1.5, 2, and 3 hour improvements
- Baseline-adjusted “off” time as a percentage of waking hours at Visits 6, 7 and 8
- Baseline-adjusted total “off” time at EOS and Visits 6, 7 and 8
- Baseline-adjusted total “on” time with no troublesome dyskinesia (defined as “on” time with no or non-troublesome dyskinesia) at EOS and Visits 6, 7 and 8
- Baseline-adjusted total “on” time with troublesome dyskinesia at EOS and Visits 6, 7 and 8
- Baseline-adjusted UPDRS Parts II + III, Parts I + II + III, Total UPDRS Part I, UPDRS Parts II, III and IV, as well as Part II assessed for the “off” state, at EOS and Visits 6, 7 and 8
- Patient Global Impression (PGI) and Clinical Global Impression (CGI) at EOS, examined as continuous variables and as percentage of subjects improved

Patient Disposition

A substantial number (N=57) of patients with advanced PD discontinued prematurely from the IPX066 limb of the trial during the conversion phase, less than half the number of patients (N=21)

that discontinued from the IR CD LD dose adjustment phase. In addition to the possibility that IPX066 is less tolerable than IR CD LD, it may also be explained by the fact that patients in the IR CD LD arm limb were selected because they were already tolerating IR CD LD before trial entry. Most of the patients withdrew from the dose conversion phase of IPX088 because of an adverse event but another 12 patients were classified as “withdrawn by the subject”. The sponsor should have made additional effort to determine the reason for premature withdrawal. As defined I the protocol , patients who withdrew prematurely because of adverse event would not be counted as experiencing an adverse event in the maintenance phase of the trial. This is consistent with the goal of the trial to determine if IPX066 is superior to IR CD LD.

Fig 6: Flowchart of Subject Disposition in Study IPX066-B09-02 (Sponsor’s Figure)

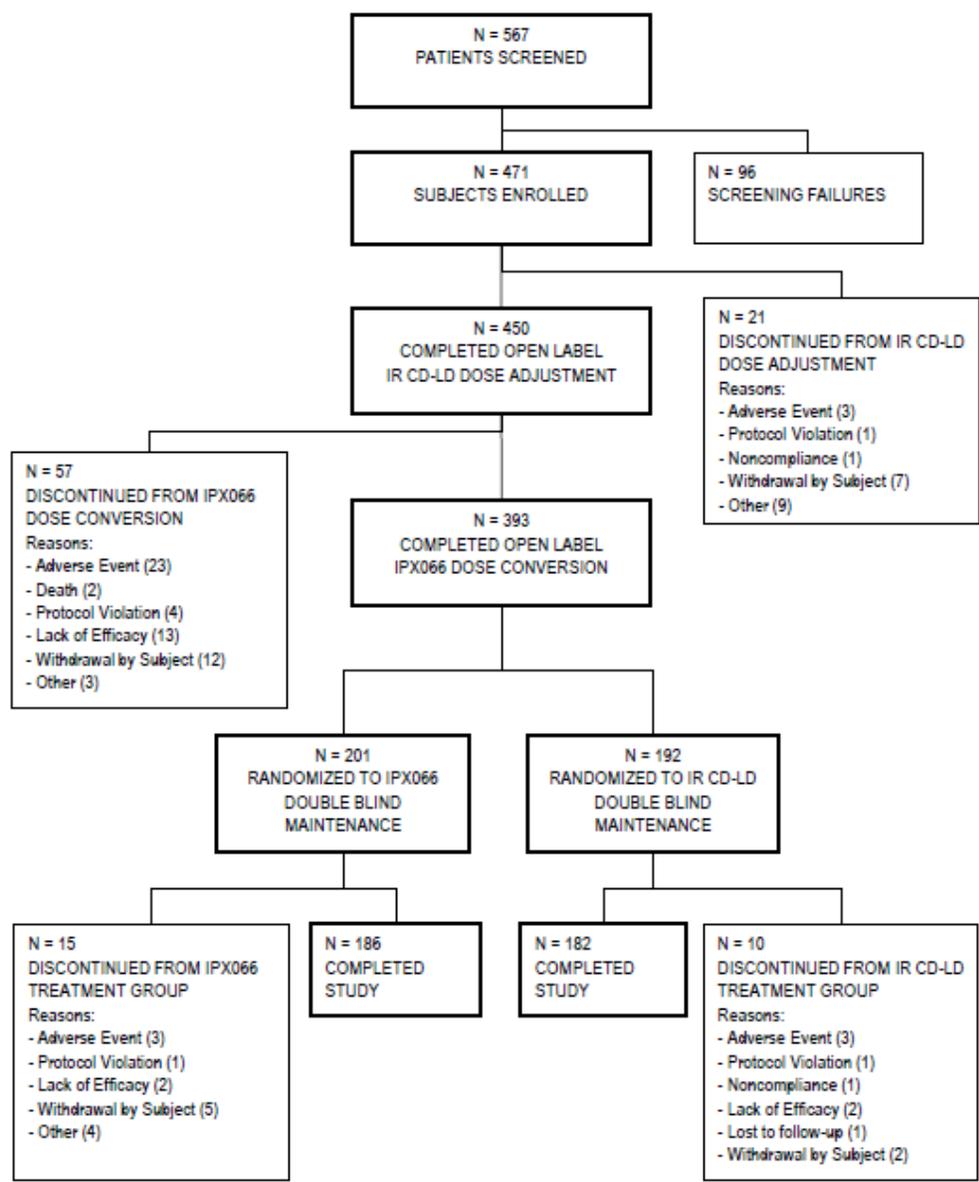


Table 17: Primary Efficacy Outcome IPX066-B09-02

Table 11: Summary of Parkinson’s Disease Diary Data for Randomized Subjects in Study IPX066-B09-02

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

^a Baseline-adjusted analysis of covariance

Source: Tables 14.2.1.1-4, 14.2.1.1-5, 14.2.1.1-8, 14.2.1.1-9, 14.2.1.1-10.

The mean difference between patients treated with IPX066 and IR CD LD for the primary efficacy endpoint, Off time as a percentage of waking hours in a day was statistically significant. The difference in Off hours was also statistically significant (P<0.05) in favor of IPX066.

Table 18: Number of Doses Taken Per Day IPX066-B09-02

TABLE 14.2.8.3 (Page 1 of 1)
Distribution of Final Number of Doses Taken Daily by Treatment
(All Randomized Subjects)

Number of Doses per Day	IPX066 (N=393)	IR CD-LD (N=393)
< 3	0	0
3	205 (52.2%)	1 (0.3%)
4	156 (39.7%)	172 (43.8%)
5	31 (7.9%)	105 (26.7%)
6	0	64 (16.3%)
> 6	1 (0.3%)	51 (13.0%)
N (%)	393 (100%)	393 (100%)
Mean (SD)	3.6 (0.7)	5.1 (1.5)
Median	3.0	5.0
(Min, Max)	(3, 7)	(3, 18)

Patients in the study were permitted to increase the number of doses of IPX066 taken during the day, approximately 8% of patients taking IPX066 required more than 4 doses per day. Only 1 patient took more than 6 doses per day compared to 57 (13%) in the IR CD LD group.

Table 19: Number of Capsules Taken Per Day by Strength of IPX066

TABLE 14.2.8.2 (Page 5 of 5)
Distribution of Final IPX066 Frequency and Capsules Taken by IPX066 Dose Strength
(All Randomized Subjects)

IPX066 245 mg

Number of Capsules	Daily Dose Frequency			Total (N=60)
	3 (N=13)	4 (N=31)	5 or more (N=16)	
3 to 4	0	2 (6.5%)	0	2 (3.3%)
5	0	0	0	0
6	1 (7.7%)	0	1 (6.3%)	2 (3.3%)
7	0	6 (19.4%)	1 (6.3%)	7 (11.7%)
8	1 (7.7%)	8 (25.8%)	0	9 (15.0%)
9	8 (61.5%)	2 (6.5%)	0	10 (16.7%)
10	1 (7.7%)	3 (9.7%)	3 (18.8%)	7 (11.7%)
11	1 (7.7%)	1 (3.2%)	1 (6.3%)	3 (5.0%)
12	1 (7.7%)	6 (19.4%)	2 (12.5%)	9 (15.0%)
13 to 15	0	2 (6.5%)	3 (18.8%)	5 (8.3%)
>=16	0	1 (3.2%)	5 (31.3%)	6 (10.0%)
N (%)	13 (100%)	31 (100%)	16 (100%)	60 (100%)
Mean (SD)	9.2 (1.4)	9.3 (2.8)	13.6 (4.8)	10.4 (3.8)
Median	9.0	8.0	13.0	9.5
(Min, Max)	(6, 12)	(4, 16)	(6, 22)	(4, 22)

CDTL Comment:

The sponsor listed 6 patient taking > 16 capsules of 245 mg of patients in the study required > 16 capsules of 245 mg IPX066 per day. The highest doses recorded were in 2 patients, one taking 22 capsules of 245 mg (Total LD component dose=5390 mg/d) of IPX066 and another taking 21 capsules of the 245 mg strength of IPX066 (Total LD component dose=5145 mg/d). The Sponsor listed twenty-three patients (3.8%) were listed as taking more than 10 capsules/day. The number of patients taking more than 10 capsules factors into the consideration of the safety margin for the HED for the animal NOAEL and the maximum amount of (b) (4) patients may receive with use of this product. It appears that few patients may require greater than 10 capsules of the 245 mg strength (containing the highest amount of (b) (4)) to control their PD motor symptoms.

Table 20: Summary of United Parkinson's Disease Rating Scale Results for Randomized Subjects in Study IPX066-B09-02 (Sponsor's Table)

UPDRS Part ^a	UPDRS Score (Mean±SD)				P value ^b
	IPX066 (N = 201)		IR CD-LD (N = 192)		
	Baseline (Visit 1)	End of Study	Baseline (Visit 1)	End of Study	
II + III	32.32±14.42	26.61±12.85	32.41±15.24	30.27±15.12	<0.0001
I + II + III	34.14±14.88	28.19±13.37	34.26±15.84	32.22±15.85	<0.0001
Total	39.34±15.18	32.96±13.71	39.22±15.88	37.00±16.37	<0.0001
I	1.82±1.29	1.58±1.42	1.85±1.44	1.95±1.69	0.0045
II "on"	9.11±4.75	7.79±4.71	8.81±5.16	8.60±5.56	0.0030
II "off"	17.35±6.80	16.27±6.80	17.14±6.32	17.04±7.03	0.0105
III	23.21±11.47	18.83±9.49	23.60±11.43	21.67±10.89	<0.0001
IV	5.20±2.15	4.77±2.59	4.96±1.86	4.78±2.17	0.5534

^a Parts I-IV in the "on" state, and Part II also in the "off" state

^b Baseline-adjusted analysis of covariance

Abbreviations: UPDRS = United Parkinson's Disease Rating Scale; IR CD-LD = immediate-release carbidopa-levodopa.

Source: Tables 14.2.1.2-1, 14.2.1.3-1, 14.2.1.6-1, 14.2.1.5-1, 14.2.1.6-1, 14.2.1.6-6, 14.2.1.7-1, 14.2.1.8-1.

The analyses of several secondary endpoints demonstrated a p-value <0.05 in favor of IPX066 such as the UPDRS parts 2 and 3 individually or combined. The sponsor did not identify key secondary outcome measures and there was no pre-specified plan to adjust for comparisons of the two treatments on multiple secondary endpoints.

Table 21: Distribution and Analysis of PGI by Treatment -End of Study (All Randomized Subjects) IPX066-B09-02 (Sponsor's Table)

Patient Global Impression	IPX066 (N=200)	IR CD-LD (N=189)	Total (N=389)
Very Much Worse (1)	0	0	0
Much Worse (2)	13 (6.5%)	22 (11.6%)	35 (9.0%)
Minimally Worse (3)	25 (12.5%)	48 (25.4%)	73 (18.8%)
No Change (4)	27 (13.5%)	39 (20.6%)	66 (17.0%)
Minimally Improved (5)	58 (29.0%)	47 (24.9%)	105 (27.0%)
Much Improved (6)	60 (30.0%)	29 (15.3%)	89 (22.9%)
Very Much Improved (7)	17 (8.5%)	4 (2.1%)	21 (5.4%)
N (%)	200 (100%)	189 (100%)	389 (100%)
Mean (SD)	4.9 (1.4)	4.1 (1.3)	4.5 (1.4)
Median (Min, Max)	5.0 (2, 7)	4.0 (2, 7)	5.0 (2, 7)
ANOVA P-Value	<0.0001		

The Patient Global Impression of their condition at the end of the study was generally rated as improved, The percentage of patients in the IPX066 group who rated their condition as being Improved (Minimally-Very Much Improved) was superior (p<0.05) compared to patients randomized to their previously optimized dose of IR CD LD.

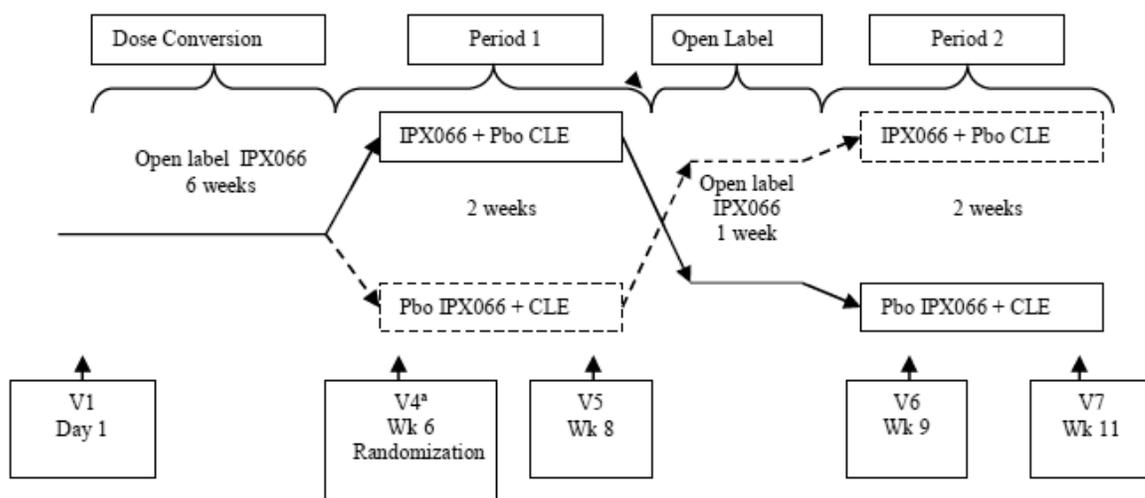
CDTL Efficacy Conclusion:

The results for the protocol specified primary endpoint, the change in the percent of the awake portion of the day spent in the off state favored the IPX066 treated group compared to the IR CD LD treated group. The analysis demonstrated the difference was statistically significant. Similar findings were reported for traditionally important endpoints such as the UPDRS Parts II (ALD) and Part III (motor) subscales. The patients perception of the changes rated by the PGI support the conclusion that the treatment difference in percentage of off time in favor of IPX066 is clinically meaningful.

Study IPX066-B09-06

Study IPX066-B09-06 was a randomized, double-blind, double-dummy, 2-treatment, two 2-week crossover study of IPX066 versus CLE (Part 1) followed by an open-label safety study (Part 2) of IPX066 in Advanced Parkinson’s disease. The double-blind crossover portion included two 2-week treatment periods separated by a 1-week washout period of IPX066 treatment.

Fig 7: Design Schematic for Study IPX066-B09-06 (Sponsor’s Figure)



Abbreviations: Pbo = placebo; CLE = carbidopa/levodopa/entacapone; V = visit; Wk = week

^aVisits 2 and 3 during Dose Conversion period are at Weeks 2 and 4.

Source: Appendix 16.1.1, section 3.0.

Table 22: Randomization Scheme Study IPX066-B09-06 (Sponsor's Table)

	Period 1	Period 2
Sequence 1	IPX066 ^a + CLE placebo ^b	IPX066 placebo ^a + CLE ^b
Sequence 2	IPX066 placebo ^a + CLE ^b	IPX066 ^a + CLE placebo ^b

^aIPX066 (active or placebo) at the same dose and frequency as that recorded at the end of Week 6 IPX066 Dose Conversion period (Visit 4).

^bCLE (active or placebo) at the same dose and frequency as that recorded at study entry (Visit 1).

The Sponsor's Trial Design Rationale

Subjects were required to be on a stable regimen of CD-LD and entacapone for at least 4 weeks prior to entering the study to ensure that the dose regimen of the comparator treatment was clinically suitable for the individual patient in the opinion of the Investigator.

Upon entry into the study, subjects were converted from stable doses of CLE to open-label IPX066 over a 6-week period. Following dose conversion, subjects were randomized in a 1:1 ratio to one of two treatment sequences and treated with either IPX066 or CLE under double-blind conditions for 2 weeks (Period 1). Subjects then received open-label IPX066 for 1-week, followed by treatment with the alternate study medication (CLE or IPX066) for 2 weeks (Period 2) under double-blind conditions.

“This regimen could be modified to optimize clinical benefit but dosing of IPX066 could not be more frequent than approximately every 4 hours, and not more than 5 times per day”

On the first day of Period 1 and Period 2, a subset of subjects (PK Cohort) received a single dose of assigned study medication in the clinic and underwent assessment of pharmacokinetics and pharmacodynamics (motor effect) for 8 hours. This cohort of subjects did not take any PD medications containing LD, CD, or entacapone starting at 6:00 PM the day before the first day of each double-blind treatment period. The IPX066 dose was given in the morning was the dose established during the dose conversion period.

If dose adjustment was necessary, the following options were considered using the same dosage strength of IPX066. The number of capsules at each dose could vary:

- If turning “On” is slow in the morning, consider taking the morning dose in the fasted state and/or increasing the morning dose.
- If turning “On” is slow later in the day or to reduce “end-of-dose” off time, consider increasing the dose before reducing the dosing interval.

If dose conversion based on the table above caused troublesome dyskinesia, the following guidelines were used:

- Reduce one capsule per dose.
- Reduce (lower) the dose before increasing the dosing interval

CDTL Comment:

The protocol allows for dose adjustment or in other words, “dose optimization” in the IPX066 Conversion Period. Although, the dose adjustment for the IPX066 dose conversion may have some limits, no dose change of CLE is permitted for the 4 weeks prior to trial entry. By design, the comparison between treatment groups is unfair because patients on unadjusted dosages of CLE are compared to patients taking doses of IPX066 after dose adjustment is permitted.

Study visits were to be scheduled at the ends of Week 2 (Visit 2) and Week 4 (Visit 3) during the Dose Conversion period. Although two dosage strengths of IPX066 could be dispensed at Visits 1 and 2, a single dosage strength of IPX066 was to be dispensed at Visit 3.

At the end of the IPX066 Dose Conversion period (Week 6), the subject was to be maintained on a single dosage strength and the dosing regimen was to remain stable for at least 5 days prior to randomization. If this was not possible, the subject was not to be randomized into the study. All subjects randomized were to be maintained throughout the study on the strength of IPX066 established at randomization.

Table 24: The Suggested Initial Dose Conversion Scheme IPX066-B09-06

Suggested Initial Dose Conversion to IPX066

Total Daily LD Dose (mg)	Suggested Initial IPX066 Dose (LD in mg) ^a		
	<u>Morning Dose</u>	<u>Midday Dose</u>	<u>Evening Dose</u>
(b) (4)	4 capsules x 95	4 capsules x 95	4 capsules x 95
	2 capsules x 245	2 capsules x 245	2 capsules x 245
	3 capsules x 195	3 capsules x 195	3 capsules x 195
	3 capsules x 245	3 capsules x 245	3 capsules x 245
	4 capsules x 245	4 capsules x 245	4 capsules x 245

Abbreviations: LD = Levodopa

^aeach dose approximately 6 hours apart during waking hours

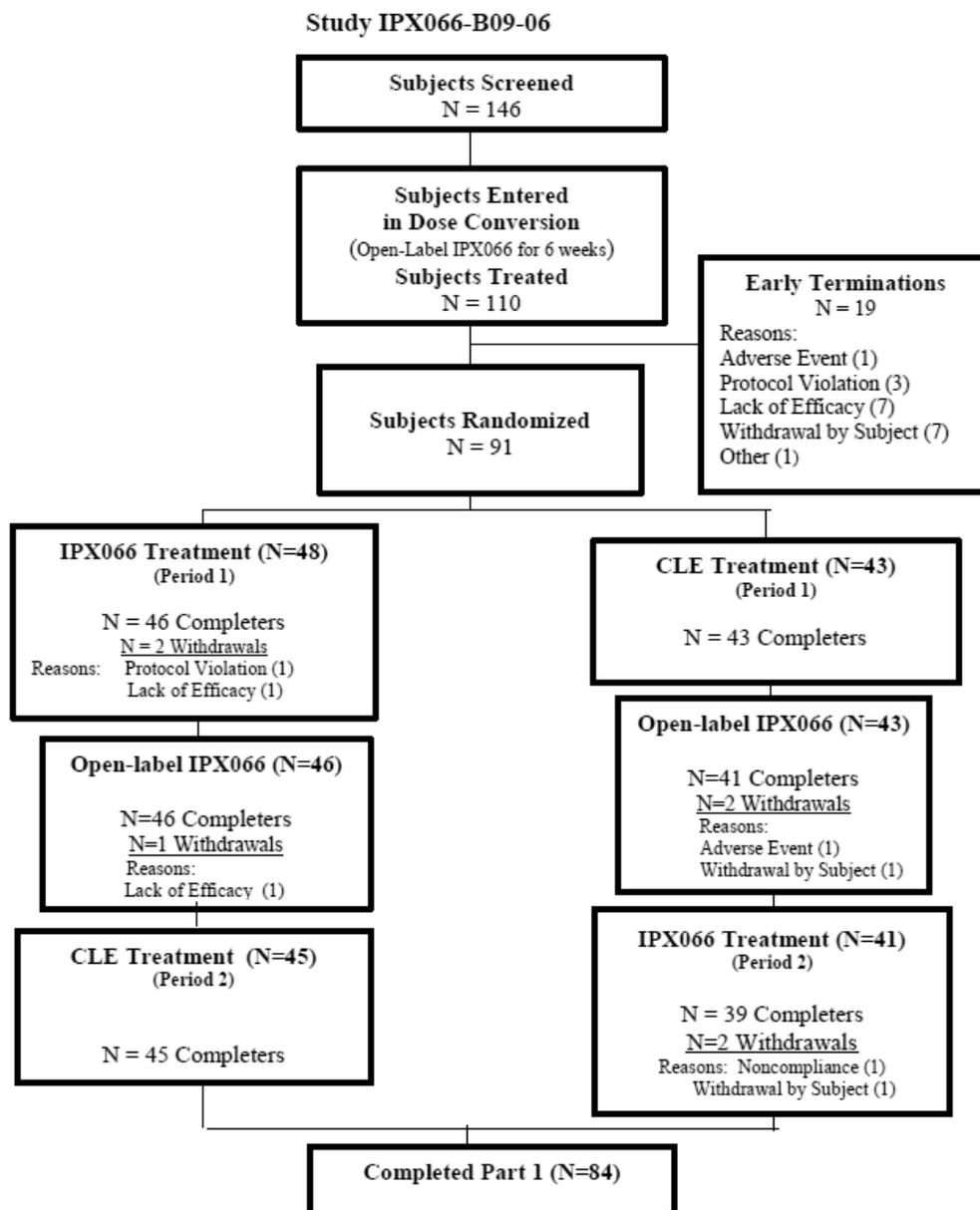
Adjustment of Dosing Frequency and Dosing Intervals:

It was recommended in the protocol that the patients take IPX066 approximately 6 hours apart during waking hours (for example, a subject may take IPX066 at 6 AM, noon, and 6 PM). Patients may also take a bedtime dose if needed. The dosing interval may vary but it should not be more frequent than every 4 hours. Patients enrolled in the trial could not receive study medication more than 5 times per day.

During crossover treatment Periods 1 and 2, the CLE (or placebo) dose was to remain the same as that of the pre-study regimen (recorded at Visit 1), and the IPX066 (or placebo) dosage was to be the same as that established during the Dose Conversion period (recorded at Visit 4). *No adjustment of the dosing regimens (number of capsules per dose and dosing frequency) was permitted during these 2-week double-blind treatment periods.*

Table 23: Patient Disposition (Sponsor’s Table)

Figure 2: Disposition of Subjects – Part 1



*Total daily dose of levodopa
 N = number, CLE = carbidopa/levodopa plus entacapone, Pbo = placebo
 Source: Table 14.1.1.1-3

Primary Efficacy Measure

The primary efficacy parameter for this study was the percent “Off” time during waking hours based on subject PD diaries (Hauser) collected at the end of each double-blind treatment period. For each day, the percent “Off” time was 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 used.

Table 24: Primary Endpoint IPX066-B09-06 (Sponsor’s Table)

Table 12: Analysis of Primary Efficacy Endpoint: Percent “Off” Time during Waking Hours

Percent “Off” Time	Baseline (N=83)	End of Conversion (N=83)	Treatment	
			IPX066 (N=83)	CLE (N=83)
Mean (SD)	36.08 (16.290)	22.82 (14.864)	23.98 (16.242)	32.48 (21.917)
Median	32.02	20.08	20.56	32.11
(Min, Max)	(15.17, 80.61)	(0.00, 67.51)	(0.00, 61.14)	(0.00, 100.00)
			P-Value	<0.0001

NOTE: P-Value based on mixed model analysis of variance including fixed effect factors of treatment, sequence, period and the random-effect inter- and intra-subject factors.

Source: Table 14.2.1.1.

Table 25: Distribution and Summary of IPX066 and CLE Total Daily LD Dose in Randomized Subjects in Study IPX066-B09-06 (N=91) (Sponsor’s Table)

Total Daily Dose (mg)	Treatment	
	IPX066 (N=91)	CLE (N=91)
< 400	0	0
400 to < 800	1 (1.1%)	65 (71.4%)
800 to < 1200	20 (22.0%)	22 (24.2%)
1200 to < 1700	28 (30.8%)	4 (4.4%)
1700 to < 2400	30 (33.0%)	0
≥ 2400	12 (13.2%)	0
Mean Dose(SD)	1791.6 (770.82)	660.4 (246.8)
Median Dose	1560.0	600.0
(Min, Max)	(735, 4900)	(400, 1600)

Source: Table 14.2.26.1

CDTL Comment:

The protocol specified analysis of the primary endpoint Difference in the percent of “Off” time during waking hours was statistically significant in favor of treatment with IPX066. However, the issue of the unfair comparison of the two treatment groups created is a major design limitation. The trial design biases the results against the null hypothesis, in favor of IPX066. The finding that the mean dose of IPX066 patients received during the trial was three times higher than the mean dose of CLE supports the conclusion of bias. The observed 3-fold increase in the LD component of IPX066 compared to CLE is much higher than the Sponsor’s recommendation for a 30% increase (of IPX066) for patients converting from CLE to IPX066 based on PK information.

10. Safety

Table 26 Summary of IPX066 Clinical Trials Program (Sponsor's Table)

Table 1: Overview of Studies in the IPX066 Clinical Development Program

Study Numbers	Study Title	Status	Number of Subjects	
			Enrolled	Completed
STUDIES IN HEALTHY SUBJECTS				
Phase 1, Pooled Studies				
IPX066-B08-08 ^a	Effect of Food on the Pharmacokinetics of IPX066 (stopped early)	Study stopped ^a	21	None
IPX066-B08-09	Assessment of Dose Proportionality of IPX066	Completed	31	28
IPX066-B08-10	Relative Bioavailability of IPX066 to Carbidopa-Levodopa Formulations	Completed	24	22
IPX066-B09-01	Effect of Food on the Pharmacokinetics of IPX066	Completed	21	19
IPX066-B09-04	Effect of Alcohol on IPX066	Completed	27	18
IPX066-B10-01	Bioequivalence study (2 sites)	Completed	39	34
Total Number of Subjects in Phase 1 Studies			163	121
STUDIES IN SUBJECTS WITH PARKINSON'S DISEASE				
Phase 2, Controlled Study				
IPX066-B08-11	A Study to Compare Pharmacokinetics and Pharmacodynamics of IPX066 to Standard Carbidopa-Levodopa	Completed	27	27
Total Number of Subjects in Phase 2 Study			27	27
Phase 3, Adequate and Well-Controlled Studies				
IPX066-B08-05	A Placebo-Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson's Disease	Completed	381	300
IPX066-B09-02	A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson's Disease	Completed	471	368
IPX066-B09-06 Part 1	A Study to Compare IPX066 and CD-LD-Entacapone in Advanced Parkinson's Disease	Completed	110	84
Total Number of Subjects in Phase 3 Controlled Studies			962	752

Study Numbers	Study Title	Status	Number of Subjects	
			Enrolled	Completed
Phase 3, Open-Label, Long-Term Safety Extension Studies^b				
IPX066-B09-03	An Open Label Extension Study of the Safety and Clinical Utility of IPX066 in Subjects with Parkinson's Disease	Completed	617 ^b	567
IPX066-B09-06 Part 2	A Study to Compare IPX066 and CD-LD-Entacapone in Advanced Parkinson's Disease	Completed	74 ^c	66
IPX066-B11-01	An Open-Label Conversion Study of Carbidopa-Levodopa Extended Release (CD-LD ER) Taken Alone or in Combination with Carbidopa-Levodopa Immediate Release (CD-LD IR) to IPX066 Followed by an Open-Label Extension Safety Study of IPX066 in Subjects with Advanced Parkinson's Disease	Ongoing	43 ^d	NA
Total Number of Subjects in Long-Term Safety Extension Studies			734	633

^a Study IPX066-B08-08 was stopped early because of a sample process error that rendered the samples unsuitable for PK analysis.

^b Since Study IPX066-B09-03 enrolls subjects from Studies IPX066-B08-05, IPX066-B08-11, and IPX066-B09-02, these subjects are not new subjects.

^c Since Study IPX066-B09-06 Part 2 is an open-label IPX066 extension study that enrolled subjects from Study IPX066-B09-06 Part 1, these subjects are also counted in Study IPX066-B09-06 Part 1.

^d Enrolled as of January 23, 2012.

Abbreviations: NA = not applicable.

Source: IPX066-B08-08 Clinical Study Report (CSR), IPX066-B08-09 CSR, IPX066-B08-10 CSR, IPX066-B09-01 CSR, IPX066-B09-04 CSR, IPX066-B10-01 CSR, IPX066-B08-11 CSR, IPX066-B08-05 CSR, IPX066-B09-02 CSR, IPX066-B09-06 Part 1 CSR, IPX066-B09-03 CSR.

Pooling Strategy Agreed to at the Pre-Phase 3 Meeting

FDA Response to Question 10: Preliminary FDA Response:

In general, we find the organization of the ISS and ISE to be acceptable. We recommend that your safety dataset submission be organized into the following:

Pool 1a: Placebo controlled studies for early PD which includes the following study:

- **IPX066-B08-05** A placebo controlled study of early Parkinson's subjects.

This study evaluated the 3 different fixed doses of IPX066 with placebo.

Pool 1b: All active controlled studies in advanced PD which includes the following studies:

- **IPX-066-B09-02** An active controlled (IR CD-LD) study in advanced PD subjects
- **IPX-066-B09-06 (part 1)** A crossover study that compares IPX066 with a combination of CD-LD and entacapone.

Pool 1c: Combined data from Pool 1a and 1b

Pool 2a: Uncontrolled, open label safety trials and trial extensions in early PD subjects

- **IPX066-B09-03:** Includes subjects who completed IPX066-B08-05.

Pool 2b: Open label extension study in advanced PD subjects includes the following studies:

- **IPX066-B08-11**
- **IPX066-B09-02**
- **IPX-066-B09-06 (part 2)**

Pool 2c: Safety data from all open label trials involving LD naïve and advanced PD patients and all open label extensions of placebo-controlled trials (pools 2a plus pool 2b).

Data from Phase 2 trials.

Study IPX066-B08-11 was an open-label, crossover study in subjects (N=27) with advanced Parkinson's disease with motor fluctuations on levodopa therapy. The objectives of the study were to compare the PK, motor effects, and safety of IPX066, with an immediate-release carbidopa-levodopa formulation in advanced Parkinson's disease.

Data from Phase 1 Trials

Data from trials involving healthy volunteers should be contained in a separate data pool.

The Sponsor and the Agency agree to the safety results for PK studies involving healthy subjects that were designed to explore the PK parameters of different formulations of IPX066 would not be included in the pooled data but the safety data would be reported separately in the ISS.

Table 27: The Sponsor’s Plan for Scheme for Integrating Data from Phase 3 Controlled Studies in Subjects with Parkinson’s Disease (Sponsor’s Table)

Individual Phase 3 Controlled Studies in Subjects with Parkinson’s Disease											
Study IPX066-08-05			Study IPX066-09-02			Study IPX066-09-06 Part 1					
Double-Blind IPX066 or Placebo 30 wk			Open-Label Dose IR CD-LD Conversion Dose Adjustment 3 wk			Double-Blind IR CD-LD or IPX066 13 wk		Open-Label Dose Conversion from CLE to IPX066 6 wk		Double-Blind Alternate CLE or IPX066 2 wk	
IPX066 (N = 299)			IPX066 (N = 450)		IPX066 (N = 201)	IPX066 (N = 110)	IPX066 (N = 89)	IPX066	CLE		
Placebo (N = 92)			IR CD-LD (N = 471)	IR CD-LD (N = 192)		CLE (N = 88)		CLE (N = 88)	IPX066		

Integrated Analyses of Subjects with Parkinson’s Disease									
Number of Subjects in Study IPX066-	IPX066			IR CD-LD			CLE	Placebo	Total Subjects
	Open-Label Period	Double-Blind Period	Total Exposed During Open-Label or Double-Blind Period	Open-Label Period	Double-Blind Period	Total Exposed During Open-Label or Double-Blind Period	Double-Blind Period	Double-Blind Period	
B08-05	—	289	—	—	—	—	—	92	381 ^a
B09-02	450	201	—	471	192	—	—	—	471 ^a
B09-06 Part 1	110	89	—	—	—	—	88	—	110 ^a
Total Subjects	560^a	579^a	849	471^a	192^a	471	88^a	92^a	962^a

^aNumber of unique subjects enrolled.

CLE = carbidopa/levodopa/entacapone
 IR CD-LD = immediate-release carbidopa/levodopa
 wk = week

CDTL Comment

The sponsor integrated the safety data from all of the Phase 3 clinical trials according to treatment phase (Double blind, open-label and total exposed). The analysis of pooled data in this case would be difficult to interpret because the clinical trial used different control medications or Placebo. The results of each trial was considered separately rather than analyzing the pooled clinical trials data to determine the frequency of adverse events.

The only study IPX066 B08-05 assessed the effects of IPX066 in patients with early PD. The safety information for patients with advanced PD rely on the results of trial IPX066-B09-02

The crossover design of study IXP066 B09-06 and the comparison of treatment groups that were not treated in a similar manner (treatment optimized for IPX066 but not for CLE active comparator) makes the safety comparison between IXP066 and CLE unreliable.

Exposure

Table 28 : Exposure for Subjects by Total Daily Dose by Cumulative Duration Including Information in the 120-Day Update (Sponsor’s Table)

IPX066-ISS: 120-DAY SAFETY UPDATE POST TEXT REPORT

**TABLE 15.3.3.1-2 (Page 1 of 1)
Exposure for Subjects on IPX066: Total Daily Dose by Cumulative Continuous Duration
(All Subjects Exposed to IPX066)**

Dose of IPX066 Received (Total Daily Dose)	Duration of Exposure to IPX066					Total (N=1539)
	<=29 Days (N=285)	30 to 89 Days (N=366)	90 to 179 Days (N=72)	180 to 364 Days (N=624)	>= 365 Days (N=192)	
< 285 mg	72	0	0	3	0	75
285 mg to < 435 mg	56	0	0	24	1	81
435 mg to < 735 mg	53	17	5	144	23	242
735 mg to <1170 mg	29	108	20	202	74	433
1170 mg to <1600 mg	29	89	18	149	40	325
1600 mg to <2400 mg	24	110	21	73	41	269
>=2400 mg	22	42	8	29	13	114

The Sponsor’s proposed Maximum recommended dose of IPX066 in patients with advanced PD is 2205 of the LD component (median total daily LD dose=1450 mg) is adequate given the safety experience of the marketed levodopa containing drugs. The number of patients taking IPXo66 for 6 and 12 months meets the number of patients agree to by the Sponsor and the Agency in the pre-submission meeting.

Deaths

Dr. Constantino’s review of the narratives describing patients who died (n=11) during the development program found that the most frequent cause of death was due to cardiovascular disease and other illnesses that commonly cause death in patients with PD. Her review of the narratives did not find an example where death appeared to be causally associated with IPX066. The sponsor only reported 6 deaths during the clinical development of IPX066. The differences in the number of deaths between the sponsor’s accounting and the clinical reviewer was the cut-off for deaths related to study medication were counted. In the 120 day safety update there were 5 death reported in total however, the sponsor only counted 1 death as a reason for termination. Two other patients died during the open-label extension studies from complication of SAEs and another patient died 4 days after discontinuing study medication. The sponsor’s cutoff for counting death related to study was

72 hours after stopping study medication, death reported more than 72 hours after stopping IPX066 were not attributed to the medication.

Table 29: Causes of Death in the Clinical Trials Program (Reviewer’s table)

Preferred Term	N
Cardiac	3
Respiratory	2
Cancer	1
Sudden Death from Unknown Cause	1
Acute Pancreatitis	1
Stroke	1
Infection	1
Immobility due to Fracture and PD	1

Serious Non-fatal Adverse Events

IPX066-B08-05 (Early PD)

There were 4 patients reporting cardiovascular ischemic events (discussed in detail below) in study IXP066-B08-05 (Early PD), 3 patients (M.I. or coronary artery disease) in the 145 mg (low dose group) and 1 (A-V Block) in the 245 mg (intermediate dose group) reported CV ischemic events. The placebo the non-fatal serious adverse events were likely unrelated to IPX066. The next most frequent (n=3 patients) serious non-fatal events was reported for the infection SOC all of the remaining non-fatal serious adverse events (n=10) were events that occurred in a single patient. Three of the remaining 10 events occurred in patients receiving Placebo, including a single patient who suffered a “cerebrovascular accident”.

IPX066-B09-02 (Advanced PD)

The trial allowed a flexible dosing with 3 Phases, a IR CD LD Dose Adjustment Phase, a Dose Conversion Phase (from IR CD-LD to IPX066). After blinded randomization patients entered the Maintenance Phase (Optimal dose of IPX066 or IR CD LD). Fourteen patients experienced SAEs in the Conversion Phase from IR CD LD to IPX066. One patients died from sudden death during this Phase. Two patients reported non-cardiac chest pain, dyskinesia or gait disturbance. The remaining SAEs were all single events. All of the patients reporting an SAE during Dose Conversion to IPX066 were withdrawn from the trial.

There was an additional 16 SAEs that occurred during the Maintenance Phase, 11 on IPX066 including a single patient who suffered an M.I. One patient in the IR CD LD group had atrial fibrillation but there were no reported cardiovascular ischemic events.

The number of patients who withdrew prematurely during the Dose Conversion Phase (table below) to IPX066 is remarkable. The majority of patients withdrew because of an adverse event and another 12 patients were listed as “withdrawn by subject” without further documentation in the study

report. The high number of patients who withdrew from the trial during Dose Conversion due to adverse event suggests that patients with advanced PD tolerate IR CD LD better than IPX066.

Table 30: Summary of Disposition During Study IPX066-B09-02 Advanced Parkinson’s Disease (Sponsor’s Table)

	Number of Subjects (%)				
	IR CD-LD Dose Adjustment	IPX066 Dose Conversion	Maintenance		
		Total	IPX066	IR CD-LD	Total
Entered	471 (100%)	450 (100%)	201 (100%)	192 (100%)	393 (100%)
Completed	450 (95.5%)	393 (87.3%)	186 (92.5%)	182 (94.8%)	368 (93.6%)
Discontinued Early	21 (4.5%)	57 (12.7%)	15 (7.5%)	10 (5.2%)	25 (6.4%)
Reason for Discontinuation					
Adverse Event	3 (0.6%)	23 (5.1%)	3 (1.5%)	3 (1.5%)	6 (1.5%)
Death	0	2 (0.4%)	0	0	0
Protocol Violation	1 (0.2%)	4 (0.9%)	1 (0.5%)	1 (0.5%)	2 (0.5%)
Noncompliance	1 (0.2%)	0	0	1 (0.5%)	1 (0.3%)
Lack of Efficacy	0	13 (2.9%)	2 (1.0%)	2 (1.0%)	4 (1.0%)
Lost to Follow-up	0	0	0	1 (0.5%)	1 (0.3%)
Withdrawal by Subject	7 (1.5%)	12 (2.7%)	5 (2.5%)	2 (1.0%)	7 (1.8%)
Other	9 (1.9%)	3 (0.7%)	4 (2.0%)	0	4 (1.0%)

Source: Table 14.1.1.1, Table 14.1.4.1.

Study IPX066-B09-06

There no reported deaths during the study and 4 patients reported SAEs one patient reported multiple SAEs. Non-of the events had a clear causal relationship to study medication. The SAEs were related to Parkinson’s disease or a co-morbidity.

Non-Serious Adverse Events in IPX066-B08-05 and IPX066-B09-02

Table 31: Summary of Adverse Events Occurring in at Least 5% of Subjects in Any Treatment Group in Study IPX066-B08-05 Early PD (Randomized Subjects) (Sponsor’s Table)

Adverse Event Preferred Term	Number of Subjects (%)				
	Placebo (N = 92)	IPX066 LD Dose Group			Total (N = 381)
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)	
Nausea	8 (8.7)	12 (13.8)	20 (19.2)	20 (20.4)	60 (15.7)
Headache	10 (10.9)	6 (6.9)	13 (12.5)	17 (17.3)	46 (12.1)
Dizziness	5 (5.4)	8 (9.2)	20 (19.2)	12 (12.2)	45 (11.8)
Insomnia	3 (3.3)	2 (2.3)	9 (8.7)	6 (6.1)	20 (5.2)
Abnormal Dreams	0	2 (2.3)	6 (5.8)	5 (5.1)	13 (3.4)
Dry Mouth	1 (1.1)	3 (3.4)	2 (1.9)	7 (7.1)	13 (3.4)
Vomiting	3 (3.3)	2 (2.3)	2 (1.9)	5 (5.1)	12 (3.1)
Constipation	1 (1.1)	2 (2.3)	6 (5.8)	2 (2.0)	11 (2.9)
Dyskinesia	0	2 (2.3)	4 (3.8)	5 (5.1)	11 (2.9)
Anxiety	0	2 (2.3)	3 (2.9)	5 (5.1)	10 (2.6)
Depression	5 (5.4)	1 (1.1)	2 (1.9)	2 (2.0)	10 (2.6)
Orthostatic Hypotension	1 (1.1)	1 (1.1)	1 (1.0)	5 (5.1)	8 (2.1)

Note: A subject may be reported in more than one System Organ Class or Preferred Term. The total number of subjects exposed to study treatment is the denominator for percentage calculation.
Source: Table 14.3.1.1-5.

The frequency of Dyskinesia, Nausea and Dizziness all appear to increase with the dose of study medication in patients with early PD in study IXP066-B-08-05

Table 32: Non-serious Adverse Events ≥ 2% and Greater in IPX066 Compared to IR CD LD In Patients with Advanced PD (Sponsor’s Table)

Trial IPX066-B09-02				
Randomized Treatment	IPX066 N=201)		IR CD LD (N=192)	
Period	Dose Conversion	Maintenance	Dose Conversion	Maintenance
Preferred Term				
Constipation	4 (2.0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)
Dyskinesia	9 (4.5%)	5 (2.5%)	7 (3.6%)	2 (1.0%)
Headache	7 (3.5%)	2 (1.0%)	4 (2.1%)	2 (1.0%)
Anxiety	4 (2.0%)	2 (1.0%)	1 (0.5%)	0
Insomnia	3 (1.5%)	4 (2.0%)	3 (1.6%)	1 (0.5%)

Preferred terms listed are at least ≥ 2% (either period) and greater in IPX066 group compared to IR CD LD

The data from the 2 controlled pivotal trials found dyskinesia was more frequent in study IPX066-B09-02 (patients with advanced PD) converted from IR CD LD to IPX066. Dyskinesia was more frequent in the IPX066 treated group in the dose conversion and maintenance phases of the study. In general, nausea and dizziness was not reported frequently in IPX066 IR CD LD because patients had to tolerate a stable dose if IR CD LD to enter the trial.

IPX066-B09-06

In this trial patients in a stable (non-optimized dose of CLE for 1 month entered the Dose conversion Phase to IPX066. Patients were randomized to either their optimized dose of IPX066 or their non-optimized dose of CLE.

Two subjects discontinued from the study early due to AEs. During the 6-week Dose Conversion period (N=110), one subject (0.9%) prematurely discontinued from the study due to an AE. The patient withdrew after reporting 3 gastrointestinal system AEs (dyspepsia, nausea, and vomiting). All 3 AEs were assessed as treatment related (“possibly related”) and of moderate severity. During the double-blind crossover period (N=91), one subject (1.1%) withdrew early from the study due to dyskinesias.

During the Dose Conversion period (N=110), 2 subjects (1.8%) reported SAEs. One subject reported 3 SAEs of atrial fibrillation, constipation and chemical gastroenteritis. He developed chemical gastroenteritis and dehydration secondary to over-aggressive self-medication with laxatives for constipation. One subject had mild hypercalcemia but continued in the study after rapid resolution.

Analysis of Pooled Safety Data

Table 33: Disposition of Subject in Controlled Phase 3 Studies-Overall PD Population (All Enrolled Subjects) (Sponsor’s Table)

Status/Reason for Discontinuation	Number of Subjects (%) in Overall PD Population							
	IPX066			IR CD-LD			CLE Double Blind	Placebo Double Blind
	Open Label	Double Blind	Total Exposed	Open Label	Double Blind	Total Exposed		
Received Treatment	560 (100)	579 (100)	849 (100)	471 (100)	192 (100)	471 (100)	88 (100)	92 (100)
Completed Treatment	481 (85.9)	500 (86.4)	691 (81.4)	450 (95.5)	182 (94.8)	440 (93.4)	88 (100)	71 (77.2)
Discontinued Treatment Early	79 (14.1)	79 (13.6)	158 (18.6)	21 (4.5)	10 (5.2)	31 (6.6)	0	21 (22.8)
Reasons for Discontinuation								
Adverse Event*	25 (4.5)	38 (6.6)	63 (7.4)	3 (0.6)	3 (1.6)	6 (1.3)	0	4 (4.3)
Death	2 (0.4)	1 (0.2)	3 (0.4)	0	0	0	0	0
Protocol Violation	7 (1.3)	5 (0.9)	12 (1.4)	1 (0.2)	1 (0.5)	2 (0.4)	0	0
Non-Compliance	0	3 (0.5)	3 (0.4)	1 (0.2)	1 (0.5)	2 (0.4)	0	0
Lack of Efficacy	21 (3.8)	8 (1.4)	29 (3.4)	0	2 (1.0)	2 (0.4)	0	12 (13.0)
Lost To Follow-Up	0	2 (0.3)	2 (0.2)	0	1 (0.5)	1 (0.2)	0	0
Study Terminated by Sponsor	0	0	0	0	0	0	0	0
Withdrawal by Subject	20 (3.6)	13 (2.2)	33 (3.9)	7 (1.5)	2 (1.0)	9 (1.9)	0	4 (4.3)
Other	4 (0.7)	9 (1.6)	13 (1.5)	9 (1.9)	0	9 (1.9)	0	1 (1.1)

* TEAEs leading to study discontinuation are discussed in section.3.3.4

Abbreviations: CD-LD = carbidopa-levodopa, CLE = carbidopa-levodopa-entacapone, IR = immediate release, PD = Parkinson’s disease.

IPX066 columns: Include subjects treated in Studies IPX066-B08-05, IPX066-B09-02, and IPX066-B09-06 Part 1.

IPX066 Double Blind column: Includes subjects who received double-blind IPX066 treatment. The IPX066 Double Blind column includes some subjects who were included in the open-label column, if the subjects completed conversion to double-blind treatment from open-label treatment.

IPX066 Open-Label columns: Includes only those subjects who received open-label IPX066 treatment (during Dose Conversion in Study IPX066-B09-02 and IPX066-B09-06 Part 1), or during open-label washout in IPX066-B09-06 Part 1.

IPX066 Total Exposed column: Represents all subjects who received at least one dose of IPX066.

IR CD-LD columns: Includes subjects treated in Study IPX066-B09-02.

IR CD-LD Double Blind column: Includes subjects (Study IPX066-B09-02) who received only double-blind IR CD-LD treatment. The IR CD-LD Double Blind column includes some subjects who were included in the IR CD-LD open-label column, if the subjects had been converted to double-blind treatment after completing Dose Conversion to IPX066 treatment.
 IR CD-LD Open-Label column: Includes only those subjects who received IR CD-LD treatment during Dose Adjustment in Study IPX066-B09-02.
 IR CD-LD Total Exposed column: Represents all subjects who received at least one dose of IR CD-LD.
 CLE column: Includes subjects who received CLE in Study IPX066-B09-06 Part 1.
 Placebo column: Includes subjects who received placebo in Study IPX066-B08-05.

Source: ISS Posttext Table 15.1.1.2-1.

CDTL Comment:

The number of patients treated with IPX066 who withdrew prematurely for adverse events or withdrawal by the patient were significantly greater compared to patients in the placebo or active comparator arms.

Deaths and Nonfatal SAEs Reported in the 120 Day Safety Update

Deaths that were reported in the 120-Day Safety Update were discussed with the other cases of deaths reported during the clinical trials program. There were 5 additional SAEs reported in the 120-Day Safety Update that were not included in the NDA submission.

Non-Serious Adverse events in Pooled open label Data

Table 34: Adverse Events Reported in 5 or More Subjects Post NDA (All Subjects in B09-03 and B09-06 Part 2) (Sponsor’s Table)

AEs Preferred Term	AEs Reported in NDA N=691	AEs Reported Post NDA N=392
Dyskinesia	44 (6.4%)	9 (2.3%)
Fall	46 (6.7%)	8 (2.0%)
Constipation	28 (4.1%)	6 (1.5%)
Respiratory Tract Infection	2 (0.3%)	6 (1.5%)
Insomnia	51 (7.4%)	5 (1.3%)
Arthralgia	25 (3.6%)	5 (1.3%)
Headache	68 (9.8%)	5 (1.3%)

Abbreviation: AE = adverse event, NDA = New Drug Application.
 Note: Post-NDA AEs are those that were reported in the extension studies.
 Source: NDA120 Posttext Table 14.3.1.1-7, 14.3.1.3-1

Ongoing Study IPX066-B11-01 (Total N=43)

Study IPX066-B11-01 is an ongoing multicenter, open-label conversion study of Carbidopa-Levodopa Extended Release (CD-LD ER) taken alone or in combination with IR CD-LD to IPX066 followed by an open-label extension safety study of IPX066 in subjects with advanced PD.

Deaths and Serious Adverse Events

There was one death reported in an 85-year-old male patient who died in hospice during recovery from surgery to repair a hip fracture. A single SAE was reported by the cut-off date for the 120 Day Safety Update in 81-year-old male patients suddenly developed atrial fibrillation with a rapid ventricular response. The atrial fibrillation resolved and the patient continued trial participation on the same dose of IPX066.

Table 35: Summary of Modified Minnesota Impulsive Disorders Interview (m-MIDI) Results during the Maintenance Period in Study IPX066-B09-02 (Sponsor’s Table)

m-MIDI Category	Number of Subjects (%) with Positive Screens Subject ID Number (Treatment Group)		
	Visit 5 Randomization/ End of Dose Conversion (N = 393)	Visit 6 (N = 377)	Visit 8 or Early Termination (N = 389)
No Abnormal Behavior	392 (99.7%)	374 (99.2%)	386 (99.2%)
Pathological Gambling	0	0	1 (0.3%) 127-006 (IPX066) ^a
Compulsive Sexual Behavior	1 (0.3%) 603-002 (IPX066) ^b	2 (0.5%) 603-002 (IPX066) ^b 801-017 (IPX066)	1 (0.3%) 801-017 (IPX066)
Buying Disorder	0	1 (0.3%) 801-011 (IR CD-LD)	0
Binge Eating Disorder	0	0	0

^a Subject 127-006 AE of gambling compulsion led to early termination from study.

^b Subject 603-002 did not complete the compulsive sexual behavior questionnaire and was counted as positive at Visits 5 and 6.

Source: Table 14.2.7.1, Appendices 16.2.6.8-1 to 16.2.6.8-4.

CDTL Comment:

In study IPX066-B09-02 the Sponsor performed prospective testing for adverse events of special interest such as hallucinations (psychosis) or Impulse Control Disorders (ICD) such as binge eating, hypersexuality, pathological gambling and compulsive buying. Compulsive punning behavior (repeated purposeless activity , hobbying and walk-about (wondering). Four patients who did not present with an ICD at trial entry developed one during the course of the trial. Over few patients with advanced PD developed ICDs.

CARDIOVASCULAR DISEASE

The Sponsor identified a disproportion in the number of cardiovascular (CV) ischemic events reported as adverse events in their clinical trials development program. All reported CV ischemic events that occurred on IPX066 and none were reported in patients taking placebo or an active comparator.

In total there were 15 ischemic events, 4 myocardial infarctions, 1 cardiovascular death, 1 unstable angina event, 4 angina/chest pain events, 1 transient ischemic attack, 1 ischemic stroke, 2 percutaneous coronary interventions, and 1 coronary artery bypass surgery. Because of the disproportionate distribution of the events, the Sponsor commissioned the (b) (4) to conduct a blinded review of the adverse event data from the 3 efficacy trials where placebo or an active comparator was incorporated into the design. The events were identified without regard to possible causal relationship to treatment.

Table 36: Summary of Cardiovascular Adverse Events ((b) (4) Analysis (Sponsor's Table)

Table 3. Number of patients with an event and number of events for each composite and individual event type across the three IPX066 studies.						
Characteristic	Open-Label Phase (N=558) (Person-years=63.62)		Double-Blinded Phase (N=579) (Person-years=189.17)		Overall (N=847) (Person-years=252.79)	
	Patients	Events	Patients	Events	Patients	Events
Any Ischemic event	3 (0.5%) 0.0471	3	8 (1.4%) 0.0423	12	11 (1.3%) 0.0435	15
Any Cardiovascular event	3 (0.5%) 0.0471	3	6 (1.0%) 0.0317	10	9 (1.1%) 0.0356	13
Any Cerebrovascular event	0 (0%) 0	0	2 (0.3%) 0.0106	2	2 (0.2%) 0.0079	2
MACE	2 (0.4%) 0.0314	2	4 (0.7%) 0.0211	4	6 (0.7%) 0.0237	6
Ischemic stroke or TIA	0 (0%) 0	0	2 (0.3%) 0.0106	2	2 (0.2%) 0.0079	2
Any-Cause Mortality	2 (0.4%) 0.0314	2	0 (0%) 0	0	2 (0.2%) 0.0079	2
Cardiovascular Mortality	1 (0.2%) 0.0157	1	0 (0%) 0	0	1 (0.1%) 0.0040	1
Cerebrovascular Mortality	0 (0%) 0	0	0 (0%) 0	0	0 (0%) 0	0
Non-CV Mortality	2 (0.4%) 0.0314	2	0 (0%) 0	0	2 (0.2%) 0.0079	2
Unknown Cause of death	0 (0%) 0	0	0 (0%) 0	0	0 (0%) 0	0
MI	1 (0.2%) 0.0157	1	3 (0.5%) 0.0158	3	4 (0.5%) 0.0158	4
USA	0 (0%) 0	0	1 (0.2%) 0.0053	1	1 (0.1%) 0.0040	1

Table 36 Continued: Summary of Cardiovascular Adverse Events ((b) (4) Analysis (Sponsor’s Table)

Table 3. Number of patients with an event and number of events for each composite and individual event type across the three IPX066 studies.						
Characteristic	Open-Label Phase (N=558) (Person-years=63.62)		Double-Blinded Phase (N=579) (Person-years=189.17)		Overall (N=847) (Person-years=252.79)	
	Patients	Events	Patients	Events	Patients	Events
Angina	1 (0.2%) 0.0157	1	3 (0.5%) 0.0158	3	4 (0.5%) 0.0158	4
Ischemic Stroke	0 (0%) 0	0	1 (0.2%) 0.0053	1	1 (0.1%) 0.0040	1
TIA	0 (0%) 0	0	1 (0.2%) 0.0053	1	1 (0.1%) 0.0040	1
PCI	0 (0%) 0	0	2 (0.3%) 0.0106	2	2 (0.2%) 0.0079	2
CABG	0 (0%) 0	0	1 (0.2%) 0.0053	1	1 (0.1%) 0.0040	1

*MACE Myocardial Infarction, Ischemic Stroke, Cardiovascular Death; CV Cardiovascular; MI Myocardial Infarction; USA Hospitalization for Unstable Angina; Angina Angina Pectoris / cardiac chest pain; TIA Transient Ischemic Attack; PCI Percutaneous Coronary Intervention; CABG Coronary Artery Bypass Grafting.

Patients refers to number of patients with an event
 Events refers to the number of events, allowing for multiple events per patient
 Values displayed are number of events, percent of patients with the event and events per person-years

The (b) (4) Reviewer’s Conclusions

“The one-sided Fisher’s exact p-values ranged from 0.03 to 1.00. The imbalance of the ischemic events observed in this analysis should be interpreted with caution given the relatively small sample size and modest number of events. Additionally, 3 of the 6 patients who reported ischemic events in the advanced studies had them during the open-label dose conversion to IPX066 period. These data should be considered in the design of future trials of IPX066 including inclusion/exclusion criteria, a strategy for standardized and systematic data collection and adjudication of suspected cardiovascular and cerebrovascular events, and mechanistic ancillary studies to explore potential pathobiological mechanisms.”

CDTL Comment

The (b) (4) analysis dismissed 3 of 6 patients because the events occurred during open label conversion to IPX066. I disagree with the exclusion since open-label conversion occurred early in the respective trials and it occurred over a few (3) weeks. However, the conclusion of the (b) (4) review that the trials were small and there were only a few patients with CV events therefore, the finding of disproportionate CV events should be interpreted with caution is reasonable. Cardiac disease is one of the most frequent causes of death in patients with PD and in patients who are similar in age to patients enrolled in the 3 clinical efficacy trials included in this NDA. None of the 3 controlled trails were not designed to study CV safety endpoints. Subjects were not stratified or matched for CV risk factors prior to trial entry. Randomization is not expected to correct for these potential imbalances in small trials where the number of placebo treated patients was very small compared to the patients enrolled in active treatment limbs. IR CD LD and CLE contain the same (CD-LD) active components as IPX066 reported but there were no reported CV ischemic events in

these groups, suggesting the disproportion in the number of CV ischemic events is a chance finding rather than being associated with CD or LD.

CDTL Safety Conclusions:

The safety profile of IPX066 based on the information provided in the NDA including the information presented in the 120-Day Safety Update and the information requests made by the Division, do not indicate a new safety concern related to the product. The profile of adverse events indicate a modest increase in the risk for nausea and dyskinesia that increases with increasing dose but only a few patients discontinued trial participation or met criteria for a serious adverse event due to dyskinesia or nausea. The results of study IPX066-B-09-02 did not indicate that patients experienced a significant increase in time spent in the “on” state with troublesome dyskinesia. Although, the method the sponsor used to describe deaths related to treatment with study medication are not the same as the typically used by the Division’s clinical reviewers the information listing and describing the deaths that occurred during trial participation are acceptable. The patient deaths did not appear to be caused by IPX066. The total number of patients who died in relation to patient exposure is not greater than deaths reported in published reports of clinical trials involving patients with PD. The presentation of events reported as serious, non-fatal adverse events appear to be related to PD, other medical co-morbidities or the events such as falls and injury. The frequency of reported adverse events of special interest psychiatric (hallucinations and psychosis) adverse events and impulse control disorders was relatively low. The inclusion and exclusion criteria would screen out many of patients with ICD at baseline likely resulting in a lower frequency of these events reported during the trials. The entry criteria would also exclude patients with cognitive impairment. A greater number of cardiovascular ischemic adverse events were reported among patients who received IPX066 in the clinical trials program. The small number of events, design limitations and relatively small number of patients followed for a short time make it difficult to draw conclusions. In addition, CV disease is one of the most common causes for death in patients with PD and people of similar age. All of these factors limit the conclusions about disproportion in the CV event data. It is reasonable to describe the events in labeling and the results of the adjudicated analysis of CV ischemic events.

11. Advisory Committee Meeting

The application did not require an advisory committee meeting.

12. Pediatrics

PeRC granted the Sponsor’s request for a PREA waiver on August 8, 2012. The reason for granting the waiver was that conducting studies in children with Parkinson’s disease was impractical because of the small number of children with the disorder and their geographic dispersion.

13. Other Relevant Regulatory Issues

Office of Scientific Investigations

Three clinical investigation sites for study IPX066-B08-05 were inspected sites 101, 108 and 205. One site was issued a VAI for transcription errors in transferring information from source documents

to the CRF. A single patient that met the protocol specified exclusion criteria was enrolled at the site. Site 126 in for study IPX066-B09-02 was also the same as study site 101 in study IPX066-B08-05, there were no actions recommended from deficiencies related to study IPX066-B09-02.

14. Labeling

Proprietary Name Review

The Division of Medication Error Prevention and Analysis (DMEPA) Comments: The re-evaluation of the proposed proprietary name, Rytary, did not identify any vulnerabilities that would result in medication errors. Thus, DMEPA has no objection to the proprietary name, Rytary, for this product at this time.

Carton and Immediate Container Labels

The Division of Medication Error Prevention and Analysis reviewed of the revised container labels and carton labeling show that the Applicant implemented DMEPA's previous recommendations.

15. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Complete Response

Risk Benefit Assessment

The manufacturing facilities deficiencies identified by the Office of Compliance are sufficient to withhold approval of this application. The issues raise questions about the validity of the information provided in the CMC section of the NDA. The non-clinical toxicology issues related the (b) (4) are addressed in the postmarketing requirements. Although the PMR language will not be included in the action letter the sponsor is aware of the need to complete the additional non-clinical studies. Labeling negotiations with the sponsor are near final, however, a final version of the product label will not be sent with the action letter. The actual PMR language was sent to the Sponsor during labeling negotiations and verbal agreement was obtained during a teleconference with the sponsor prior to the action on the application. Review of the clinical portion of the application did not find deficiencies or safety issues that would preclude approval of IPX066. Results of the two pivotal efficacy trials support the conclusion the IPX066 is effect in treating the symptoms of with early and advanced Parkinson's disease.

Recommendation for Postmarketing Risk Management Activities

None in this cycle.

Recommendation for other Postmarketing Study Commitments

A teleconference was held with the Sponsor on December 4, 2012 to discuss the Agency's intention to impose Postmarketing requirements for two nonclinical toxicology studies. The first study is required to test the potential for systemic absorption of orally administered

(b) (4). The second requirement is a study to evaluate the potential of (b) (4) to cause systemic toxicity in a 6-month study in rat. The study will focus on but it will not be limited to signs of thyroid injury associated with high dosages of (b) (4). The study must be GLP compliant and include histopathology of all major organs.

The Postmarketing Requirement will not appear in the regulatory action letter however, the sponsor is aware of the PMR that will be imposed if the application is resubmitted and approved.

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/s/

GERALD D PODSKALNY
01/18/2013

CLINICAL REVIEW

Application Type NDA
Application Number(s) 203312
Priority or Standard Standard

Submit Date(s) December 21, 2011
Received Date(s) December 21, 2011
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Division / Office CDER/OND/DNP

Reviewer Name(s) Anne E. A. Constantino
Review Completion Date December 12, 2012

Established Name IPX066
(Proposed) Trade Name Rytary
Therapeutic Class Anti-Parkinsonian Drug
Applicant IMPAX Pharmaceutical

Formulation(s) Oral
Dosing Regimen 95 mg, 145 mg, 245 mg, 390 mg
Indication(s) Early and Advanced Parkinson's Disease
Intended Population(s) Parkinson's Disease

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	12
1.4	Recommendations for Postmarket Requirements and Commitments	12
2	INTRODUCTION AND REGULATORY BACKGROUND	12
2.1	Product Information	13
2.2	Tables of Currently Available Treatments for Proposed Indications	15
2.3	Availability of Proposed Active Ingredient in the United States	16
2.4	Important Safety Issues With Consideration to Related Drugs.....	16
2.5	Summary of Presubmission Regulatory Activity Related to Submission	16
2.6	Other Relevant Background Information	17
3	ETHICS AND GOOD CLINICAL PRACTICES.....	17
3.1	Submission Quality and Integrity	17
3.2	Compliance with Good Clinical Practices	19
3.3	Financial Disclosures.....	19
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	19
4.1	Chemistry Manufacturing and Controls	19
4.2	Clinical Microbiology.....	20
4.3	Preclinical Pharmacology/Toxicology	20
4.4	Clinical Pharmacology	21
4.4.1	Mechanism of Action.....	21
4.4.2	Pharmacodynamics.....	22
4.4.3	Pharmacokinetics.....	22
5	SOURCES OF CLINICAL DATA.....	25
5.1	Tables of Studies/Clinical Trials	26
5.2	Review Strategy	28
5.3	Discussion of Individual Studies/Clinical Trials.....	29
6	REVIEW OF EFFICACY	42
	IPX066 B08-05 for Early Parkinson’s Disease.....	43
	IPX066 B09-02 for Advanced Parkinson’s Disease	56
7	REVIEW OF SAFETY.....	80
7.1	Methods.....	80
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	80

7.1.2	Categorization of Adverse Events	83
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	83
7.2	Adequacy of Safety Assessments	86
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	87
7.2.2	Explorations for Dose Response.....	89
7.2.3	Special Animal and/or In Vitro Testing	90
7.2.4	Routine Clinical Testing	90
7.2.5	Metabolic, Clearance, and Interaction Workup	91
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	92
7.3	Major Safety Results	92
7.3.1	Deaths.....	92
7.3.2	Adverse Events.....	104
	STUDY B08-05: EARLY PD STUDY	102
	STUDY B09-02: ADVANCED PD STUDY.....	114
	STUDY B09-06: ADVANCED PD STUDY.....	129
	STUDY B09-03 : OPEN LABEL STUDY.....	135
7.4	Supportive Safety Results	139
7.4.1	Laboratory Findings	139
7.4.3	Vital Signs	144
7.4.4	Electrocardiograms (ECGs)	148
7.4.5	Special Safety Studies/Clinical Trials.....	152
7.4.6	Immunogenicity	152
7.5	Other Safety Explorations.....	152
7.5.1	Dose Dependency for Adverse Events	152
7.5.2	Time Dependency for Adverse Events.....	152
7.5.3	Drug-Demographic Interactions	153
7.5.4	Drug-Disease Interactions.....	153
7.5.5	Drug-Drug Interactions.....	153
7.6	Additional Safety Evaluations	154
7.6.1	Human Carcinogenicity	154
7.6.2	Human Reproduction and Pregnancy Data.....	154
7.6.3	Pediatrics and Assessment of Effects on Growth	154
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	155
7.7	Additional Submissions / Safety Issues	155
8	POSTMARKET EXPERIENCE.....	156
9	APPENDICES	157
9.1	Literature Review/References	157
9.2	Labeling Recommendations	157
9.3	Advisory Committee Meeting.....	157

Tables

Table 1: Available Treatments for Parkinson's Disease (Reviewer's Table).....	15
Table 2: Summary of Levodopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate Release CD-LD (Sponsor's table).	23
Table 3: Statistical Analysis of the Log Transformed Pharmacokinetic Parameters for LD in Study IPX066 B08-09 (N=28). (Sponsor's table).	24
Table 4: Description of Clinical Efficacy Studies Included in NDA 203312. (Sponsor's table).	26
Table 5: Schedule of Trial Visits with Planned Efficacy and Safety Assessments. (Sponsor's table).	32
Table 6: Suggested Initial Dose Conversion to IPX066 in Study B09-02 (Sponsor's table).	37
Table 7: Procedures and Evaluation Tests Done at Each Visit in Study B09-02 (Sponsor's Table).	38
Table 8: Suggested Initial Dose Conversion of CLE to IPX066 (Sponsor's table).	40
Table 9: Summary of Subjects Who Discontinued Study Treatment in Study B08-05 (Sponsor's table).	45
Table 10: Baseline Demographics by Treatment Group in Study B08-05) (Sponsor's table)	47
Table 11: Baseline Disease Characteristics by Treatment Group in Early PD Patients in Study B08-05 (Sponsor's table).....	49
Table 12: Summary Change from Baseline to End of Study by Treatment Group in Study IPX066-B08-05 (Sponsor's table).....	51
Table 13: Comparisons for All Pairs Using Tukey-Kramer. (Reviewer's table).....	52
Table 14: MMRM Sensitivity Analysis of Change in UPDRS II + III at Week 30 (FDA Biometrics Reviewer's table).	53
Table 15: Summary of Responders by Treatment at the End of Study with Subjects who Discontinued Early and were Treated as Non-responders in Study IPX066 B08-05. (Sponsor's table).	53
Table 16: Percent of Subjects who Reported "Much or Very Much Improved" at EOS on PGI and CGI in Study IPX066 B08-05 (Sponsor's Table).	54
Table 17: Summary of Change from Baseline to End of Study in Mean PDQ 39 Score in Early PD Patients (Sponsor's table). Reviewer's Comments:.....	55
Table 18: Summary of Subject Disposition in Advanced PD Study B09-02 (Sponsor's table).	58
Table 19: Summary of Baseline Demographic Characteristics for Randomized Subjects in Study IPX066-B09-02 (Sponsor's table).	59
Table 20: Summary of Baseline Characteristics of Parkinson's Disease for Randomized Patients in Study B09-02 (Sponsor's table).	60
Table 21: Summary of Parkinson's Disease Diary Data for Randomized Subjects in Study B09-02 (Sponsor's table).....	62

Table 22: Mean % OFF Time at Patient's Last Available Assessment, Study B09-02 (Biometric Reviewer's Table).....	64
Table 23: Responders at the End of Study in IPX066 B09-02 Randomized Subjects (Sponsor's table).	64
Table 24: Summary of UPDRS Rating Scale REsults for Randomized Subjects in Study IPX066 B09-02 (Sponsor's table).....	65
Table 25: Summary of Results of Parkinson's Disease Questionnaire -39 for Subjects in Study B09-02 (Sponsor's table).....	66
Table 26: Distribution of Analysis of PGI by Treatment at EOS, Study B09-02 (Sponsor's table).	67
Table 27: Distribution and Analysis of CGI by Treatment at EOS, Study B09-02 (Sponsor's table).	67
Table 28: Distribution and Analysis of CGI by Treatment at EOS, B09-02 (Sponsor's table).	69
Table 29: Suggested Initial Dose Conversion of CLE to IPX066 in Study B09-06 (Sponsor's table).	69
Table 30: Guidelines for Initial Conversion from IR CD-LD Product to IPX066 in PD Patients as Proposed in the Sponsor's Label (Sponsor's table).	70
Table 31: Ratio of IPX066 to Immediate Release (IR) CD-LD as a Function of IR CD-LD Dose for Subjects in Study B09-02 (Sponsor's table).	71
Table 32: Schedule of Assessments and Procedures for Study IPX066-B09-03 (Sponsor's table).	73
Table 33: Distribution of Duration of PD in Study B09-03 (Sponsor's table).....	75
Table 34: Summary of Mean UPDRS Part II + III Scores Over Time in Study B09-03 (Sponsor's table).	77
Table 35: Summary of Mean Total UPDRS Score Over Time in Study B09-03 (Sponsor's table).	78
Table 36: Distribution of PGI in Study B09-03 (Sponsor's table).	79
Table 37: Description of Individual Clinical Studies Submitted to the NDA (Cut-off date: June 30, 2011) (Modified by Reviewer from Sponsor's table 2, p. 33, ISS)	81
Table 38: Completed and Ongoing Open Label, Long Term Extension STudies that Provided New Safety Information to the 120-Day Safety Update (Sponsor's table).	82
Table 39: Sponsor's Plan for Integrating Data from Phase 3 Controlled Studies in Subjects with Parkinson's Disease (Sponsor's table).	85
Table 40: Cumulative Exposure to IPX066 in Original and Extension Trials in Study IPX066 B09-03 as of 30 June 2011 (Sponsor's table).....	86
Table 41: Exposure for Subjects by Total Daily Dose and by Cumulative Duration (Sponsor's table).	87
Table 42: Summary of Age, Sex, Race, Weight and Body Mass Index in Controlled Phase 3 Studies--Overall PD population, All Enrolled Subjects (Sponsor's table).	88
Table 43: Distribution and Summary of Hoehn and Yahr Scores in Advanced PD Patients (Sponsor's table)	89
Table 44: Distribution and Summary of Pre-Study Duration of Treatment with Levodopa in Advanced PD Patients (Sponsor's table).....	89

Table 45: Distribution and Summary of Pre-Study Duration of Treatment with Levodopa in Advanced PD Patients (Sponsor's table).	93
Table 46: Number of Deaths Per Study at the NDA Submission and 120-Day Safety Update (Reviewer's table).	94
Table 47: Causes of Death in NDA 203312 (Reviewer's table).	94
Table 48: Deaths from All Studies Submitted to NDA 203312 (Original Submission and 120-Day Safety Update, Cut -off date: January 23, 2012). (Reviewer's table)	95
Table 49: Treatment Emergent Adverse Events in All Enrolled Subjects with Early PD (Sponsor's table).	102
Table 50: Summary of Serious Adverse Events by Treatment Study B08-05 (Sponsor's table).	102
Table 51: Disposition of Subjects in Early PD (Sponsor's table).	104
Table 52: Dose Regimen for Titration Period in Study B08-05 (Sponsor's table).	105
Table 53: Adverse Events that Led to Withdrawal from the Study According to Dose and Treatment Phase (Reviewer's table).b	106
Table 54: Gastrointestinal Disorders in B08-05 (Sponsor's table).	107
Table 55: Frequency of Nausea and Vomiting on IPX066 Treatment and Placebo by Treatment Phase (Reviewer's table).	Error! Bookmark not defined.
Table 56: Summary of Adverse Events Occurring in at Least 5% of Subjects in Any Treatment Group in Study B08-05 (Sponsor's tble).	108
Table 57: Most frequent AEs in Study B08-05 (Early PD) in at least 2% of Patients Classified by Treatment Phase and Dose (Reviewer's table)	109
Table 58: Frequency Distribution by Treatment Arm of Preferred Terms for Sleep (Sponsor's table).	111
Table 59: Frequency Distribution by Treatment Arm of Vascular Orders Preferred Term (Sponsor's table).	113
Table 60: Preferred Terms Searched That May Correspond to Orthostatic Hypotension (Reviewer's table created with JMP from sponsor's dataset).	113
Table 61: Frequency of Oerthostatic Hypotension During Maintenance and Titration Phase in IPX066 Treatment and Placebo Groups, Study B08-05 (Reviewer's table)..	114
Table 62: Adverse Events During Dose Conversion Phase (Sponsor's table).	115
Table 63: Overall Summary of Adverse Events During the Maintenance Period in All Randomized Subjects, B09-02 (Sponsor's table)	116
Table 64: SAEs During the Different Treatment Periods That Are Likely Related to Drug in Advanced PD Patients, Study B09-02 (Reviewer's table).	117
Table 65: Summary of Serious Treatment Emergent AEs Starting During IPX066 Dose Conversion Classified by System Organ Class and Preferred Term, Study B09-02 (Sponsor's table).	119
Table 66: Adverse Events Leading to Early Termination During the Conversion Phase, B09-02 (Reviewer's table).	121
Table 67: Summary of Treatmen-emergent AEs Leading to Early Termination from Maintenance in Study 09-02, by System Organ Class and Preferred Term (Sponsor's table).	122

Table 68: Treatment Emergent Adverse Events by Preferred Term in the Dose Conversion Phase of IPX066 Study B09-02 (Sponsor's table)..... 124

Table 69: Adverse Events Reported by at least 1% of subjects in IPX066 or IR CD-LD treatment during Maintenance Phase, Study B09-02 (Sponsor's table).Table 126

Table 70: Comparison of Frequency of Adverse Events Related to IR CD-LD or IPX066 by Dose Following the Conversion Table Proposed in Study B09-02 (Reviewer's table). 129

Table 71: Dose Conversion Scheme of CLE to IPX066 in Study B09-06 in Patients with Advanced PD (Sponsor's table). 130

Table 72: Overall Summary of TEAEs in Enrolled Subjects in the IPX066 Dose Conversion Period in Study B09-06 (Sponsor's table). 131

Table 73: Overall Summary of TEAEs during Randomized Cross Over Period in Study B09-06 (Sponsor's table)Table 132

Table 74: Serious Adverse Events Reported in Study B09-03 (Sponsor's table). 135

Table 75: Summary of Patients Who Discontinued Early due to SAEs (Sponsor's table). 136

Table 76: Most Frequently Reported AEs (>2%) in Study B09-03, Open Label Study (Sponsor's table). 138

Table 77: Hematology Values mean, Median and Standard Deviation in All Comparator Studies (Summarized from Sponso's table) 140

Table 78: Hematology Values Outside the Reference Range at Post Baseline Assessment in study B09-03 (Reviewer's table). 140

Table 79: Clinical Chemistry Values Mean, Median and STandard Deviation in All Studies (Reviewer's table). 142

Table 80: Clinical Chemistry Values Outside the Reference Range at Post Baseline Assessment in the Safety Population Classified According to Treatment Groups (Reviewer's table)..... 143

Table 81: Sponsor's Criteria for Evaluating Markedly Abnormal Vital Signs (Sponsor's table). 145

Table 82: Frequency of Patients with Diastolic Blood Pressure Changes from Supine to Standing Position, B08-05 (Reviewer's table). **Error! Bookmark not defined.**

Table 83: Frequency of Patients who had Systolic Blood Pressure Change from Supine to Standing Position, B08-05 (Reviewer's Table). **Error! Bookmark not defined.**

Table 84: Diastolic and Systolic Blood Pressure Change According to Treatment with IPX066 or IR CD-LD at Each Study Visit in Study 09-02 (Reviewer's table). **Error! Bookmark not defined.**

Table 85: Distribution and Summary of Ventricular Rate in All Phase 3 Controlled Studies (Sponsor's table). 147

Table 86: QT Interval Meeting Outlier Criteria in Study B08-05 (Reviewer's table). ... 148

Table 87: QTC>500 and QTC change from baseline in patients on IPX066 and IR CD-LD, Study B09-02 (Reviewer's table). 149

Table 88: QTC>500 and QTC Change from Baseline in Study B09-06 (Reviewer's table). 150

Table 89: QTcF changes > 30 and > 60 at Baseline Screening and End of Study in B09-02 (Sponsor's table).....	151
Table 90: Frequency of Patients who had Prolonged QTcB/QTcF > 500 in Study B09-03 (Reviewer's table).....	151
Table 91: Occurrence of Nausea, Vomiting and Dyskinesias in Males and Females (N (%)), (Reviewer's table).....	153

FIGURES

Figure 1: Study Design and Schedule of Assessments (Source: Sponsor).....	30
Figure 3: Study Design Diagram (Source: Sponsor)	34
Figure 4: Schematic Diagram for Study Design of IPX066 B09-06 Part 1 (Source: Sponsor).	40
Figure 5: Disposition of Subjects in Study IPX066-B08-05 Randomized Subjects (Source: Sponsor).	44
Figure 6: Flowchart of Subject Disposition in Advanced PD Study B09-02 (Source: Sponsor)	57
Figure 7: Mean "OFF" Time by Visit for Randomized Subjects (N=393) in Study IPX066 B09-02 (Source: Sponsor).....	63
Figure 8: IPX066 B09-03 Study Design (Source: Sponsor).....	72
Figure 9: Disposition of Subjects in Study IPX066 B09-03 (Source: Sponsor).....	75
Figure 10: Mean UPDRS Part II + Part III Scores for Study IPX066 B09-03 Month 5 and Original Trial (Source: Sponsor).....	77
Figure 11: Disposition of Subjects in Study B09-03 (Source: Sponsor)	134

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A Complete Response (CR) action is recommended for NDA 203312 because of GMP deficiencies identified in the Impax manufacturing facility in Hayward, California. The FDA Office of Compliance New Drug Manufacturing Branch concluded:

“During recent inspections of the Impax Laboratories (Hayward, CA) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. This facility continues to perform operations in support of commercial manufacturing and distribution for NDA 203-312 based on current inspectional findings and corrective action commitments provided by the firm to FDA field investigators on January 16, 2013. Satisfactory resolution of the deficiencies identified in the recent inspections and regulatory meeting have not been verified and are required before this application may be approved.

We are also concerned that manufacturing data within the CMC section of the application (e.g., method validation, stability) was generated at a facility that is considered not compliant based on recent inspectional findings relating to quality control laboratory testing.”

The IPX066 clinical development showed that the drug is safe and effective for the treatment of the motor signs and symptoms of early and advanced Parkinson’s disease. The side effect profile of IPX066 in patients with early and advanced Parkinson’s disease is similar to adverse events described in the Sinemet, Sinemet CR and Stalevo product labels.

1.2 Risk Benefit Assessment

Review of clinical data presented by the sponsor finds sufficient evidence that IPX066 is effective and safe for the treatment of early and advanced Parkinson’s disease. The submission includes two adequate and well controlled clinical trials and a long term safety study.

The first trial in early Parkinson’s disease (PD) patient is a 30-week efficacy trial in early PD whose endpoint was the change from baseline of the sum of UPDRS Parts II (Activities of Daily Living) and III (Motor Function) score of the UPDRS. The mean change in UPDRS Parts II and III from baseline was 11.12, 12.37, and 14.38 for the 145 mg, 245 mg and 390 mg respectively. The p value is <0.0001.

The second pivotal efficacy trial in advanced PD, is a 22 week efficacy trial with “off” time as a percent of waking hours as the primary endpoint. The Agency’s Biometrics reviewer confirmed that the mean % OFF time was 23.7% for IPX066 group and 30.0% for the IR group.

In both trials, IPX066 showed a statistically significant difference in the efficacy endpoints compared to patients on placebo or on a comparator (IR).

A third study report was included in the NDA, a 2-treatment, 2-period (2 weeks/period) randomized crossover study that compared patients on a stable dose of carbidopa/levodopaentacapone (CLE) to IPX066. The trial design did not result in a fair comparison between patients on IPX066 and CLE because the sponsor did not allow the latter group to optimize their dose while the IPX066 group was permitted dose adjustment. The study was not included in the efficacy review.

There were no new or unexpected safety events reported in the course of this clinical development program compared to what is available in the approved product labels for other levodopa products.

The common adverse events reported in the Early PD clinical trial (IPX066 B08-05) include nausea/vomiting and dyskinesias. These adverse events were more frequent with higher doses of IPX066. Additional analysis based on dosing period show an increase of adverse events during the titration phase. As expected, titrating to higher doses result in more frequent adverse events such as nausea and vomiting.

In trial IPX066-B09-02, patients were converted from a stable dose of IR to IPX066. The sponsor proposed a conversion scheme that was based on pharmacokinetic studies but without any pharmacodynamic basis. Utilizing the sponsor's conversion table, adverse events were compared between IR and IPX066. Nausea/vomiting, dyskinesias and hallucinations were common in both groups. However, the frequencies and percentages of these adverse events are higher in the IPX066 group. A dose response is also noted especially in the case of dyskinesias and hallucinations. Likewise, impulse control behavior disorders which are not reported in IR were reported by patients on IPX066 and this followed a dose response trend. The sponsor's conversion seems to deliver a higher dose of levodopa but it appears that the dose of IPX066 was adjusted to maximize benefit in the individual patient. Clinical Pharmacology however has looked into the dose/dosing regimen for initial conversion and believes that they are reasonable but posed a similar conclusion regarding the dose used in the clinical trials.

IPX066 is effective in the treatment of both Early and Advanced Parkinson's Disease and although the adverse events that were reported in their clinical development were also seen with other approved levodopa drugs, the risks of developing adverse events is increased because of the increased amounts of levodopa in the IPX066 dose. The recommended conversion scheme is still acceptable but in initiating treatment with IPX066 especially in Advanced PD patients, lower doses and a slow titration phase should be considered. There were questions raised about the potential safety of the excipients (b) (4) which will be given at a total daily dose that exceeds the unit amounts specified in the Inactive Ingredients Database (IID). There are no approved products that support the daily

dose of (b) (4) at the maximum recommended daily dose of IPX066 of 15 capsules a day. The sponsor's proposal to decrease the maximum recommended dose of IPX066 to 10 capsules per day is not an effective method to limit human exposure to high levels of (b) (4). Additional non-clinical studies are required to better characterize these findings. Effects of potential systemic exposure to high levels of (b) (4) would be appropriate to study in the post-marketing period. If the non-clinical studies confirm a systemic effect or systemic absorption, then additional clinical trials will have to be done.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no current recommendation for Postmarket Risk and Mitigation Strategies

1.4 Recommendations for Postmarket Requirements and Commitments

The safety issue that was raised in this review will be addressed through Post-Marketing requirements that include the following suggestions

1. A study in an appropriate species to evaluate the potential for systemic absorption of (b) (4) following oral ingestion
2. A study to evaluate potential systemic effects (including the thyroid) following oral ingestion of (b) (4).

2 Introduction and Regulatory Background

Parkinson's disease (PD) is a distinct clinical and pathologic entity characterized by massive loss of pigmented neurons in the substantia nigra and presence of Lewy bodies. Movement disorder specialists consider the presence of two of three cardinal motor signs (tremor, rigidity, bradykinesia) and a consistent response to L-dopa indicative of clinical PD. It affects about 1 percent of the population over age 55.

Incidence of PD is 4.5 to 19 per 100,000 populations per year and prevalence in the US falls between 100 and 200 per 100,000 persons. PD death rates do not reflect the true distribution of the disease because the disease is not a direct cause of death and is influenced by variability in diagnostic accuracy. Mortality rates for PD increase with age with rates up to 100 per 100,000 or more in those above 80 years. Common causes of death in patients with PD are from cardiovascular and respiratory complications that may also be due to comorbid illnesses in this age group.

L-dopa (L-3,4-dihydroxyphenylalanine), a dopamine precursor, is taken up by the dopaminergic neurons, decarboxylated by AADC (Aromatic Amino acid decarboxylase) and converted to dopamine in the surviving cells in the brain and synaptically released. Since dopamine cannot cross the blood brain barrier, peripheral decarboxylase inhibitors were developed to allow for a 4-fold increase in the availability of a given dose because

peripheral metabolism to dopamine is blocked. Combination and L- dopa with carbidopa into a single tablet was commercially marketed under the trade name Sinemet, a more potent preparation that also reduced gastrointestinal adverse events. Treatment with L- dopa continues to dominate the current therapy of Parkinson's disease. (Fahn, 2008)

IPX066 is an extended release (ER) capsule formulation of carbidopa-levodopa intended to treat the motor symptoms of PD. The proposed regulatory pathway to approval for PX066 is defined under Section 505 (b)(2) of the Federal Food, Drug and Cosmetics Act and relies on previous findings of safety and efficacy of Carbidopa-Levodopa in PD as evidenced by the approved product labeling for CD-LD products such as Sinemet, Sinemet CR and Stalevo, combined with clinical studies demonstrating the safety and efficacy of IPX066 in PD patients.

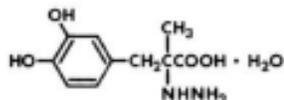
The drug product contains numerous inactive ingredients amongst which are (b) (4). The maximum amount of this inactive ingredient would exceed the proposed daily doses of (b) (4). The Sponsor submitted a major amendment to provide safety information that these ingredients are safe at higher daily doses. The sponsor provided only copies of published literature and safety reports on excipients at a maximum human daily dose of 10 capsules. Although there were no human safety concerns at a dose of 10 capsules, draft labeling of IPX066 provides for up to 61.25-245 mg LD CD capsules. We had to extend the goal date by three months to provide time for a full review of the submission.

2.1 Product Information

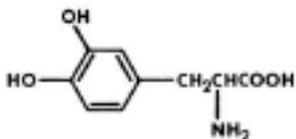
IPX066 is an extended release (ER) capsule formulation of carbidopa-levodopa intended to treat the motor symptoms of PD. The proposed regulatory pathway to approval for PX066 is defined under Section 505 (b)(2) of the Federal Food, Drug and Cosmetics Act and relies on previous findings of safety and efficacy of Carbidopa-Levodopa in PD as evidenced by the approved product labeling for CD-LD products such as Sinemet, Sinemet CR and Stalevo, combined with clinical studies demonstrating the safety and efficacy of IPX066 in PD patients.

IPX066 is a multi-particulate, extended-release capsule formulation of CD-LD designed to provide rapid attainment of therapeutic LD plasma concentrations for longer time periods to allow less frequent dosing. As with the other carbidopa levodopa preparations, it contains carbidopa—an inhibitor of aromatic amino acid decarboxylation, and levodopa, an aromatic 1 amino acid which is the metabolic precursor of dopamine in a 1:4 ratio.

The structural formula of carbidopa is shown below. Its capsule content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226. (b) (4).



Levodopa has a molecular weight of 197 ^(b)₍₄₎ g/mol and its molecular formula is C₉H₁₁N₀₄. Its structural formula is shown below:



IPX066 is indicated for the treatment of idiopathic PD, post-encephalitic Parkinsonism, and symptomatic Parkinsonism which may follow injury to the nervous system by carbon monoxide and/or manganese intoxication in early and advanced PD. The following strengths are provided: 23.75-95, 36.25-145, 75-195 and 61.25-245 mg of carbidopa-levodopa.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Available Treatments for Parkinson’s Disease (Reviewer’s Table)

Medication	Available Doses	Initial Dosing
Levodopa Preparations	None	
Carbidopa/Levodopa (Sinemet ®)	10/100 mg, 25/100 mg, 25/250mg	25/100 2 to 3x daily
Carbidopa Levodopa controlled release (Sinemet CR ®)	25/100 mg, 50/200 mg	50/200 mg 2x a day
Carbidiopa/Levodopa/Entacapone (Stalevo ®)	12.5/50/200 mg, 25/100/200 mg, 18.75/75/200 mg, 31.25/125/200 mg, 37.5/150/200 mg, 50/200/200 mg	12.5/50/200 mg
Carbidopa/Levodopa Orally Disintegrating tablet (Parcopa ®)	10/100 mg, 25/100 mg, 25/250 mg	25/100 mg 2 to 3x/day
Dopamine Agonists		
Apokyn injection (apomorphine HCL)	0.02-0.06 ml	0.02 ml during “off” periods
Bromocriptine (Parlodel ®)	2.5 mg, 5 mg	2.5 mg 3x a day
Rotigotine Transdermal System (Neupro ®)	2mg/24 hrs, 4 mg/24 hrs, 6 mg/24 hrs	One 2 mg patch a day
Pramipexole (Mirapex ®)	0.125, 0.25, 0.5, 1 and 1.5 mg	0.125 mg 3x a day
Pramipexole dihydrochloride extended release (Mirapex ER ®)	0.375, 0.75, 1.5, 3, 4.5 mg	0.375 mg once a day increased gradually
Ropinirole (Requip ®)	0.25, 0.5, 1, 2, 3, 4, 5	0.25 mg 2x a day
Ropinirole extended release tablets (Requip ® XL)	2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 mg	2 mg once a day
Anti cholinergics		
Benzotropine mesylate (Cogentin)	0.5 mg	0.5 mg 2x a day
Trihexyphenidyl HCL (Artane ®)	1 and 2 mg	1-2 mg 2x a day
MAO Inhibitor		
Selegiline (Eldepryl ®, Carbox ®)	5 mg	5 mg 2x a day
Selegiline HCl Orally disintegrating tablet (Zelapar ®)	1.25 mg	1.25 mg 2x daily
Rasagiline (Azilect ®)	0.5, 1 mg	0.5 mg once daily
COMT inhibitor		
Entacapone (Comtan®)	200 mg	200 mg with levodopa
Tolcapone (Tasmar®)	100 mg, 200 mg	100 mg 3x a day
Amantadine (Symmetrel ®)	100 mg	100 mg 2x to 3x a day

2.3 Availability of Proposed Active Ingredient in the United States

Carbidopa/levodopa, the active ingredients in RYTARY is marketed here in the US in the immediate release formulation.

2.4 Important Safety Issues With Consideration to Related Drugs

The Sponsors proposed a conversion table to calculate the initial dose of IPX066 in patients treated with a stable dose of carbidopa levodopa. The proposed conversion table was based on a PK comparison and not on pharmacodynamic information. The clinical response (pharmacodynamic effects) PD patients have after taking levodopa is not tightly correlated to PK and that the clinical effects can vary by stage of disease and loss of striatal dopamine storage and release of exogenously administered dopamine (levodopa). In the controlled clinical trial, 85% of patients converted to IPX066 from carbidopa levodopa using the table needed subsequent dose adjustments shortly after conversion to IPX066. If patients are overdosed, it may lead to adverse effects such as dyskinesia, orthostatic hypotension/syncope, hallucinations and too little carbidopa levodopa would lead to a return of PD symptoms. In general, advanced PD patients are more likely to develop motor fluctuations such as dyskinesias, wearing “off” and psychiatric adverse events such as hallucinations and/or psychotic behavior. Impulse control disorders such as pathologic gambling, binge eating, shopping and hypersexuality have been reported in patients treated with dopaminergic medications.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- Pre-IND Meeting April 8, 2008
- The IND was opened on July 3, 2008. The sponsor submitted two draft protocols: Study IPX066 B08-05, a clinical trial that would compare 4 groups of patients with early Parkinson’s disease assigned to 1 of 3 doses of IPX066 or placebo. Study IPX066 B08-11, an exploratory PK/PD, crossover design study of IPX066 in 24 subjects with motor complications associated with more advanced PD.
- On January 8, 2009, Protocol IPX066 B08-05: A Placebo Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson’s Disease, was submitted as a special protocol assessment (SPA) and an SPA Agreement Letter was sent to the sponsor on February 27, 2009.
- On February 6, 2009, the Sponsor submitted Protocol IPX066 B08-06, evaluating the safety and efficacy of IPX066 in three strengths for the treatment of Advanced Parkinson’s disease compared to standard carbidopa-levodopa and carbidopa-levodopa plus entacapone, as an (b) (4)

(b) (4)

- On June 23, 2009, the sponsor submitted Protocol IPX066 B09-02, a randomized controlled double blind trial to compare IPX066 to standard carbidopa levodopa in patients with advanced Parkinson’s disease with motor fluctuations. The major change from the previous protocol was the exclusion of the carbidopa-levodopa plus entacapone arm. This protocol also included a statistical methodology for the primary efficacy analysis plan. FDA agreed to the protocol and the statistical methodology for the primary efficacy analysis plan.

2.6 Other Relevant Background Information

The following issues were raised during the review process:

1. The Sponsor’s manufacturing site in Hayward, California was withdrawn by the sponsor on December 6, 2011 because FDA has issued an OAI letter for GMP deficiencies. The sponsor states in their letter that “it appears unlikely that a GMP re-inspection to close the Hayward site’s Warning Letter and Pre-approval Inspection can be completed in the limited time”. The Sponsor has their facility in Jhunan , Taiwan as their sole commercial manufacturing site.

The Hayward, California site was re-inspected on the first week of January 2013 and FDA noted that despite the OAI letter and the withdrawal of this site from the NDA, Hayward, California continues to perform manufacturing activities related to IPX066 (Rytary).

2. The PDUFA date was extended for this submission because of a major amendment (non-clinical) submission regarding the safety of (b) (4) which will be given in higher doses than what has been given in the past. The safety issue is further discussed in the Pharmacology Review of this NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor’s submission was in eCTD using CDISC and SDTM data standards. However, the subject identifier did not maintain the same USUBID as when patients

moved from controlled trials to the long-term open label study. This made it difficult to calculate exposure across trials and follow treatment assignment and dose in patients who enrolled in the controlled studies into their enrollment into the open label study.

The submission met the standard for filing, however during the course of the review, there were some concerns with the data the Sponsor provided.

In the efficacy analysis, 16 patients in study B08-05 (Early PD Study) were excluded post-randomization. These 16 patients withdrew prematurely from the trial but had their early termination visit more than 3 days after the last dose of study medication. Although the protocol permitted these exclusions, it would have been preferable to see the results of an analysis that included the data from these patients to maintain the principles of ITT. Dr. Massie (statistical reviewer) concluded the efficacy results did not change by excluding these 16 patients.

There was a discrepancy noted between the number of deaths reported in the original NDA submission and the revised total number of deaths reported in the 120-day safety update. The sponsor readily corrected these deficiencies.

It was also noted that the advanced PD (B09-02, B09-06, B09-03) analysis datasets did not contain a column providing the actual dose of study medication patients were taking when the adverse event occurred. The FDA clinical reviewer sent an information request to the sponsor to submit revised AE tables listing the actual dose patients were taking when the adverse event occurred. The Sponsor could not provide this information in datasets.

Likewise, in the long-term open label study, the sponsor did not report (because it appears to not have been done) orthostatic (supine and standing) blood pressure changes to allow us to correlate the reports of complaints of “orthostatic hypotension” with an objective measure of blood pressure.

Three sites (one domestic—PI: Paul Nausieda, MD in Milwaukee, WI and two foreign—PI: Emmanuelle Pourcher, MD, Quebec, Canada and Lyudmiyla Dzyak, M.D. Dnipropetrovsk, Ukraine) were selected for inspection by DSI based on having the largest/highest enrollment and large effect size. Regulatory violations were noted at Dr. Nausieda’s site with transcription errors in source documents when compared to case report forms and data listings for at least seven subjects. Similarly, transcription errors were noted leading to discrepancies in Dr. Pourcher’s site. The medical records and source documents for 15 subjects in Dr. Dzyak sites had numerical values of PDQ-39 questionnaires that could not be verified from the source document. However, these errors were minor and did not impact on the data acceptability. The reviewer’s assessment concluded that *”the inspection of Drs. Pourcher and Dzyak revealed no regulatory violation and the final classification for Dr. Pourcher is No Action Indicated (NAI). Pending classification for Dr. Dzyak is NAI, pending final review of the*

establishment inspection report. While regulatory violations were identified during the inspection of Dr. Nausieda, the findings are not likely to critically impact primary efficacy and safety analysis and OSI does not consider the effect on overall data integrity to be significant. Final classification for the inspection of Dr. Nausieda is Voluntary Action Indicated (VAI.) Overall, the data submitted from these three sites are considered acceptable in support of the pending application”.

3.2 Compliance with Good Clinical Practices

The Sponsor certified that it did not use any debarred investigators. They indicated that the clinical trials submitted for FDA review complied with national and international Helsinki Agreement ethical principles for protection of human subjects in clinical research trials. The protocol, informed consent and subject information forms were reviewed and approved by the local Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) and approved by the appropriate regulatory authorities in the participating countries. I did not find any evidence of unethical conduct on the part of the sponsor or study site personnel.

3.3 Financial Disclosures

All financial disclosures were submitted and were reviewed. There was one reported disclosure but this did not potentially bias the outcome of the clinical trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review was completed by Dr. Charles Jewel, CMC Reviewer and Dr. Sandra Suarez Sharp, Biopharmaceutics reviewer. Both reviewers concluded that the fixed dose combination extended release capsules for Carbidopa/Levodopa is recommended for approval.

The following issues were discussed with the sponsor and were resolved during the review process. Please refer to the CMC and Biopharmaceutics Review for details.

1. The dissolution ranges at time points indicated in the dissolution specification for the final drug product were deemed higher than acceptable by the biopharmaceutics reviewer. Recommendations were made for ranges supported completely by batches of drug product used in the phase III studies. The Sponsor agreed to the recommended dissolution ranges that were accepted by the biopharmaceutics reviewer.

2. The applicant was also directed to add tartaric acid dissolution to release and tartaric acid assay and dissolution to stability evaluation. The Sponsor has agreed to do this and limits have been approved by the biopharmaceutical reviewer.

3. The biopharmaceutics reviewer required tightening of the dissolution specification limits on the proposed applicant's (b) (4) weight ranges.

Inspections at the sponsor's manufacturing sites are completed. The sponsor had to withdraw the Hayward, California site because of pending alerts placed by the Office of Compliance. The inspections at two other sites: manufacture of drug product in Taiwan and manufacture of Levodopa in Japan, have been completed.

The reader is further referred to the CMC review for detailed CMC information.

4.2 Clinical Microbiology

This submission did not contain microbiology information other than what was reported by CMC.

4.3 Preclinical Pharmacology/Toxicology

Impax Laboratories has reviewed the published literature and the repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental studies of CD, LD and CD-LD in support of NDA 017555, NDA 019856, NDA 017830 and NDA 021485 for the approval of Sinemet. The sponsor has concluded that there are no new relevant toxicological findings that have an impact on the clinical safety and labeling for IPX066. Impax Laboratories performed no additional toxicological studies of CD and LD in support of the IPX066 development.

The non-clinical pharmacology/toxicology reviewer, Dr. McKinney, concluded that there are no safety concerns assuming a maximum human daily dose (MHDD) of ten LD-CD capsules 61.25-245 mg. The sponsor's labeling allows IPX066 up to fifteen 61.25-245 mg LD-CD capsules. At this dose, the excipients-- (b) (4) -- present in IPX066 at per capsule amounts, would exceed those resulting from therapeutic use of approved drug products containing one or more of these excipients. The reviewers requested the sponsor to submit support for the safety of the proposed daily doses of (b) (4). On October 31, 2011, the sponsor submitted a summary evaluation of the safety data for these excipients prepared by (b) (4) and a Letter of Authorization (LOA) from (b) (4) to DMF (b) (4).

The documents submitted by the sponsor did not provide information that would support the daily dose of (b) (4) at the maximum recommended daily dose of IPX066 of 15 capsules. Although systemic exposure would be expected to be relatively low because of

the molecular weight of the excipient, oral absorption would also be relatively low. However, systemic effects were observed with (b) (4) in multiple species.

The primary toxicity is thyroid “activation” observed in multiple species (mouse, rat and rabbit) with (b) (4). The NOAEL for thyroid activation in mouse, rat and rabbit was 100 mg/kg/day although chronic administration was assessed only in rat. The NOAEL provides no safety margin on a body surface area (mg/m²) in the mouse (most sensitive species). The safety margin is (b) (4) for (b) (4) based on a mg/kg and 10 capsules per day but based on the MHDD of 15 capsules per day, the safety margin on a mg/kg basis is (b) (4). Although the 100 mg/kg dose was the NOAEL in all species tested, the available data is not sufficient to conclude that a dose of 100 mg/kg/day would remain a NOAEL in mouse or rabbit with chronic administration. Likewise, the thyroid findings would suggest systemic, not local effects, and body surface area comparisons appear the more appropriate. (b) (4) also has a high molecular weight, hence systemic toxicity is unexpected and thus would argue for a more thorough assessment of toxicity.

The Pharmacology Supervisor, Dr. Lois Freed, concludes that the “data provided by the sponsor do not adequately support the safety of the daily dose of the excipient, (b) (4), at the MHDD of IPXo66. The sponsor was asked to provide additional information on the safety of (b) (4) particularly addressing concerns regarding thyroid effects observed in multiple species”.

4.4 Clinical Pharmacology

The Clinical Pharmacology Reviewers reviewed 7 clinical pharmacology study reports on the following:

- Dose Proportionality
- Single Dose and Multiple Dose Study
- Food Effect
- Alcohol Dose Dumping
- PK-PD
- Bioanalytical reports

4.4.1 Mechanism of Action

Parkinson’s disease symptoms are related to dopamine depletion in the corpus striatum. Treatment with dopamine is ineffective because it does not penetrate the blood brain barrier. Levodopa, the metabolic precursor of dopamine crosses the blood brain barrier and is converted to dopamine in the brain thus relieving the symptoms of Parkinson’s disease. Carbidopa inhibits peripheral decarboxylation of peripheral levodopa to allow more levodopa delivery to the brain. Carbidopa given with levodopa increases the plasma levels of levodopa and prolongs the plasma half-life of levodopa from 50 minutes to 1.5 hours.

4.4.2 Pharmacodynamics

Pharmacodynamic effects of IPX066 were evaluated using data from the phase 2 randomized, multicenter, open labeled, single and multiple oral dose treatment, 2 period crossover study to evaluate PK and PD in subjects with Parkinson's disease. The study used finger tapping rate, UPDRS Part III scores and Investigator Assessments of Dyskinesias as pharmacodynamic and efficacy endpoints. The study showed that IPX066 has an onset of action that was comparable to that noted with IR of less than 1 hour and IPX066 has a longer duration of effect compared to IR for both the finger tapping (7.6 hours compared to 5.6 hours) and UPDRS Part III (7.4 hours compared with 4.5 hours), consistent with the plasma concentration from the ER formulation.

Food delayed absorption of levodopa for 2 to 3 hours. High protein, excessive acidity and iron salts also delay LD absorption and decrease the bioavailability.

They also reviewed the alcohol dumping studies and concluded that alcohol concentrations above 25% had a concentration-dependent effect on increasing the in-vitro solution.

4.4.3 Pharmacokinetics

Single and multiple doses PK of IPX066 capsule formulations were compared with IR in Study IPX066 B08-11. The study was a randomized, multicenter, open label, two treatments, two period cross over study in LD experienced subjects with Parkinson's disease. Reference and test treatments were administered every 6 hours for 7 days.

LD is absorbed at fast to moderate rate from IPX066 with a Tmax ranging from 0.5 to 11 hours after single or multiple dose administrations. Compared to levodopa, carbidopa was absorbed at a slower rate with a T max ranging from 1.5 to 12 hours. The initial rise in LD concentrations was comparable to that for immediate release carbidopa levodopa. The relative bioavailability of LD from IPX066 was approximately 70% and 50% for CD relative to IR CD LD in patients.

Following multiple dose administration of IPX066, accumulation of LD when dosed approximately every 6 hours was comparable to IR CD LD. The peak concentration is approximately 30% and 35% for LD and CD respectively.

The sponsor has presented the summary of levodopa pharmacokinetics (Table 2) that the Pharmacology reviewer had included in his review.

Table 2: Summary of Levodopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate Release CD-LD (Sponsor's table).

Treatment/ First AM Dose (mg)	Number of Subjects	T _{max} hrs ^a	C _{max} ng/mL ^b	AUC ₀₋₁₂ hr.ng/mL ^b	Accum Index ^{b,c}	Invariance ^b	Fluct % ^{b,c}
IPX066	27	3.0 (0.5 - 11.0)	NA	NA	1.42 ± 0.85	1.15 ± 0.66	1.51 ± 0.41
1 capsule x 245	3	6.0 (1.5 - 9.0)	2107 ± 937	13400.00 ± 6887.88	0.65 ± 0.15	0.52 ± 0.07	1.60 ± 0.19
2 capsules x 245	7	3.0 (0.5 - 9.0)	3227 ± 1089	19481.86 ± 6213.81	1.30 ± 0.40	1.11 ± 0.34	1.66 ± 0.36
3 capsules x 195	3	1.5 (1.5 - 3.0)	3927 ± 306	26976.75 ± 8150.06	2.90 ± 1.26	2.28 ± 1.03	1.48 ± 0.64
3 capsules x 245	11	8.0 (0.5 - 11.0)	4166 ± 1787	27792.03 ± 9329.93	1.33 ± 0.76	1.05 ± 0.56	1.36 ± 0.45
4 capsules x 245	3	2.0 (0.5 - 2.0)	5423 ± 678	35715.92 ± 6124.04	1.28 ± 0.28	1.10 ± 0.20	1.62 ± 0.34
IR CD-LD	27	1.0 (0 - 12.0)	NA	NA	1.11 ± 0.34	0.90 ± 0.31	3.23 ± 1.26
1 tablet x 100	11	0.5 (0 - 12.0)	2209 ± 744	8889.96 ± 2441.67	1.05 ± 0.35	0.85 ± 0.23	3.03 ± 1.05
1.5 tablets x 100	2	3.75 (0.5 - 7.0)	2195 ± 714	6533.59 ± 351.21	1.09 ± 0.25	0.97 ± 0.13	3.94 ± 1.04
2 tablets x 100	9	1.5 (0.5 - 12.0)	3057 ± 1108	11633.64 ± 4602.62	1.12 ± 0.25	0.88 ± 0.32	3.29 ± 1.00
2.5 tablets x 100	3	1.0 (0.5 - 4.0)	3963 ± 186	13783.06 ± 6091.66	0.89 ± 0.19	0.78 ± 0.26	4.17 ± 2.62
3 tablets x 100	2	1.25 (1.0 - 1.5)	3240 ± 806	18648.75 ± 6676.50	1.67 ± 0.62	1.36 ± 0.72	1.88 ± 0.11

^a Data reported as median (range)

^b Data reported as mean and standard deviation

^c Accumulation index was calculated as AUC₀₋₇ on Day 8/AUC₀₋₇ on Day 1 and fluctuation was calculated as (C_{max} - C_{min})/C_{avg} (maximum [peak] drug concentration minus minimum drug concentration divided by average drug concentration), C_{avg} = average drug concentration.

Dose proportionality of LD PK parameters following administration of IPX066 was assessed by dose normalized to IPX066 245 mg. The T_{max} of LD ranged from 2.75 to 4 hours. The half-life of LD ranged from 1.44 to 1.53 hours. The C_{max} and AUC of LD from IPX066 increased in a dose proportional manner over the LD dose strengths of 95 mg to 245 mg as shown in the Table 3 below.

Table 3: Statistical Analysis of the Log Transformed Pharmacokinetic Parameters for LD in Study IPX066 B08-09 (N=28). (Sponsor's table).

PK Parameters	Contrast IPX066 Dose (mg)	Ratio (%)	90% Confidence Interval	
			Lower	Higher
C _{max}	95/245	105.30	96.86	114.47
AUC _{0-t}	95/245	89.57	83.07	96.57
AUC _{0-∞}	95/245	89.95	83.93	96.41
C _{max}	145/245	107.83	99.17	117.24
AUC _{0-t}	145/245	94.52	87.65	101.92
AUC _{0-∞}	145/245	94.41	88.08	101.19
C _{max}	195/245	101.84	93.68	110.71
AUC _{0-t}	195/245	98.22	91.10	105.89
AUC _{0-∞}	195/245	97.74	91.20	104.76

The proposed dosing guidelines are reasonable for initial conversion. However, the proposed conversion strategy to IPX066 dose for a range of starting IR doses will not have a similar C_{max} of LD at all doses. To overcome this issue, the sponsor proposes that patients can take additional IPX066 dose during bedtime.

5 Sources of Clinical Data

The sponsor submitted results of three phase 3 clinical trials:

- a placebo controlled in patients with early PD
- an active control (CD/LD) in patients with advanced PD
- a second crossover trial in patients with advanced PD comparing patients treated with IPX066 to patients treated with CD/LD + entacapone (CLE) as the active comparator.

5.1 Tables of Studies/Clinical Trials

Table 4: Description of Clinical Efficacy Studies Included in NDA 203312. (Sponsor's table).

Study ID, No. of Centers, Location	Study Start Date Enrollment Status and Date Total Enrollment/ Planned	Design	Study and Control Drugs Dose, Route, Regimen, Formulation	Study Objective	No of Subjects by Arm Who Entered/ Completed	Duration	M/F Mean Age, yr (range), Race (W/B/A/A /O) ^a	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint Other Efficacy Assessments
Controlled Studies									
IPX066- B08-05 56 centers: United States and Canada (30); Europe (26 in Ukraine, Romania, Lithuania, Latvia, Estonia)	Started: 13Apr2009 Completed: 5Oct2010 381/350	Phase 3, randomized, double- blind, placebo- controlled, parallel-arm, multicenter, study using a three fixed doses of IPX066 in LD-naïve subjects. Prestudy PD therapies maintained throughout the study.	IPX066, oral capsule Three fixed IPX066 doses: 145 mg LD TID 245 mg LD TID 390 mg LD TID Placebo TID	To evaluate the safety and efficacy of IPX066 in the treatment of subjects with early PD. Additional objective: evaluate QOL.	Three fixed IPX066 doses 145 mg LD: 87/72 245 mg LD: 104/83 390 mg LD: 98/74 Placebo : 92/71	30 weeks (Titration Period = 4 weeks; Maintenance Treatment Period = 26 weeks)	212M/169F 64.8 (36- 87) 375W/2B/ 2A/2O	Early PD; LD naïve, ≥30 yrs old at PD diagnosis, UPDRS Part II plus Part III score ≥18, MMSE score ≥26, Hoehn & Yahr stage I-III, liver enzymes <2×ULN, creatinine <1.5×ULN	Change from Baseline in UPDRS Part II + Part III Total UPDRS, UPDRS I, II, III, PGI, CGI

Clinical Review
 Anne E. A. Constantino, MD
 NDA 203312
 Ryтары/IPX066/Carbidopa-Levodopa Extended Release

Study ID, No. of Centers, Location	Study Start Date Enrollment Status and Date	Design	Study and Control Drugs	Study Objective	No of Subjects by Arm Who Entered/ Completed	Duration	M/F Mean Age, yr (range), Race (W/B/AI/A /O) ^a	Diagnosis	Primary Efficacy Endpoint
	Total Enrollment/ Planned		Dose, Route, Regimen, Formulation				Inclusion Criteria	Other Efficacy Assessments	
IPX066- B09-06 Part 1 27 Centers: United States (12) Germany (7), Italy (6), France (2)	110/96	Phase 3, randomized, double- blind, double- dummy, 2-treatment, 2-period crossover study in subjects with advanced PD. Each treatment period was 2 weeks with a 1-week, open-label IPX066 washout period. Prestudy non-LD anti-PD therapies maintained through the study.	IPX066, oral capsule CLE: IR CD-LD (25–100 mg) plus entacapone (200 mg), both oral tablets Both IPX066 and CLE doses were individualize d; CLE dose was same as baseline regimen Study Periods: Dose Conversion— IPX066. Blinded Treatment Periods— 1 IPX066 or CLE. 2 CLE or IPX066	1. To compare the efficacy of IPX066 and CLE 2. To assess the PK/PD of IPX066 and CLE	Dose Conversion: 110/84 Period 1: 48/45 Period 2: 43/39	11 weeks (Dose Conversion = 6 wks; Treatment 1 = 2 wks, washout = 1 wk, Treatment 2 = 2 wks)	76M/34F 64.6 (39– 88) 108W/20	Advanced PD, on stable regimen of CLE, requiring ≥400 mg LD TDD with a dosing frequency of ≥ 4×/d; ≥30 yrs old at PD diagnosis, MMSE score ≥26, Hoehn & Yahr stage I–IV in “on” state; predictable “on” and average “off” states, ≥2.5 h/d “off” time, UPDRS Item 33 score <3 or Items 32–34 score <5, liver enzymes <2×ULN, creatinine <1.5×ULN	“Off” time as a percent of awake hours “Off” time, “on” time with no troublesome dyskinesia, “on” time with troublesome dyskinesia , UPDRS Part II + Part III, Patient Preference

Study ID, No. of Centers, Location	Study Start Date Enrollment Status and Date Total Enrollment/Planned	Design	Study and Control Drugs Dose, Route, Regimen, Formulation	Study Objective	No of Subjects by Arm Who Entered/Completed	Duration	M/F Mean Age, yr (range), Race (W/B/AI/A/O) ^a	Diagnosis Inclusion Criteria	Primary Efficacy Endpoint Other Efficacy Assessments
IPX066-B09-02 68 centers: United States (35), Canada (3), France (3), Germany (5), Poland (7), Romania (3), Spain (5), Ukraine (7)	Started: 29Sep2009 Completed: 19Jan2011 471/420	Phase 3, randomized, double-blind, double-dummy, active-comparator-controlled, parallel-group, multicenter study. Prestudy non-LD anti-PD therapies maintained throughout the study.	IPX066, oral capsule IR CD-LD, tablet Study periods: Dose Adjustment—IR CD-LD Dose Conversion—IPX066 Randomized Maintenance — IPX066 or IR CD-LD	To evaluate the safety and efficacy of IPX066 in the treatment of advanced PD subjects in comparison to IR CD-LD	Study periods: Dose Adjustment —IR CD-LD, 471/450 Dose Conversion —IPX066, 450/393 Maintenance — IPX066, 201/186 or IR CD-LD, 192/182	22 weeks (Dose Adjustment = 3 wks; Dose Conversion = 6 wks; Maintenance Treatment = 13 wks)	292M/179F 63.5 (40–90) 456W/5B/2A/4AI/3O/1 unknown	Advanced PD, on stable regimen of CD-LD, requiring ≥ 400 mg LD TDD with a dosing frequency of $\geq 4 \times/d$; ≥ 30 yrs old at PD diagnosis, MMSE score ≥ 26 , Hoehn & Yahr stage I–IV in “on” state, predict-able “on” and average “off” states”, ≥ 2.5 h/d “off” time, UPDRS Item 33 score < 3 or Items 32–34 score < 5 , liver enzymes $< 2 \times$ ULN, creatinine $< 1.5 \times$ ULN	“Off” time as a percent of awake hours “Off” time, “on” time with no troublesome dyskinesia, “on” time with troublesome dyskinesia, UPDRS Part II + Part III, PGI, CGI

5.2 Review Strategy

The review strategy focuses upon the following areas:

- Is the new carbidopa-levodopa formulation, IPX066, superior to placebo in relieving the symptoms of early PD?
 - The Phase 3 placebo controlled trial in 381 early PD patients (IPX066-B08-05) will be the source of efficacy data to provide answers to this question.
- Is the new carbidopa-levodopa ER formulation (IPX066), superior to “optimal treatment” with marketed carbidopa-levodopa (Sinemet) for the reduction in “Off” time in patients with advanced PD?

- The Phase 3, 22-week study in 471 patients with advanced PD comparing IPX066 to IR CD-LD will be the source of efficacy data for this application.
- Are the treatment effects of IPX066 maintained for longer use?
 - Study IPX066-B09-03, an ongoing open-label safety extension trial that includes patients who completed controlled trials IPX066-B08-11, IPX066-B08-05 and IPX066 B09-02 will be reviewed to provide information on long term treatment of IPX066.
- Is the new formulation of CD-LD safe?
 - Review of safety data from the different trials is found in section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Trial in Early PD: IPX066 B08-05

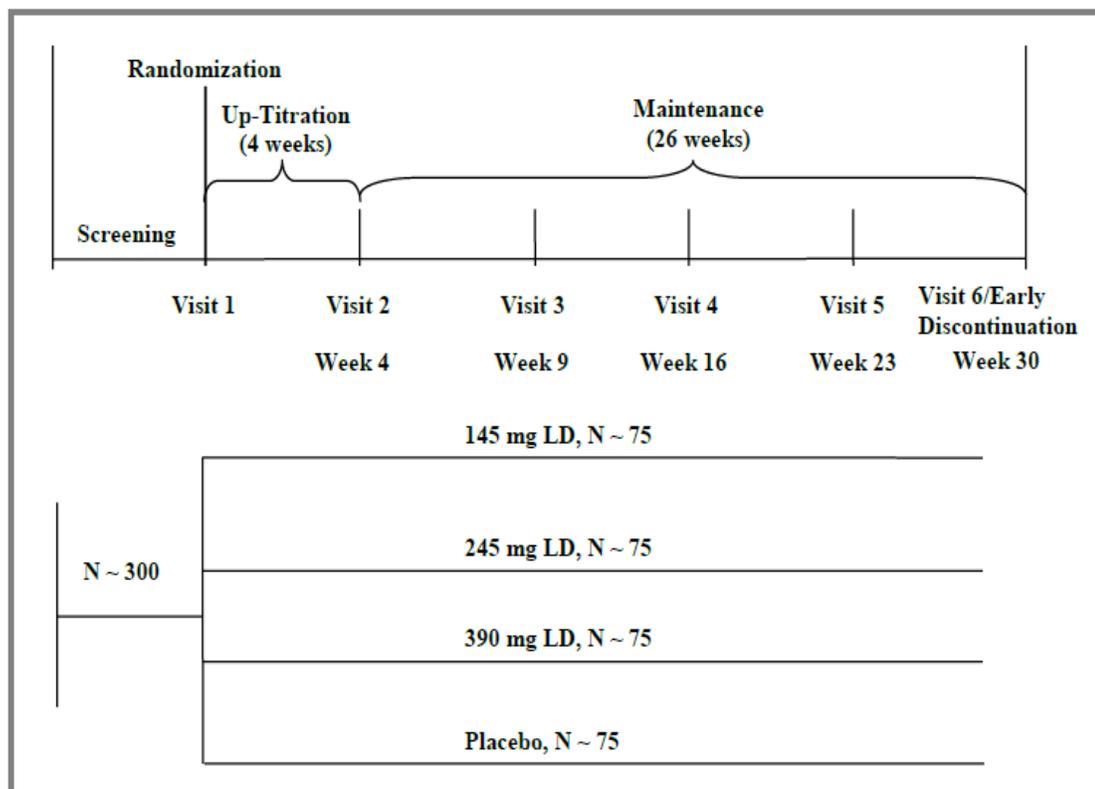
This Phase 3, placebo controlled study compared the safety and efficacy of IPX066 to placebo. The three highest tablet strengths (145 mg, 245 mg and 390 mg) were selected as targeted doses in this trial. The 95 mg tablet was only used for titration and it was not included in the efficacy assessment. LD-naïve patients with early PD selected for participation were 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 prior to study enrollment. Treatment with dopamine agonists was not permitted during the trial. The sponsor conducted a stratified analysis based on previous treatment with PD medications compared to those never treated with PD medications. The primary endpoint was the change from baseline in the sum of UPDRS Part II (Activities of Daily Living) and III (Motor Function) scores at the end of the 30-week study (Visit 6) or the last valid post-baseline measurement collected if the patient discontinued early. The UPDRS score is a validated, physician rated clinical symptom scale used to evaluate the motor symptoms of PD. The UPDRS total score and parts 2+3 is a frequently used endpoint in clinical trials that support regulatory submissions of other PD drugs.

Secondary endpoints in this study include the change in UPDRS Part II plus III scores from Baseline to Weeks 4, 9, 16, 23 and the sum of Parts I to III of the UPDRS, PGI, CGI and PDQ 39 at end of study.

The trial design (shown in the figure below) includes 4 weeks of up-titration from a starting dose of 95 mg 3 times a day (0 mg for placebo) to the assigned dose according to the randomized treatment until the end of the study. Each subject was given identical placebo

capsules to maintain the blind. Subjects who could not tolerate the titration schedule or who required rescue medications were discontinued from the study.

Figure 1: Study Design and Schedule of Assessments (Source: Sponsor)



The three IPX066 dosing regimens were administered three times daily (every 6 hours) in the belief it would provide stable plasma concentrations of LD during the dosing interval (36.25-145 mg, 61.25-245 mg or 97.5-390 mg CD_LD given as 2 caps of 48.75-195 mg).

The target population was symptomatic PD patients who were treated with dopamine agonists and have met the following key inclusion/exclusion criteria:

Key Inclusion Criteria:

1. Diagnosed with idiopathic PD as defined by meeting of the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria without any known cause for parkinsonism.
2. Male or female and at least 30 years old at the time of diagnosis.
3. PD was Hoehn and Yahr Stage I, II or III.

4. Mini Mental State Examination score was ≥ 26 at screening.
5. Levodopa naïve. Subject could not have used levodopa (LD) or COMT inhibitors for more than 30 days and the exposure was not within 4 weeks before study enrollment.
6. Sum of UPDRS Parts II and III was ≥ 18 at Screening and at Baseline.

Key Exclusion Criteria

1. Was diagnosed with atypical Parkinsonism or any known secondary Parkinsonian syndrome.
2. Had undergone prior functional neurosurgical treatment for PD.
3. Used nonselective MAO inhibitors, used dopamine agonists within 30 days before screening.
4. Had a history of treatment of psychosis with antipsychotic within 2 years before screening. Treatment for conditions other than psychosis such as sleep aid was allowed.
5. Had a history of seizure, epilepsy and taking anti-convulsants.
6. Had the following medical conditions: peptic ulcers, narrow angle glaucoma, malignant melanoma or had a suspicious undiagnosed skin lesion, which in the opinion of the Investigator could be melanoma, history of myocardial infarction, upper gastrointestinal hemorrhage, neuroleptic malignant syndrome, abnormal kidney function (creatinine 1.5x upper limit of normal at screening or required dialysis), had liver transaminases that were $\geq 2x$ ULN at screening

Concomitant Medications:

The following medications were prohibited beginning 30 days before the initial dose of study medication and throughout study participation: investigational medications, COMT inhibitors e.g. enatacapone and tolcapone, dopamine blocking agents (chlorpromazine, ergotamine, metoclopramide and prochlorperazine), nonselective MAO inhibitors, dopamine agonists, anticonvulsants (e.g. adrenocorticotrophic hormone, acetazolamide, benzodiazepines, bromides, carbamazepine, chlormethiazole, ethotoin, ethosuximide, felbamate, fosphenytoin sodium, gabapentin, lamotrigine, mephobarbital, methusuximide, oxcarbazepine, paraldehyde, pentobarbital, primidone, progabide, tiagabine, topiramate, trimethadione, valproic acid, vigabatrin, zonisamide), neuroleptic agents.

Schedule of Trial Activities

Table 5: Schedule of Trial Visits with Planned Efficacy and Safety Assessments. (Sponsor's table).

Procedure	Screening	Visit 1 Baseline	Visit 2 Week 4	Visit 3 Week 9	Visit 4 Week 16	Visit 5 Week 23	Visit 6 Week 30 or Early Discontinuation
Informed consent, HIPAA	√						
Assign 6-digit ID number	√						
Medical history	√						
Complete physical examination	√						√
Vital signs ^a	√	√	√	√	√	√	√
12-lead ECG	√				√		√
Clinical laboratory studies ^b	√				√		√
Urine pregnancy test ^c	√	√					
UPDRS ^d	√	√	√	√	√	√	√
MMSE ^d	√						
PDQ-39 ^d		√	√	√	√	√	√
PGI ^d			√	√	√	√	√
CGI ^d			√	√	√	√	√
Hoehn and Yahr staging ^d	√						
BDI-II ^d	√						√
Randomization		√					
Account for study medication			√	√	√	√	√
Dispense study medication		√	√	√	√	√	
Adverse events		√	√	√	√	√	√
Concomitant medications	√	√	√	√	√	√	√

^a Blood pressure, heart rate, temperature, and respiratory rate were measured after remaining supine for 5 min. Blood pressure and heart rate were also measured after standing for 2 minutes.

^b Laboratory tests performed are defined in Appendix B of the study protocol in Appendix 16.1.1.

^c Females of childbearing potential only.

^d Instruments are provided in the appendices of the study protocol in Appendix 16.1.1.

Abbreviations: BDI-II = Beck Depression Inventory—II, CGI = Clinical Global Impression, ECG = electrocardiogram, HIPAA = Health Insurance Portability and Accountability Act, ID = identity, MMSE = Mini-Mental State Examination, PDQ-39 = Parkinson's Disease Questionnaire, PGI = Patient Global Impression (39 questions), UPDRS = Unified Parkinson's Disease Rating Scale.

Source: Appendix 16.1.1.

REVIEWER'S COMMENTS:

Formal testing for sleep disorders (e.g. Epworth) was not conducted in the early PD patient study.

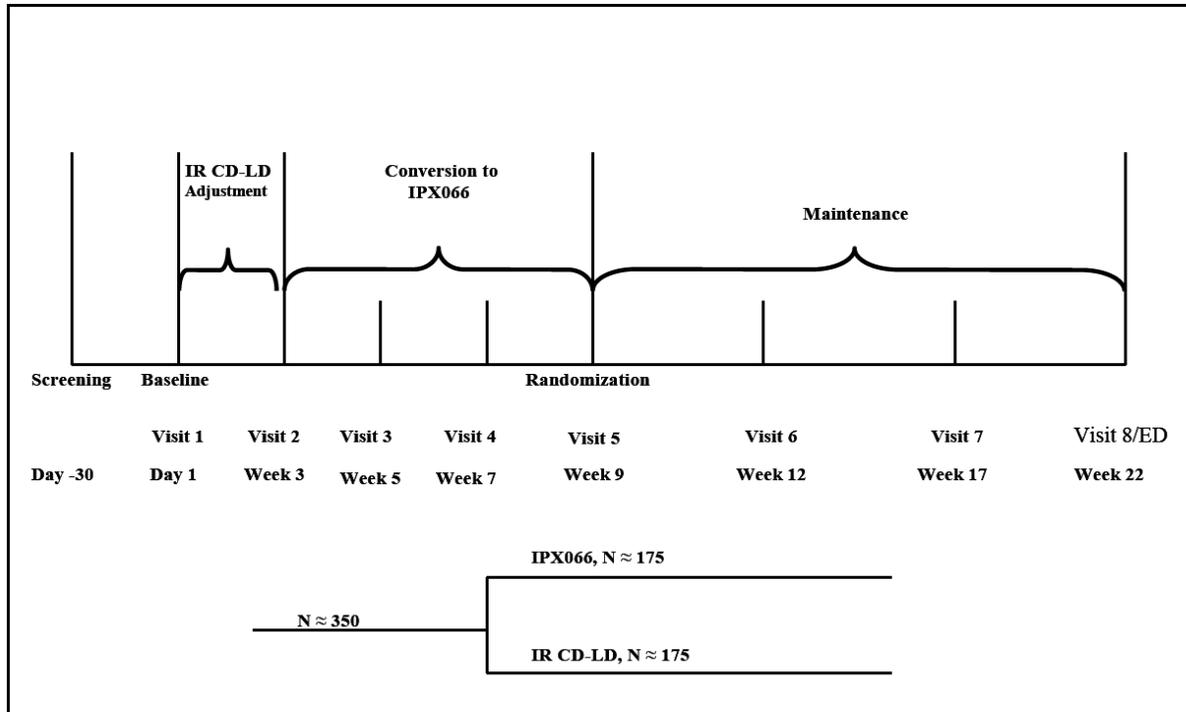
Pivotal Trial in Advanced PD: IPX066 B09-02

This phase III study was a randomized, double blind, double dummy, active control, parallel group study that evaluated the efficacy of IPX066 in patients with advanced Parkinson's disease with motor fluctuations compared to standard immediate release carbidopa/levodopa. The primary endpoint was the change in the percent awaking "off" time from baseline to EOS. Reporting of "off time" relied heavily on the patient's compliance in keeping a complete and timely diary entry (utilizing the Hauser Parkinson's disease Diary) in accordance with the protocol.

Qualified subjects must have maintained a stable standard LD regimen with a total daily LD dose of at least 400 mg and experiencing at least 2.5 hours of "off" time per day during waking hours.

The figure below summarizes the study design that includes a 3-week IR CD LD treatment period to allow for dose adjustment of their IR CD LD regimen. This is followed by a 6-week dose conversion to IPX066. Subsequently, subjects were equally randomized into one of parallel treatment arms of either IPX066 or IR CD LD. Following randomization, patients underwent 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 end of Week 9 (Visit 5) for IPX066.

Figure 2: Study Design Diagram (Source: Sponsor)



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

Other secondary endpoints were:

- Responder analysis of improvement in “off” time was also performed.
- Analyses of PD Diary data at Visit 5 (end of Dose Conversion), Visits 6, 7 and 8 were also conducted.
- UPDRS measures include Part II + Part III, Parts I, II and III, Total UPDRS, UPDRS Part I; UPDRS Part II (“on” and “off” states); UPDRS Part III and UPDRS Part IV. Most important measure was UPDRS Part II + Part III at EOS.
- PGI and CGI are presented for completers at EOS Visit 8 or Termination of Study
- Quality of Life (Q of L) related analyses

Presubmission Advice from the Division to the Sponsor

The original protocol for this study was submitted on June 9, 2009. There were 3 amendments prior to the final protocol submission on October 29, 2009. The major protocol change was a simplification of the design that reduced the number of arms from the proposed three to two by dropping the combined entacapone CD-LD arm. The sponsor also incorporated the FDA suggestion to monitor treatment emergent impulse control disorders (by using the Minnesota Impulsive Disorders Interview (mMIDI) and to include quality of life, health and disability measures.

The target population consisted of subjects with advanced PD with motor fluctuations who met the following key inclusion and exclusion criteria.

Key Inclusion Criteria:

1. Diagnosed with idiopathic PD as defined by meeting UK PD Society Brain Bank Diagnostic Criteria without secondary Parkinsonism
2. At least 30 years old at time of PD diagnosis
3. Hoehn and Yahr Stage I – IV in the “on” state.
4. Mini Mental State Exam ≥ 26 at Screening
5. Treated with IR LD and a stable regimen of IR LD for at least 4 weeks before Screening visit and
 - a. Required a total daily IR CD-LD dose of at least 400 mg
 - b. Minimum dosing frequency of 4 times daily
6. Able to differentiate “on” from “off” state as defined by at least 75% concordance with a trained rater in “on/off” ratings for at least four ratings over the 4 hour training period. The concordance must have included at least one “on” and one “off” rating and must have been achieved within two four-hour training sessions.
7. Predictable “off” periods defined as “yes” response to Question # 36 on the UPDRS

Key Exclusion Criteria:

1. Diagnosed with atypical Parkinsonism or any known secondary Parkinsonian syndrome
2. Non-responsive to LD therapy

3. Had scored a combined total of ≥ 5 on Questions # 32, 34 of UPDRS or ≥ 3 on Question 33 of UPDRS
4. Prior neurosurgical treatment for PD or such procedures were anticipated during study participation.
5. Had received within 4 weeks of Screening Visit or planned to take during participation in the clinical study any controlled release LD product, additional CD or benserazide, Catechol-O-Methyl transferase inhibitors, non-selective MAO inhibitors, apomorphine, antipsychotics for purpose of treating psychosis
6. Had a history of seizure, epilepsy and taking anti-convulsants.
7. Had the following medical conditions: peptic ulcers, narrow angle glaucoma, malignant melanoma or had a suspicious undiagnosed skin lesion, which in the opinion of the Investigator could be melanoma, history of myocardial infarction, upper gastrointestinal hemorrhage, neuroleptic malignant syndrome, abnormal kidney function (creatinine 1.5x upper limit of normal at screening or required dialysis), had liver transaminases that were ≥ 2 x ULN at screening

Concomitant Medications:

- Subjects were on a stable dose of IR LD or benserazide for at least 4 weeks prior to screening
- Concomitant therapy with amantadine, anticholinergics, selective MAO type B inhibitors (selegiline/rasagiline) or dopamine agonists was allowed as long as doses and regimen have been stable for at least 4 weeks prior to screening
- Medications prohibited in the study: Any LD products including non study IR, controlled release LD, additional CD or benserazide, apomorphine, other investigational medications, COMT inhibitors, nonselective MAO inhibitors, antipsychotics except those that are used to treat conditions other than psychosis or bipolar disorder are allowed

The investigational drug in this study was IPX066, an ER capsule formulation of CDLD with a ratio of 1:4 for all dosing strengths:

IPX 23.75-95 mg CD_LD capsule (IPX066 95 mg)
IPX066 36.25-145 mg CD_LD capsule (IPX066 145 mg)
IPX066 48.75-195 mg CD_LD capsules (IPX066 195 mg)
IPX066 61.25-245 mg CD_LD capsules (IPX066 245 mg)

Other study medication was IR CD_LD 25-100 mg and matching placebo.

Each subject was titrated to individualized dosing regimens of IR CD-LD and IPX066 during the Open Label and Double Blind maintenance portions.

At study entry, subjects were taking a stable regimen of IR CD-LD with a total daily dose of at least 400 mg LD/day with minimum dosing frequency of 4 times daily. During the first 3 weeks of the study (Dose Adjustment period), the Investigators could adjust the dose and frequency of IR CD-LD open label to achieve maximum benefit.

Based on the dosing regimen of IR CD-LD during the Dose Adjustment period, an initial IPX066 dosing regimen was recommended as shown in the conversion table below:

Table 6: Suggested Initial Dose Conversion to IPX066 in Study B09-02 (Sponsor's table).

Total Daily IR LD Dose (mg)	Suggested Initial IPX066 Dosage (LD in mg) Each Dose Approximately 6 Hours Apart During Waking Hours		
	Morning Dose	Midday Dose	Evening Dose
400 - 550	3 capsules x 95	3 capsules x 95	3 capsules x 95
551 - 750	4 capsules x 95	4 capsules x 95	4 capsules x 95
751 - 950	3 capsules x 145	3 capsules x 145	3 capsules x 145
951 - 1250	3 capsules x 195	3 capsules x 195	3 capsules x 195
1251 - 1650	4 capsules x 195 OR 3 capsules x 245	4 capsules x 195 OR 3 capsules x 245	4 capsules x 195 OR 3 capsules x 245
>1650	4 capsules x 245	4 capsules x 245	4 capsules x 245

Abbreviations: IR = immediate release, LD = levodopa.
 Source: Appendix 16.1.1.

At the end of the IPX066 dose conversion period, the goal was to maintain patients on single dosage strength and the dosing regimen was stable for at least 5 days prior to randomization. If this was not possible, then the subject was not randomized into the study.

Regular phone calls were to be made during the Dose Conversion period to assess the need for dose adjustment. Three days were allowed for each adjustment. The Investigators could make more frequent adjustments, if needed during the initial phase of the IPX066 Dose Conversion Period. Dosing frequency could be reduced or IPX066 dose could be decreased if treatment emergent AEs occurred.

Randomization occurred at Week 9 (Visit 5) and at the end of the Dose Conversion period. The subjects were randomized in a 1:1 ratio in a blinded fashion into either IPX066 or IR CD-LD group.

Clinical Review
 Anne E. A. Constantino, MD
 NDA 203312
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The next part of the study was the Double Blind Maintenance Period from weeks 10 to 22. This period lasted for 13 weeks and subjects received only double blind study treatment.

The table below summarizes the procedures and evaluation tests performed at each visit.

Table 7: Procedures and Evaluation Tests Done at Each Visit in Study B09-02 (Sponsor's Table).

Procedures	Screening	Dose Adjustment of IR CD-LD	Conversion to IPX066				Maintenance			
		Visit 1 Baseline	Visit 2 Week 3	Visit 3 Week 5	Visit 4 Week 7	RANDOMIZATION Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 17	Visit 8/Week 22 or Early Discontinuation	
Informed consent, HIPAA	√									
Contact IVRS/TWRS	√	√	√	√	√	√	√	√	√	
Assign 6-digit ID number	√									
Training "on/off" and PD Diary	√									
Medical history	√									
Complete physical exam	√								√	
Contact subject		√ ^{a,b}	√ ^{a,b}	√ ^b	√ ^b	√ ^a	√ ^a	√ ^a	√ ^a	
Vital signs ^c	√	√	√	√	√	√	√	√	√	
12-lead ECG	√								√	
Clinical laboratory studies	√					√			√	
Urine pregnancy test ^d	√	√								
UPDRS	√ ^e	√ ^f	√ ^f			√ ^f	√ ^f	√ ^f	√ ^f	
MMSE	√									
Hoehn and Yahr staging	√									
PDQ-39		√	√			√			√ ^g	
EQ-5D		√	√			√			√ ^g	
SF-36 Health Survey		√	√			√			√ ^g	
SCOPA-S		√	√			√			√ ^g	
mRS		√	√			√			√ ^g	
PGI									√ ^g	
CGI									√ ^g	
m-MIDI	√					√	√		√ ^g	
Randomization						√ ^h				
Dispense PD Diary	√	√			√	√	√	√		
Collect and review PD Diary		√	√			√	√	√	√	

Clinical Review
 Anne E. A. Constantino, MD
 NDA 203312
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Procedures	Screening	Dose Adjustment of IR CD-LD	Conversion to IPX066				Maintenance			
		Visit 1 Baseline	Visit 2 Week 3	Visit 3 Week 5	Visit 4 Week 7	RANDOMIZATION Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 17	Visit 8/Week 22 or Early Discontinuation	
Dispense study medication		√	√	√	√	√	√	√		
Collect used and empty medication bottles			√	√	√	√	√	√	√	
Adverse events		√	√	√	√	√	√	√	√	
Concomitant medications	√	√ ^d	√	√	√	√	√	√	√	

^a Except for Visit 3 and Visit 4, site was to contact the subject 4 days prior to the visit and remind him/her to complete the 3-day PD diaries. Site was to contact the subject 1 day prior to the visit to remind him/her to bring the PD diaries to the next visit and to bring back any unused medication and empty medication bottles (not applicable for Visit 1).

^b Site was to make regular phone calls to the subject throughout the IR CD-LD Dose Adjustment and IPX066 Dose-Conversion periods to evaluate the subject's adjustment to the study medication.

^c Vital signs included blood pressure, heart rate, temperature, and respiratory rate after supine for 5 minutes, plus blood pressure and heart rate after standing for 2 minutes.

^d Females of childbearing potential only.

^e At Screening Visit, UPDRS Parts I – IV were to be completed during “on” state.

^f UPDRS Parts I – IV were to be completed during “on” state. UPDRS Part II was also to be completed for the “off” state.

^g Procedures were not to be completed if the subject withdrew from the study prior to randomization.

^h The subject was to have been maintained on the same regimen of IPX066 for at least 5 days prior to Randomization.

ⁱ Site was to ensure no change in IR CD-LD or concomitant anti-PD medications since the Screening Visit.

Abbreviations: HIPAA = Health Insurance Portability and Accountability Act; IVRS/TWRS=interactive voice/web response system; ECG = electrocardiogram; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination; PDQ 39 = Parkinson's Disease Questionnaire-39; EQ-5D = EuroQoL Group Health Questionnaire; PGI=Patient Global Impression; CGI = Clinical Global Impression; m-MIDI=modified-Minnesota Impulsive Disorders Interview and scoring sheet; PD = Parkinson's Disease; SCOPA-S = Scales for Outcomes in Parkinson's Disease Sleep Scale; mRS=Modified Rankin Scale.

Source: Protocol IPX066-B09-02, [Appendix 16.1.1](#)

Advanced Parkinson's Disease Study: IPX066-B09-06 Part 1

Trial IPX066-B09-06 was a phase III active comparator design that compared IPX066 with carbidopa levodopa entacapone (CLE) in patients with advanced PD (see trial design schematic below). The study recruited patients with advanced PD who were maintained on a stable dose of CLE prior to trial entry. Patients were converted from a dose of CLE which has not been optimized. The conversion from CLE to IPX066 was done by phone and the table below (Table 8) was used as a guide for conversion of patients from CLE to the study drug IPX066. Once converted to IPX066, the protocol allowed for changes to the dosing regimen: “This regimen could be modified to optimize clinical benefit of IPX066 but the dosing interval of IPX066 could not be more frequent than approximately every 4 hours, or more than 5 times per day”. In Period 1 patients were maintained on the stable dose of IPX066 for 5 days prior to randomization in the “Double Blind Crossover Phase”.

The conversion proposed in this study is presented in the table below.

Table 8: Suggested Initial Dose Conversion of CLE to IPX066 (Sponsor's table).

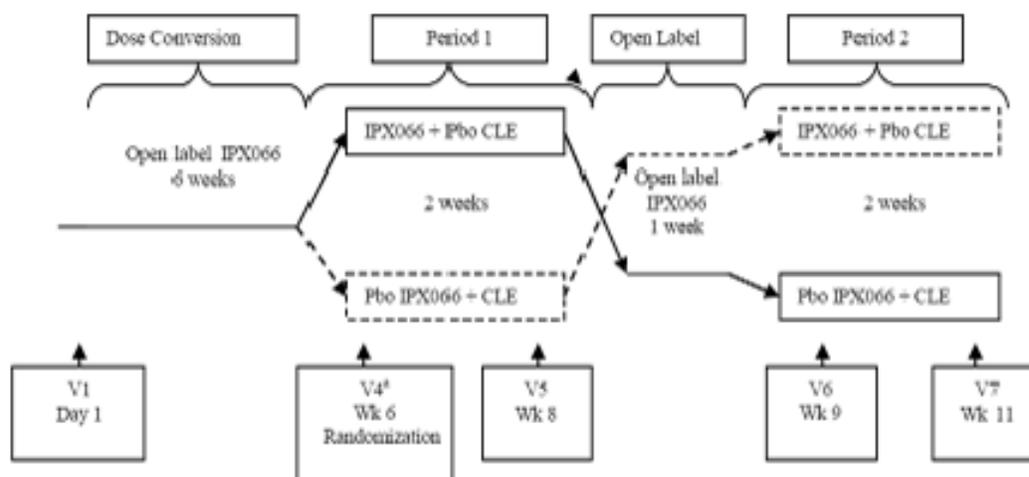
Total Daily LD Dose (mg)	Suggested Initial IPX066 Dose (LD in mg) ^a		
	Morning Dose	Midday Dose	Evening Dose
	4 capsules x 95	4 capsules x 95	4 capsules x 95
	2 capsules x 245	2 capsules x 245	2 capsules x 245
	3 capsules x 195	3 capsules x 195	3 capsules x 195
	3 capsules x 245	3 capsules x 245	3 capsules x 245
	4 capsules x 245	4 capsules x 245	4 capsules x 245

Abbreviations: LD=levodopa; CLE=carbidopa/levodopa/entacapone

^aEach dose approximately 6 hours apart during waking hours

During crossover treatment Periods 1 and 2, the CLE (or placebo) dosage was to remain the same as that of the pre-study regimen (recorded at Visit 1), and the IPX066 (or placebo) dosage was to be the same as that established during the Dose Conversion period (recorded at Visit 4). No adjustment of the dosing regimens (number of capsules per dose and dosing frequency) was permitted during these 2-week double-blind treatment periods. The figure below illustrates the study design.

Figure 3: Schematic Diagram for Study Design of IPX066 B09-06 Part 1 (Source: Sponsor).



Abbreviations: Pbo = placebo; CLE = carbidopa/levodopa/entacapone; V = visit; Wk = week

²Visits 2 and 3 during Dose Conversion period are at Weeks 2 and 4.

Source: Appendix 16.1.1, section 3.0.

In general, the severity of disease and demographics of patients enrolled in this study (B09-06) were similar to the Advanced PD Study (B09-02) comparing IPX066 to IR. The protocol had the same trial inclusion and exclusion criteria except for these additional inclusion criteria:

- Prior to the Screen Visit, the subject had to have an average of at least 2.5 cumulative hours per day of “Off” Time during the waking hours for the last 2 weeks. At Visit 1, subject had to have an average of at least 2.5 hours over 3 days and at least 1 hour each of “Off” time based on the 3 day PD diaries recorded on the 3 consecutive days immediately prior to Visit 1.
- Subjects of the PK Cohort had to have at least a 10% increase in finger tapping rate during the 1 minute period in the “On” state compared to “Off” state at Screening.
- For the control treatment of CLE, subjects were required to be taking a stable regimen of CLE for at least 4 weeks with a LD total daily dose of at least 400 mg, a minimum CLE dosing frequency of 4 times per day at least 400 mg daily dose of LD in at least four divided doses at study entry. These requirements were to ensure that subjects participating in this study were not inadequately treated.

REVIEWER’S COMMENTS:

The trial design did not result in a fair comparison between the patients on IPX066 and CLE because patients enrolled in this trial were maintained on a stable dose of CLE for 4 weeks prior to trial entry but the protocol did not require investigators to maximize or optimize patient’s response to treatment with CLE before conversion to IPX066. The minimum dose of CLE received by patients entering the trial was modest. Meanwhile, the protocol permitted the investigators to adjust the IPX066 dose to the patient’s individual requirements. As stated in the protocol: “The timing and doses of IPX066 used in the double-blind crossover periods were determined individually for each subject during the open label IPX066 Dose Conversion periods between IPX066 and IR”. The trial design resulted in comparison of IPX066 to suboptimal doses of CLE that biased the results towards IPX066. The protocol design allowed “off time” comparisons for patients after they were potentially maximally treated on IPX066 to their amount of “off time” on non-maximized CLE.

6 Review of Efficacy

Efficacy Summary

- The sponsored submitted three double blind, randomized studies, one in LD naïve subjects with early Parkinson’s disease (Study IPX-066 B08-05) and two in subjects with advanced Parkinson’s disease (Studies IPX066 B09-02 and IPX066 B09-06). The design of study B09-06 did not allow a fair comparison of the Carbidopa-Levodopa-Entacapone to the IPX066 group because the design did not allow CLE dose optimization prior to randomization. To be able to make a decision on the approvability of IPX066 for Advanced PD patients, we had to rely on solely on study B09-02.
- The primary endpoint in the B08-05 study in early PD is the sum of the UPDRS Parts 2 and 3 scores at end of study. IPX066 is statistically superior to placebo at EOS for changes in the primary endpoint.
- The biometrics reviewer performed an analysis that included the missing patient data Week 30 UPDRS assessment data using a different mixed model repeated measures which assumed a categorical effect of the visits. His analysis supported the sponsor’s results for the primary endpoint.
- The results for the secondary endpoints demonstrate a difference between the treatment groups ($p < 0.05$ without multiplicity correction) and placebo. However, the treatment effect is less consistent with the higher doses as was seen in the UPDRS Parts II and III Scores.
- The Patient and Clinician global rating scale scores (CGI) also showed “improvement” over placebo with all treatment groups.
- The total PDQ 39 outcome supported the results of the primary efficacy endpoint in all treatment group with nominal p value $p < 0.05$. However, the PDQ 39 was driven by results of the motor subscale.
- Despite the statistically significant difference in the UPDRS scores Parts II and III that show improvement with all three treatment arms, the UPDRS part IV which assesses dyskinesias, and other adverse events showed worsening with the higher doses of IPX066 compared to placebo. A dose related increase in dyskinesia is consistent with the results of the ELLDOPA trial and it is not as unique to this drug.
- In study B09-02, the primary endpoint was the 3 day PD diary results “off” time as a % of waking hours at study endpoint week 22. Efficacy results demonstrate that patients treated with IPX066 experienced a

improvement of 2.2 hours compared to 1 hour among subjects randomized to IR. The difference between the two groups was statistically significant. Amount of “ON” time with troublesome dyskinesias was greater by about 25 minutes in the IPX066 treatment group. The responder analysis support the primary endpoint as it showed that the number of responders who had improved “off” time from baseline was significantly different and favored the IPX066 group. PDQ 39 scores though showed only a significant difference in motor subscale but not in the other aspects of the of quality of life such as ADL Scores, emotional wellbeing, stigma, social support, cognition, communication and bodily discomfort.

- The proposed dose conversion scheme for converting patients on stable IR CD- LD dose to a comparable dose of IPX066 relied on the PK studies but does not have any pharmacodynamic study to support it. As a result, adjustments in dose (titrating up or down) and dose frequency may need to be done more often by a prescribing physician. This also requires the physician to follow up the patient more closely because of the risk of adverse events that may occur while titrating the patient.

IPX066 B08-05 for Early Parkinson’s Disease

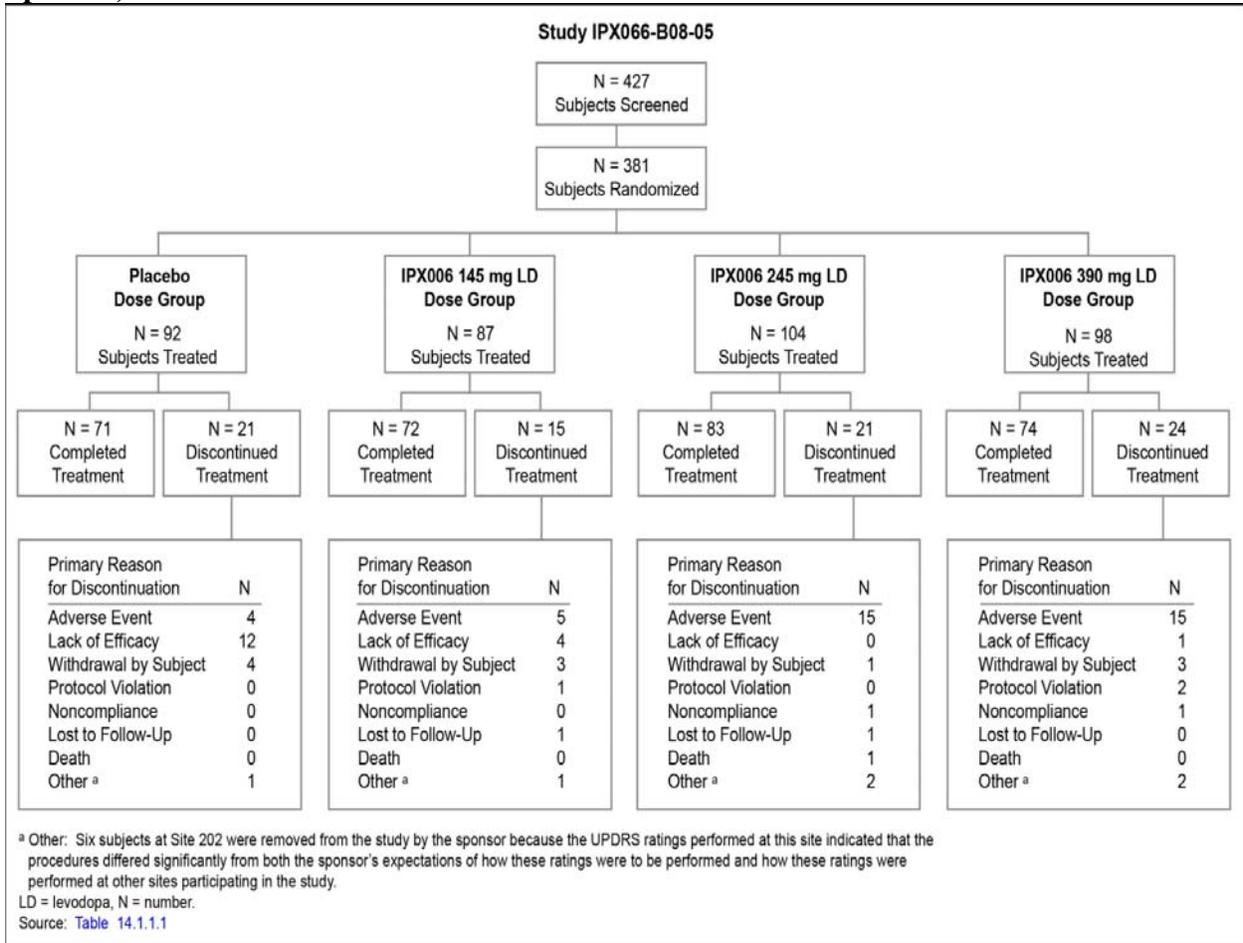
Methods

The objective of Study B08-05 was to assess the safety and efficacy of IPX066 in patients with early Parkinson’s Disease who were LD naïve (defined as less than 4 weeks exposure to any LD product prior to screening). The study was a randomized, double blind, placebo controlled group with three fixed doses of IPX066: 145 mg LD TID, 245 mg LD TID and 390 mg LD TID and placebo. Subjects were titrated to their assigned dose over 4 weeks with 3 weeks of dose escalation and 1 week of dose stabilization and a 26-week maintenance phase.

Patient Disposition

Four hundred twenty seven (427) subjects were screened and 381 were randomized to one of the four treatment groups in a 1:1:1:1 ratio. The flowchart of subject disposition for the early PD study is summarized in Figure 4.

Figure 4: Disposition of Subjects in Study IPX066-B08-05 Randomized Subjects (Source: Sponsor).



Premature Discontinuations

Table 9 summarizes the number of enrolled patients who discontinued from the study and the reasons for early discontinuations.

Table 9: Summary of Subjects Who Discontinued Study Treatment in Study B08-05 (Sponsor's table).

All Treated Subjects	Number of Subjects (%)				
	Placebo (N = 92)	IPX066 LD Dose Group			Total (N = 381)
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)	
Received Study Treatment	92 (100)	87 (100)	104 (100)	98 (100)	381 (100)
Discontinued Study Treatment	21 (22.8)	15 (17.2)	21 (20.2)	24 (24.5)	81 (21.3)
Primary Reasons for Early Discontinuation					
Adverse Event	4 (4.3)	5 (5.7)	15 (14.4)	15 (15.3)	39 (10.2)
Lack of Efficacy	12 (13.0)	4 (4.6)	0	1 (1.0)	17 (4.5)
Withdrawal by Subject	4 (4.3)	3 (3.4)	1 (1.0)	3 (3.1)	11 (2.9)
Protocol Violation	0	1 (1.1)	0	2 (2.0)	3 (0.8)
Noncompliance	0	0	1 (1.0)	1 (1.0)	2 (0.5)
Lost to Follow-Up	0	1 (1.1)	1 (1.0)	0	2 (0.5)
Death	0	0	1 (1.0)	0	1 (0.3)
Other ^a	1 (1.1)	1 (1.1)	2 (1.9)	2 (2.0)	6 (1.6)

^a Six subjects at Site 202 were removed from the study by the Sponsor because the UPDRS ratings performed at this site indicated that the procedures differed significantly from both the Sponsor's expectations of how these ratings were to be performed and how these ratings were performed at other sites participating in the study.

Source: Table 14.1.1.1.

Adverse event was the most common reason for early discontinuations in the IPX066 treated group. The number of patients who withdrew because of an adverse event in the IPX066 group increased with the dose. This will be discussed in detail in the safety portion of this review. In the placebo group, "lack of efficacy" was the most common reason for premature discontinuation.

Six subjects discontinued due to "other" reasons. These patients were all from Site 202 and were removed from the study by the sponsor and the reason for removal was that "*the UPDRS ratings performed at this site indicated that the procedures differed significantly from both the Sponsor's expectations of how these ratings were to be performed and how these ratings were performed at other sites participating in the study*".

Of the 381 subjects, there were only 361 subjects included in the efficacy analysis plan as 4 subjects had no post Baseline visits and 16 subjects had early termination visit more than 3 days after the last dose date and had no other post baseline visits. This will further be discussed in the statistical analysis.

There were 3 protocol violations that led to discontinuation in the treatment group and one in the placebo group. One patient had a low UPDRS score at screening, another patient was randomized without results from central laboratory and the third patient was diagnosed with melanoma. I reviewed the other protocol deviations that were considered as “minor”. I agree with the sponsor on judging them as “minor” based on the reasons that they had given. Most of the reasons for protocol deviations under “inclusion criteria” were procedural (e.g. initialing pages but forgot to sign ICF).

Demographic Characteristics

There were no notable differences across the four treatment groups by age, weight and BMI. There were more males than females enrolled in this study. This reflects the higher incidence of the disease among males as shown in table 10.

Table 10: Baseline Demographics by Treatment Group in Study B08-05 (Sponsor's table)

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)

Characteristic	Number of Subjects (%)			
	Placebo (N = 92)	IPX066 LD Dose Group		
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)
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.

Baseline Disease Characteristics

There were no significant differences in PD characteristics at baseline across treatment groups with regard to mean age of onset (63 years) and duration of disease at study entry (1.98 years). Hoehn and Yahr Stage and UPDRS scores were also comparable among treatment groups as shown in the table below.

Table 11: Baseline Disease Characteristics by Treatment Group in Early PD Patients in Study B08-05 (Sponsor's table).

Characteristics	Number of Subjects				Total (N = 381)	P Value
	Placebo (N = 92)	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						0.5538 ^{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)	
Hoehn and Yahr Stage (%)						0.8500 ^{a, b}
I	7 (7.6)	6 (6.9)	13 (12.5)	14 (14.3)	40 (10.5)	
II	69 (75.0)	62 (71.3)	65 (62.5)	62 (63.3)	258 (67.7)	
MMSE Scores						0.3529 ^a
Mean (SD)	28.9 (1.18)	29.0 (1.27)	28.7 (1.21)	28.9 (1.18)	28.9 (1.21)	
Median	29.0 (26-30)	29.0 (26-30)	29.0 (26-30)	29.0 (26-30)	29.0 (26-30)	
BDI-II Score ^d						0.9458 ^{a, c}
Mean (SD)	11.7 (8.81)	12.3 (8.84)	12.1 (9.01)	11.8 (10.33)	12.0 (9.25)	
Median (Range)	9.5 (0-43)	10.0 (0-38)	10.5 (0-44)	8.0 (0-39)	10.0 (0-44)	
Total PDQ-39 Score (% of Maximum)						0.7704 ^{a, c}
Mean (SD) ^e	24.0 (15.54)	26.0 (16.88)	25.2 (18.63)	25.1 (17.12)	25.1 (17.08)	
Median (Range)	21.5 (0-77)	23.7 (1-72)	22.8 (0-84)	23.0 (1-62)	21.8 (0-84)	

^a Overall treatment significance.

^b P-value is calculated using Cochran-Mantel-Haenszel method.

^c UPDRS, BDI-II, PDQ-39: Three-factor main effects ANOVA model.

^d BDI-II score: minimal = 0-13, mild = 14-19, moderate 20-28, severe = 29-63.

^e Mean/median of total score. Questions 1 through 30.

Analysis of Efficacy Data

The primary efficacy endpoint for this trial was the change in the sum of Parts II and III of the UPDRS from Baseline to End of Study (EOS) at Visit 6 (Week 30) or the last value reported if the subject leaves the study prematurely.

The analysis set was to include all treated subjects with at least one efficacy measurement post dose. Analysis was to be done assuming three factor main effects model that included treatment, center and strata. Stratum 1 included subjects who have never taken PD medications and Stratum 2 included subjects who have been treated or currently using non CD_LD medications for PD.

The analysis for UPDRS II and III included the following processes:

1. An overall test for treatment effect conducted at the end of study
2. Assuming a significant treatment effect ($p < 0.05$), tests of the three pairwise comparisons of interest (IPX066 145 mg vs. placebo, IPX066 245 mg vs. placebo and IPX066 390 mg vs. placebo) would then be conducted.
3. Sensitivity analysis was to be conducted using Dunnett's procedure to individually compare the three active treatments to placebo.
4. The same analyses were to be conducted with the available data for the variable at Weeks 4, 9, 16, 23 and 30 to further categorize timing and duration of effect.

Additional efficacy variables such as the PGI, CGI and change from baseline in various UPDRS configurations were also examined.

Efficacy Analysis population for this study included all treated subjects with at least one efficacy measurement after dosing. Subjects who had an early termination visit where UPDRS and PDQ 39 were administered 3 days after the last dose of the study were excluded from the analysis set. Sixteen patients were excluded from this analysis set. The sponsor's rationale for this exclusion was that "*PD patients tend to alter their medications soon after discontinuing treatment and alternative medications could confound UPDRS assessments.*"

REVIEWER'S COMMENTS:

The Sponsor excluded patients from the efficacy analysis if they had an early termination visit and had the UPDRS administered 3 days after the last dose. This is not consistent with the "intent to treat" principle. In early P D patients, the effects of treatment with levodopa could vary in duration and may not even be affected several days after treatment even with alternative medications taken. The risk of having their UPDRS assessments confounded is almost negligible in these patients.

The table below summarizes the mean change from baseline to EOS between each of the treatment groups and placebo. All three active treatments were statistically superior compared to placebo ($p < 0.0001$). For each of the components of the Total UPDRS, the mean change between

each of the treatment groups and placebo was statistically significant except for the results of UPDRS IV that evaluated complications of therapy by asking multiple choice questions about adverse events in PD treatment like dyskinesias, nausea, and orthostatic hypotension. A higher mean score in this section suggests there were more adverse events and both the higher doses of 235 mg and 390 mg worsened by 0.3 units compared to placebo.

Table 12: Summary Change from Baseline to End of Study by Treatment Group in Study IPX066-B08-05 (Sponsor's table).

UPDRS Parts	IPX066 LD Dose Group Compared with Placebo (N = 90)		
	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	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
Total UPDRS			
Mean Change (units)	-12.2 vs -0.3	-12.9 vs -0.3	-14.9 vs -0.3
P-Value	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
UPDRS I			
Mean Change (units)	-0.4 vs +0.2	-0.3 vs +0.2	-0.3 vs +0.2
P-Value	<i>P</i> = 0.0110	<i>P</i> = 0.0316	<i>P</i> = 0.0317
UPDRS II			
Mean Change (units)	-2.8 vs +0.2	-3.1 vs +0.2	-3.9 vs +0.2
P-Value	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
UPDRS III			
Mean Change (units)	-8.9 vs -0.7	-9.8 vs -0.7	-11.0 vs -0.7
P-Value	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001
UPDRS IV			
Mean Change (units)	-0.1 vs +0.1	+0.3 vs +0.1	+0.3 vs +0.1
P-Value	<i>P</i> = 0.5330	<i>P</i> = 0.5498	<i>P</i> = 0.5617

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

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

Reviewer's analysis of pairwise (Tukey-Kramer) comparisons of IPX066 groups to Placebo are similar to the Sponsor's analysis that showed a significant difference between all treatment groups and placebo in the primary endpoint. In addition, the comparisons between IPX066 treatment arms demonstrate a numerical trend for the primary outcome indicating dose response when compared to the placebo group but a closer look at comparison of effect between treatment groups show a non-statistically significant numerical significance.

Table 13: Comparisons for All Pairs Using Tukey-Kramer. (Reviewer’s table).

Level	• Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
PLACEBO	IPX066 390 mg	14.37778	1.666085	10.0773	18.67828	<.0001*
PLACEBO	IPX066 245 mg	12.37273	1.627779	8.1711	16.57436	<.0001*
PLACEBO	IPX066 145 mg	11.12846	1.706237	6.7243	15.53280	<.0001*
IPX066 145mg	IPX066 390 mg	3.24932	1.706237	-1.1548	7.65347	0.2280
IPX066 245mg	IPX066 390 mg	2.00505	1.627779	-2.1966	6.20668	0.6070
IPX066 145mg	IPX066 245 mg	1.24427	1.666853	-3.0634	5.55192	0.8765

The FDA biometrics reviewer also supports the results for the primary endpoint. The biometrics review included the patients with early termination visits. His results are stated below.

“Eight subjects assigned to 390 mg, four to 245 mg, two at 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. The 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 and 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 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.”

The FDA biometrics reviewer also performed a post hoc sensitivity analysis using a mixed model for repeated measures. The model analyzed all the observed post baseline UPDRS data simultaneously to include adjustments for baseline, region, treatment, visit and treatment by visit interactions and assumed a general “unstructured” covariance matrix for the measurement for the same subject. The estimated differences based on the MMRM model is presented in the biometric reviewer’s table below.

Table 14: MMRM Sensitivity Analysis of Change in UPDRS II + III at Week 30 (FDA Biometrics Reviewer's table).

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

The model that our biometrics reviewer used was different from the MMRM model the sponsor who used which was a model that assumes a categorical effect of visit instead of the sponsor's method of forcing a linear slope a relationship between UPDRS II and III and Visit. FDA biometrics reviewer also incorporates 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. Based on these results, there is no obvious indication that the primary result is sensitive to the Week 30 UPDRS assessment data that excluded the 16 patients.

The responder analysis was also as an alternative approach to examine the efficacy results. The protocol defined a responder as a subject who improved by at least 25% from Baseline in the UPDRS Part II and Part III Score. The three active treatments were statistically significantly superior to placebo at EOS (p<0.0001).

Table 15: Summary of Responders by Treatment at the End of Study with Subjects who Discontinued Early and were Treated as Non-responders in Study IPX066 B08-05. (Sponsor's table).

Treatment	Number (%) of Subjects Who Responded with an Improvement of at Least				
	5 Units	20%	25%	30%	40%
Placebo (N = 92)	28 (30.4)	21 (22.8)	13 (14.1)	11 (12.0)	7 (7.6)
IPX066					
145 mg LD (N = 87)	61 (70.1)	54 (62.1)	50 (57.5)	44 (50.6)	30 (34.5)
245 mg LD (N = 104)	83 (79.8)	75 (72.1)	70 (67.3)	56 (53.8)	39 (37.5)
390 mg LD (N = 98)	71 (72.4)	69 (70.4)	64 (65.3)	57 (58.2)	50 (51.0)

Abbreviations: LD = levodopa.

Notes:

Responder was defined as a subject whose UPDRS Part II plus Part III score improved at least 5 units from Baseline. Additional analyses were performed using 25% improvement as the definition of response with sensitivity analyses at 20%, 30%, and 40% improvements.

For all definitions of responder and for each active treatment versus placebo, P = 0.0001.

Cochran-Mantel-Haenszel test.

Source: Tables 14.2.1.2-14 14.2.1.2-15, 14.2.1.2-16, 14.2.1.2-17, and 14.2.1.2-18.

The results of the secondary endpoints from the CGI and PGI evaluations also support the results of the primary endpoint that each of the active treatments are superior to placebo at EOS as shown by the table 12 below. This tabulation is only for those who responded with a response of "Much" or "Very Much Improved."

Table 16: Percent of Subjects who Reported "Much or Very Much Improved" at EOS on PGI and CGI in Study IPX066 B08-05 (Sponsor's Table).

Global Impression of Change	145 mg LD	245 mg LD	390 mg LD	Placebo
PGI				
Much or Very Much Improved)	33/84 (39.3%)	42/103 (40.8%)	43/98 (43.9%)	8/92 (8.7%)
<i>P</i> -Value vs. Placebo	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001	—
CGI				
Much or Very Much Improved	34/84 (40.5%)	40/103 (38.8%)	45/98 (45.9%)	8/92 (8.7%)
<i>P</i> -Value vs. Placebo	<i>P</i> < 0.0001	<i>P</i> < 0.0001	<i>P</i> < 0.0001	—

The PDQ-39, is a Quality of Life Assessment, that has 39 questions measuring the eight dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily pain. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). Analysis of the scores for the PDQ-39 also supports the primary efficacy endpoint that the three active treatments were superior to placebo in the mean change in total score that includes mobility, ADL's, emotional well-being, stigma, social support, cognition, communication and body discomfort. However, exploration of the individual elements of the PDQ 39 show that although there is a numerical difference in all the components of the total score favoring the treatment groups, the difference is not robust especially in the mean scores for social support, cognition, communication and bodily discomfort scores. (Table 17 below).

Table 17: Summary of Change from Baseline to End of Study in Mean PDQ 39 Score in Early PD Patients (Sponsor's table).

PDQ-39 Dimension	IPX066 LD Dose Group Compared with Placebo		
	145 mg LD	245 mg LD	390 mg LD
Total Score			
Mean Change	-4.4 vs +0.6	-3.8 vs +0.6	-6.0 vs +0.6
P-Value	<i>P</i> = 0.0173	<i>P</i> = 0.0332	<i>P</i> = 0.0008
Mobility Score			
Mean Change	-4.0 vs +0.9	-3.6 vs +0.9	-6.8 vs +0.9
P-Value	<i>P</i> = 0.1434	<i>P</i> = 0.1733	<i>P</i> = 0.0077
Activities of Daily Living Score			
Mean Change	-7.9 vs +2.8	-8.8 vs +2.8	-11.5 vs +2.8
P-Value	<i>P</i> = 0.0005	<i>P</i> < 0.0001	<i>P</i> < 0.0001
Emotional Well being			
Mean Change	-6.1 vs +1.2	-4.0 vs +1.2	-5.2 vs +1.2
P-Value	<i>P</i> = 0.0131	<i>P</i> = 0.0657	<i>P</i> = 0.0307
Stigma Score			
Mean Change	-7.2 vs -0.8	-6.0 vs -0.8	-10.4 vs -0.8
P-Value	<i>P</i> = 0.0469	<i>P</i> = 0.1126	<i>P</i> = 0.0010
Social Support Score			
Mean Change	-1.0 vs -0.7	-2.2 vs -0.7	-1.3 vs -0.7
P-Value	<i>P</i> = 0.9998	<i>P</i> = 0.8442	<i>P</i> = 0.9929
Cognition Score			
Mean Change	-2.4 vs 0.0	+2.2 vs 0.0	+1.3 vs 0.0
P-Value	<i>P</i> = 0.3441	<i>P</i> = 0.3844	<i>P</i> = 0.8772
Communication Score			
Mean Change	-0.2 vs +0.6	-1.1 vs +0.6	-1.2 vs +0.6
P-Value	<i>P</i> = 0.9732	<i>P</i> = 0.8095	<i>P</i> = 0.7714
Body Discomfort Score			
Mean Change	-1.3 vs -1.8	-2.8 vs -1.8	-3.9 vs -1.8
P-Value	<i>P</i> = 0.9922	<i>P</i> = 0.9632	<i>P</i> = 0.3809

Abbreviations: PDQ-39 = Parkinson's Disease Questionnaire-39.

Source: Tables 14.2.4.8-1, 14.2.4.9-1, 14.2.4.10-1, 14.2.4.11-1, 14.2.4.12-1, 14.2.4.13-1, 14.2.4.14-1, 14.2.4.15-1, and 14.2.4.16-1.

REVIEWER'S COMMENTS:

The absence of a significant improvement in stigma, social support, cognition and communication scores could be attributed to the disease itself (depression in PD and cognitive deficits) which may affect these scores. Improvement in these areas may not even be expected. However, the fact that the drug does not seem to improve body discomfort despite improving ADL seems to be contradictory. I can only think of the side effects of dopaminergic agents that are contributing to these contradicting results.

IPX066 B09-02 for Advanced Parkinson's Disease

The objective of this study was to assess the efficacy and safety of IPX066 in advanced PD subjects with motor fluctuations. The study was a randomized, double blind, active comparator (IR CD LD) controlled, parallel arm 22-week study. Patients had a 3-week dose adjustment of their current LD regimen, followed by a 6-week dose conversion to IPX066 under open label conditions. Subjects were then equally randomized to a 13-week double blind treatment of either IPX066 or IR. The primary endpoint in this study is the % off time during waking hours based on the subject's 24 hour Parkinson's disease diary.

Disposition of Subjects:

Five hundred sixty seven patients were screened and 471 patients were enrolled and received at least one study treatment. A total of 393 subjects (83.4%) completed Visit 5 (End of Dose Conversion period) and were randomized to either IPX066 or IR treatment groups. Three hundred sixty three patients (93.6%) completed the 22-week study. The flowchart (Figure 4) below summarizes the subject disposition and the corresponding table shows the percent of discontinuations in relation to the enrollees.

Figure 5: Flowchart of Subject Disposition in Advanced PD Study B09-02 (Source: Sponsor)

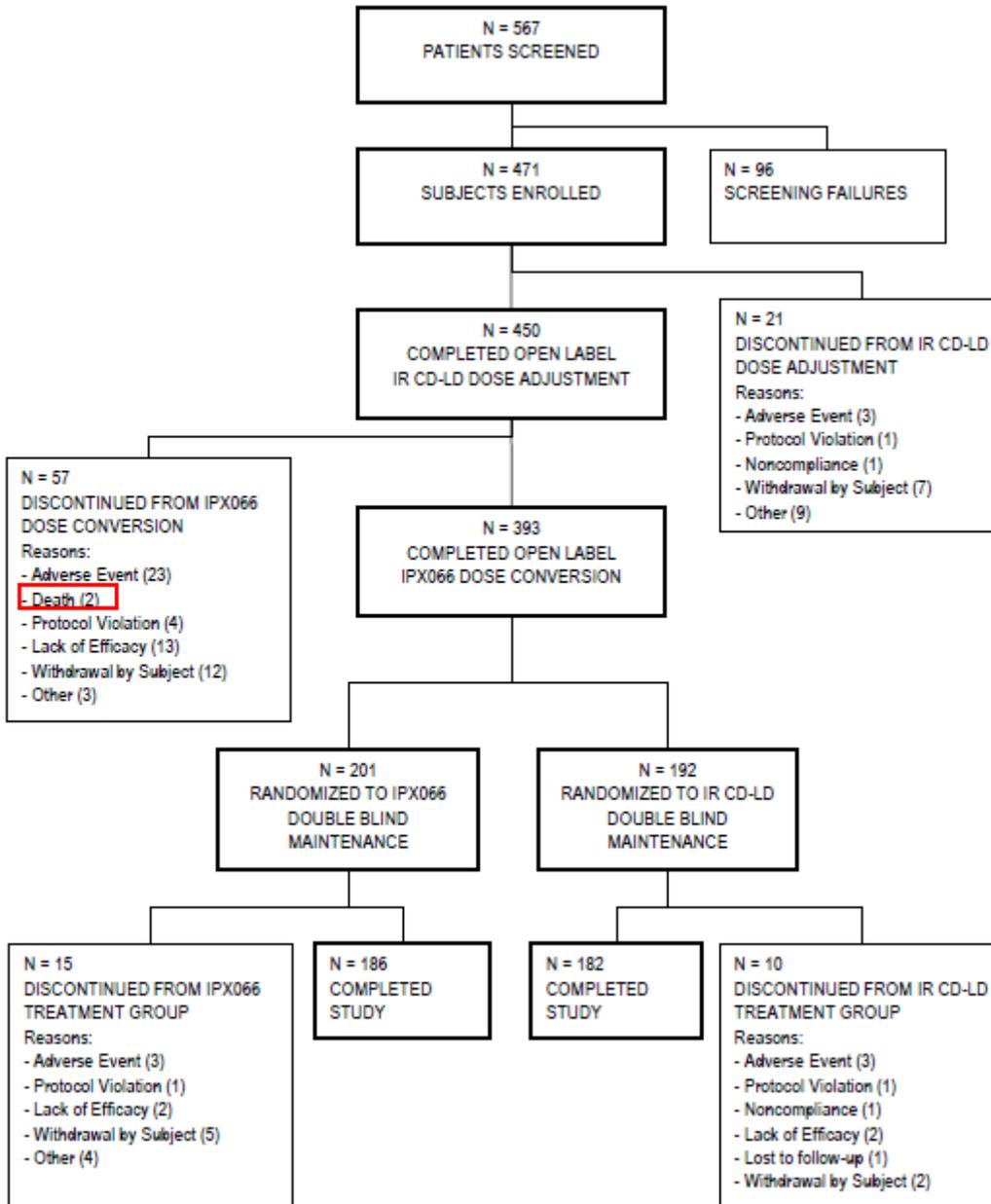


Table 18: Summary of Subject Disposition in Advanced PD Study B09-02 (Sponsor's table).

	Number of Subjects (%)				
	IR CD-LD Dose Adjustment	IPX066 Dose Conversion	Maintenance		
			Total	IPX066	IR CD- LD
Entered	471 (100%)	450 (100%)	201 (100%)	192 (100%)	393 (100%)
Completed	450 (95.5%)	393 (87.3%)	186 (92.5%)	182 (94.8%)	368 (93.6%)
Discontinued Early	21 (4.5%)	57 (12.7%)	15 (7.5%)	10 (5.2%)	25 (6.4%)
Reason for Discontinuation					
Adverse Event	3 (0.6%)	23 (5.1%)	3 (1.5%)	3 (1.5%)	6 (1.5%)
Death	0	2 (0.4%)	0	0	0
Protocol Violation	1 (0.2%)	4 (0.9%)	1 (0.5%)	1 (0.5%)	2 (0.5%)
Noncompliance	1 (0.2%)	0	0	1 (0.5%)	1 (0.3%)
Lack of Efficacy	0	13 (2.9%)	2 (1.0%)	2 (1.0%)	4 (1.0%)
Lost to Follow-up	0	0	0	1 (0.5%)	1 (0.3%)
Withdrawal by Subject	7 (1.5%)	12 (2.7%)	5 (2.5%)	2 (1.0%)	7 (1.8%)
Other	9 (1.9%)	3 (0.7%)	4 (2.0%)	0	4 (1.0%)

The majority of early discontinuations occurred during the Conversion Phase and was mostly due to adverse events (5.1%). Discontinuations due to protocol deviations and violations between IPX066 and IR groups were comparable during the maintenance phase. Most of the deviations were out of window examinations and can be considered minor violations. The major deviations include the following:

- 2 subjects terminated from the study due to PD diary errors
- 2 subjects took excluded concomitant medications

- 9 patients had medical conditions that may interfere with LD absorption (e.g. Peptic Ulcer Disease).
- 1 subject did not initial and date the first page of the consent form
- 5 subjects were dispensed the wrong study kits during Maintenance Period but as soon as the error was discovered, the subject returned the incorrect study kits/drugs to the study site and continued on the study with the correct kits/drugs

Demographic Characteristics

The tables below (Tables 19 and 20) summarize the demographics and other baseline disease characteristics. Both demographics and baseline characteristics were similar between the two groups.

Table 19: Summary of Baseline Demographic Characteristics for Randomized Subjects in Study IPX066-B09-02 (Sponsor's table).

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)

Source: Table 14.1.4.2.

Baseline Parkinson's Disease Characteristics

Table 20 summarizes the baseline characteristics of patients with Parkinson's disease enrolled in this study.

Table 20: Summary of Baseline Characteristics of Parkinson's Disease for Randomized Patients in SStudy B09-02 (Sponsor's table).

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)

In general, the patients randomized to either IPX066 or IR groups are comparable at baseline in the PD characteristics.

Efficacy Analysis:

The sponsor's efficacy analysis set for the double blind portion of the trial was to include all randomized patients. Patients were to be analyzed on as treated basis i.e. each subject was to be associated with the active treatment to which they were randomized. For errors in randomization assignment, they were to be assigned based upon the treatment received during the Maintenance Phase. For the open label conversion phase portion of the trial, the efficacy analysis set was to be all subjects entering the dose adjustment period of the trial.

The primary efficacy endpoint was the 3-day PD diary results "off" time as a percent of waking hours at study endpoint (week 22) or the imputed value, if the subject terminated early. For randomized subjects (at entry into the Maintenance Phase) with at least one post-randomization efficacy value who dropped out prior to Week 22, primary imputation method for analysis will be the Last Observation Carried Forward (LOCF). Randomized subjects who have no valid diary values at EOS will be assigned a value equal to the average of all diary values at study endpoint (Week 22). The following alternative imputation methods were assessed as sensitivity analyses:

- For subjects who were randomized but had no post randomization values, the largest value of the measures collected from the start of the Dose Conversion period to the point of randomization will be imputed for these subjects
- Subjects who were randomized but had no post-randomization values were not included in the analysis
- For subjects with at least one post-randomization efficacy measure, LOCF to Week 22 was used
- Analysis of all available data at Week 22 with no imputation was conducted
- Overall dropout rate was examined as a secondary endpoint using Chi-squared technique.

Analysis of the primary efficacy measurement was performed using a two-factor main effects Analysis of Covariance (ANCOVA) model with treatment and centers as factors and the percent of "off" time at Baseline as covariate. Sensitivity analyses 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.

PGI and 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 patient (subject) (for the

PGI) or Investigator (for the CGI) reporting improvement. The individual UPDRS aspects (Parts I, II, III and IV) were to be analyzed to further categorize any significant results. Analyses of the UPDRS were conducted in a similar manner as the Parkinson’s disease Diary measures. PDQ 39 to assess Quality of Life was to be measured using PDQ 39 and analysis followed the same approach as those use for the continuous efficacy endpoints.

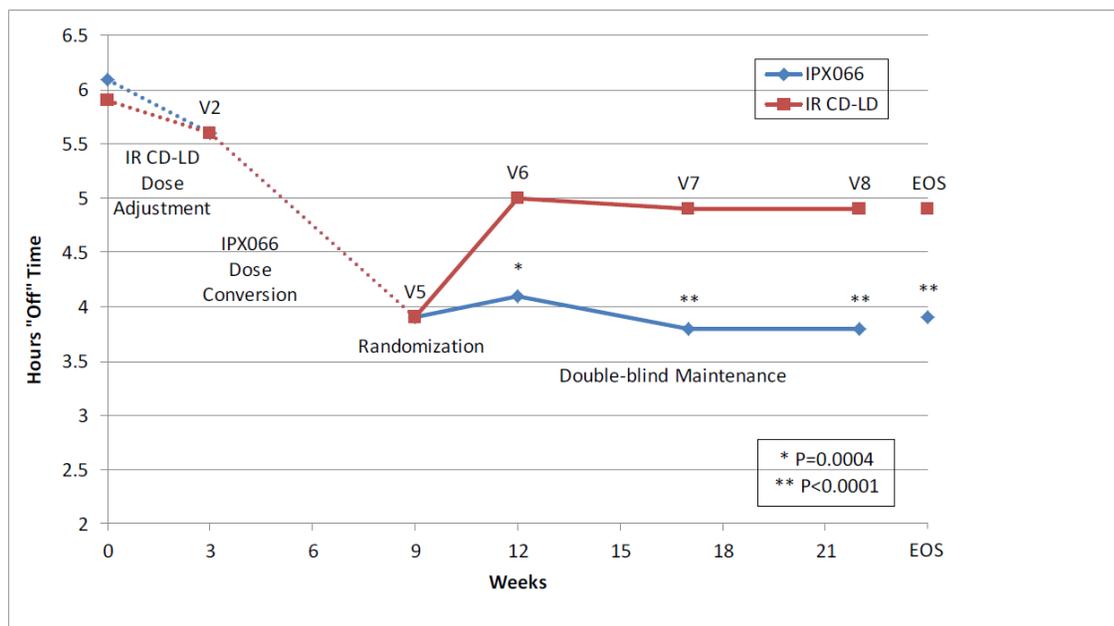
Efficacy results demonstrate IPX066 is superior to IR CD LD in improving “off” time from baseline during wake hours. The group of patients treated with IPX066 experienced a mean improvement of approximately 2.2 hours compared to 1 hour in subjects randomized to IR CD LD. This difference between the two groups was statistically significant (please refer to table below). Amount of ON time with troublesome dyskinesias was greater by about 25 minutes in the IPX066 treatment group. From the figure below, the mean “off” time persisted until the end of the maintenance period.

Table 21: Summary of Parkinson's Disease Diary Data for Randomized Subjects in Study B09-02 (Sponsor's table).

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

The sponsor’s figure presented below shows the mean% off time during waking hours at the various scheduled visits of the IPX066 and IR treatment groups.

Figure 6: Mean "OFF" Time by Visit for Randomized Subjects (N=393) in Study IPX066 B09-02 (Source: Sponsor).



The Biometrics and Clinical reviewers' analyses agreed with the sponsor's results for the primary efficacy endpoint ("off" time as percent of waking hours).

The Biometrics Reviewer (Dr. Massie) confirmed that there was no group difference in mean percent of OFF time at visit 5, just before randomization and after conversion/IPX066 titration. At the last assessment, mean % OFF time was 23.7% and 30.0% for IPX066 and IR respectively. Furthermore, the Biometrics reviewer modified the LOCF analysis excluding patients with no post-baseline maintenance period assessments as opposed to the sponsor's method of imputing the overall average mean off time at the last assessment in the maintenance period for 12 patients who did not have any post randomization assessments (7 assigned to IPX066 and 3 to IR). A total of 185 (92%) IPX066 patients and 181 (94%) IR patients had assessments at Week 22 (final) visit. An analysis of the 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 % OFF time at Week 22 of -5.67 ± 1.27 (SE), $p < 0.0001$. Dr. Massie also concluded that the results of sensitivity analyses suggest relative insensitivity of the primary analysis result to the missing data.

The Biometrics Reviewer has also looked at dropouts. He concludes that "dropouts were reasonably limited and the analysis result for % 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 reliable comparisons between dropouts and completers and, therefore, it

seems unlikely that the dropouts had much impact on the outcome of the primary analysis”. The biometrics reviewer presents his conclusion in table 23.

Table 22: Mean % OFF Time at Patient's Last Available Assessment, Study B09-02 (Biometric Reviewer's Table).

		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		
		N	Mean	Std	N	Mean	Std	N	Mean	Std	N	Mean	Std
Last Week	Week												
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
	17	3	41.7	22.7	3	29.6	27.5	3	35.7	14.3	4	16.6	11.0
22	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 conducted a percent responder analysis at the end of study an alternative way of examining “off” time by selecting a level of improvement to the responder. The results are presented in the table below and showed that there were more patients in the IPX066 group who experienced improvement in “off” time up to at least 3 hours. The responder analysis supports the primary efficacy’s endpoint showing improvement in “off” time from baseline with IPX066 treatment.

Table 23: Responders at the End of Study in IPX066 B09-02 Randomized Subjects (Sponsor's table).

Treatment Group	Number (%) of Responders ^a				
	Improvement in “Off” Time From Baseline to End of Study				
	≥0.5 Hours	≥1 Hour	≥1.5 Hours	≥2 Hours	≥3 Hours
IPX066 (N = 201)	140 (69.7%)	127 (63.2%)	111 (55.2%)	95 (47.3%)	69 (34.3%)
IR CD-LD (N = 192)	101 (52.6%)	87 (45.3%)	74 (38.5%)	61 (31.8%)	42 (21.9%)
P value	<0.0001	<0.0001	0.0003	0.0007	0.0034

^a Anyone who did not complete the trial was considered a non-responder from the point at which they dropped out.

In the initial SPA submission, FDA informed that sponsor that the PD patient diary is limited by patient compliance issues and requires training and validation and for those reasons, the secondary outcomes should support a positive finding for the primary endpoint. The secondary efficacy measures that are presented below provide support to the results of the primary efficacy endpoint.

UPDRS Parts II and III is relevant to this study because it provides an assessment of the patient’s motor functions. It is also the most widely used test to assess improvement post treatment in patients with PD. While there was a statistically significant difference in the UPDRS scores total, parts II and III between the two treatment group, there was no significant difference in the UPDRS part IV (Complications of Therapy) with a slightly higher score (which means that there were more complications) in the patients treated with IPX066. It also appears from the table below that the patients randomized to the IPX group seemingly had more complications from therapy and even a slight decrease in complications may feel better.

Table 24: Summary of UPDRS Rating Scale Results for Randomized Subjects in Study IPX066 B09-02 (Sponsor's table).

UPDRS Part ^a	UPDRS Score (Mean±SD)				P value ^b
	IPX066 (N = 201)		IR CD-LD (N = 192)		
	Baseline (Visit 1)	End of Study	Baseline (Visit 1)	End of Study	
II + III	32.32±14.42	26.61±12.85	32.41±15.24	30.27±15.12	<0.0001
I + II + III	34.14±14.88	28.19±13.37	34.26±15.84	32.22±15.85	<0.0001
Total	39.34±15.18	32.96±13.71	39.22±15.88	37.00±16.37	<0.0001
I	1.82±1.29	1.58±1.42	1.85±1.44	1.95±1.69	0.0045
II “on”	9.11±4.75	7.79±4.71	8.81±5.16	8.60±5.56	0.0030
II “off”	17.35±6.80	16.27±6.80	17.14±6.32	17.04±7.03	0.0105
III	23.21±11.47	18.83±9.49	23.60±11.43	21.67±10.89	<0.0001
IV	5.20±2.15	4.77±2.59	4.96±1.86	4.78±2.17	0.5534

^a Parts I-IV in the "on" state, and Part II also in the "off" state

^b Baseline-adjusted analysis of covariance

Abbreviations: UPDRS = United Parkinson’s Disease Rating Scale; IR CD-LD = immediate-release carbidopa-levodopa.

The PDQ 39 total score measures PD related health status that evaluates patient’s mobility, ADL’s, emotional well-being, stigma, cognition, communication, bodily discomfort and emotional support. The results of the PDQ 39 total score also shows a difference between treatments in the total PDQ 39 and the Mobility subscore but the other subscores did not reach statistical significance. As in the early PD study, the improvement in total score was mainly due to mobility. Interestingly, although there was a numerical difference in the ADL scores, the difference between the two groups was not significant (please refer to table below).

Table 25: Summary of Results of Parkinson's Disease Questionnaire -39 for Subjects in Study B09-02 (Sponsor's table).

PDQ-39 Subscore	PDQ-39 Score (Mean±SD)				P value ^a
	IPX066 (N = 201)		IR CD-LD (N = 192)		
	Baseline (Visit 1)	End of Study	Baseline (Visit 1)	End of Study	
Total	30.56±15.72	26.87±15.85	31.27±16.98	29.40±15.89	0.0345
Mobility	36.03±22.56	30.84±21.40	37.15±23.62	36.17±23.19	0.0017
ADL	37.58±22.34	31.76±21.47	36.02±22.53	32.95±20.67	0.1047
Emotional Wellbeing	28.75±18.97	25.85±19.40	28.39±21.00	27.80±19.42	0.1462
Stigma	28.33±25.16	23.81±23.19	28.44±26.40	24.48±24.01	0.8112
Social Support	15.19±18.57	15.11±17.94	16.55±20.45	16.27±19.76	0.9409
Cognition	23.13±15.20	22.64±15.93	26.63±17.99	25.15±16.15	0.4485
Communication	23.75±19.20	21.57±19.56	25.09±20.66	24.38±19.07	0.1881
Bodily Discomfort	36.61±23.11	31.87±21.33	38.09±23.72	33.98±21.55	0.3437

^a Baseline-adjusted analysis of covariance.

Abbreviations: PDQ = Parkinson's Disease Questionnaire; IR CD-LD = immediate-release carbidopa-levodopa;
 ADL = Activities of Daily Living.

REVIEWER'S COMMENTS:

Although PDQ-39 scores are improved, the effect on the total score is solely due to improvement in mobility. Patients on IPX066 had a significantly different and much more improved mobility scores than the IR patients but the treatment benefit from IPX066 did not translate into a significant improvement in their ADL's.

Another secondary endpoint, the Patient Global Impression (PGI), also supports the results of the primary endpoint. There were more subjects who felt "much improved" and "very much improved" among patients exposed to IPX066 (77/200=38.5%) than those exposed to IR (33/189=17.4%) by the end of study as shown in the table below.

Table 26: Distribution of Analysis of PGI by Treatment at EOS, Study B09-02 (Sponsor's table).

Patient Global Impression	IPX066 (N=200)	IR CD-LD (N=189)	Total (N=389)
Very Much Worse (1)	0	0	0
Much Worse (2)	13 (6.5%)	22 (11.6%)	35 (9.0%)
Minimally Worse (3)	25 (12.5%)	48 (25.4%)	73 (18.8%)
No Change (4)	27 (13.5%)	39 (20.6%)	66 (17.0%)
Minimally Improved (5)	58 (29.0%)	47 (24.9%)	105 (27.0%)
Much Improved (6)	60 (30.0%)	29 (15.3%)	89 (22.9%)
Very Much Improved (7)	17 (8.5%)	4 (2.1%)	21 (5.4%)
N (%)	200 (100%)	189 (100%)	389 (100%)
Mean (SD)	4.9 (1.4)	4.1 (1.3)	4.5 (1.4)
Median	5.0	4.0	5.0
(Min, Max)	(2, 7)	(2, 7)	(2, 7)
ANOVA P-Value		<0.0001	

A similar result was reported for the Clinician's Global Impression (CGI) Scale as shown below.

Table 27: Distribution and Analysis of CGI by Treatment at EOS, Study B09-02 (Sponsor's table).

Clinical Global Impression	IPX066 (N=200)	IR CD-LD (N=190)	Total (N=390)
Very Much Worse (1)	0	0	0
Much Worse (2)	5 (2.5%)	8 (4.2%)	13 (3.3%)
Minimally Worse (3)	22 (11.0%)	38 (20.0%)	60 (15.4%)
No Change (4)	41 (20.5%)	60 (31.6%)	101 (25.9%)
Minimally Improved (5)	52 (26.0%)	58 (30.5%)	110 (28.2%)
Much Improved (6)	71 (35.5%)	23 (12.1%)	94 (24.1%)
Very Much Improved (7)	9 (4.5%)	3 (1.6%)	12 (3.1%)
N (%)	200 (100%)	190 (100%)	390 (100%)
Mean (SD)	4.9 (1.2)	4.3 (1.1)	4.6 (1.2)
Median	5.0	4.0	5.0
(Min, Max)	(2, 7)	(2, 7)	(2, 7)
ANOVA P-Value		<0.0001	

REVIEWER'S COMMENTS:

Generally, there were more clinicians and patients who reported “much improved and “very much improved” in the IPX066 group than in the IR group.

Other exploratory efficacy endpoints that were included in the analysis such as morning effectiveness and amount of fluctuations. As expected, amounts of fluctuations, (change from “off” to “on” state or from “on” to “off” state), the daily average from the 3 days prior to each visit of ON and OFF, showed the IPX066 group to be better than IR CD_LD group at EOS with the IPX066 group in the number of fluctuations (IPX066 having a mean of 4.02 episodes compared to IR having 5.37 episodes). For morning effectiveness, there was no significant difference between the two drugs. [REDACTED] (b) (4)

[REDACTED] superiority based on the nominal p-values did not include an adjustment for multiple comparisons..

The results in the primary efficacy endpoints and the secondary efficacy endpoints show that IPX066 improves percent off time during waking hours in patients with Advanced Parkinson's disease. Secondary efficacy variables measured also showed that IPX066 is at least comparable to IR. IPX066 has a consistent treatment effect in improving mostly the motor functions of the subject.

However, since none of these secondary endpoints were pre-specified as “Key Secondary Endpoints”, there was no statistical procedure that was discussed to protect against inflation of the type 1 error rate caused by multiple comparisons.

**ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING
RECOMMENDATIONS: CONVERTING PATIENTS FROM OTHER
CARBIDIOPA-LEVODOPA PREPARATIONS TO IPX066:**

In Study IPX066 B09-02 early PD patients were stabilized on their individualized dose of regular levodopa for 4 weeks and then converted them to the IPX066 preparation following the suggested initial conversion table presented below:

Table 28: Distribution and Analysis of CGI by Treatment at EOS, B09-02 (Sponsor's table).

Total Daily IR, LD Dose (mg)	Suggested Initial IPX066 Dosage (LD in mg) Each Dose Approximately 6 Hours Apart During Waking Hours		
	Morning Dose	Midday Dose	Evening Dose
400 - 550	3 capsules x 95	3 capsules x 95	3 capsules x 95
551 - 750	4 capsules x 95	4 capsules x 95	4 capsules x 95
751 - 950	3 capsules x 145	3 capsules x 145	3 capsules x 145
951 - 1250	3 capsules x 195	3 capsules x 195	3 capsules x 195
1251 - 1650	4 capsules x 195	4 capsules x 195	4 capsules x 195
	OR 3 capsules x 245	OR 3 capsules x 245	OR 3 capsules x 245
>1650	4 capsules x 245	4 capsules x 245	4 capsules x 245

Abbreviations: IR = immediate release, LD = levodopa.
 Source: Appendix 16.1.1.

In protocol IPX066-B09-06, the suggested initial dose conversion from CLE to IPX066 is presented in a different table as shown below.

Table 29: Suggested Initial Dose Conversion of CLE to IPX066 in Study B09-06 (Sponsor's table).

Total Daily LD Dose (mg)	Suggested Initial IPX066 Dose (LD in mg) ^a		
	Morning Dose	Midday Dose	Evening Dose
(b) (4)	4 capsules x 95	4 capsules x 95	4 capsules x 95
	2 capsules x 245	2 capsules x 245	2 capsules x 245
	3 capsules x 195	3 capsules x 195	3 capsules x 195
	3 capsules x 245	3 capsules x 245	3 capsules x 245
	4 capsules x 245	4 capsules x 245	4 capsules x 245

Abbreviations: LD=levodopa; CLE=carbidopa/levodopa/entacapone

^aEach dose approximately 6 hours apart during waking hours

The sponsor proposed the conversion scheme from IR to IPX066 as shown in the table below. This table is included in the sponsor's draft label.

Table 30: Guidelines for Initial Conversion from IR CD-LD Product to IPX066 in PD Patients as Proposed in the Sponsor's Label (Sponsor's table).

Total Daily Dose of Immediate Release Levodopa (mg)	Suggested Initial Dose of [TRADE NAME] t.i.d. (Levodopa in mg) ¹	
	Dosage Strength	Capsules per Dose
400 to < (b) (4)	[TRADE NAME] 95	3 capsules
550 to < (b) (4)	[TRADE NAME] 95	4 capsules
750 to < (b) (4)	[TRADE NAME] 145	3 capsules
950 to < (b) (4)	[TRADE NAME] 195	3 capsules
(b) (4)	[TRADE NAME] 195	4 capsules
	or	
	[TRADE NAME] 245	3 capsules

In study B09-02 and B09-06, the Sponsor provided guidelines that allowed patients to receive a dose of IPX066 that was supposed to be a comparable dose of the IR or CLE that they have received. The conversion scheme that was proposed relied mainly on PK data without supportive pharmacodynamic information. IPX066 bioavailability, based on the sponsor's pharmacokinetic study (B08-11) is 74.5% of IR with the higher IPX066 dose. The sponsor states in their report that "although the observed median dose of IPX066 was approximately 1.8 times that of IR CD-LD for all randomized subjects, based on the 74.5% bioavailability relative to IR CD-LD, the estimated systemic exposure to LD with IPX066 is approximately 36% higher than with IR CD-LD". Since clinical response especially the motor functions is dependent on the exposure to levodopa, patients in the IPX066 group have received more levodopa than the IR group which may explain the much larger treatment effect, thus improving off time—which is beneficial for patients. The proposed conversion scheme proposed optimized the levodopa dose because as the efficacy analysis shows, it improved "off time" in advanced PD patients but the number of adverse events that were emergent during the treatment period also increased in the IPX066 patients compared to those who were on comparable doses of IR. The adverse events seen after conversion are already known AEs and are reversible with decreasing the dose but may be more disabling than the symptoms of PD.

Dosing frequency remained the same in 82.4% of patients and was increased in 14.1% of patients

The sponsor analyzed the ratio of IPX066 to IR after conversion following the conversion table in study B09-02. Table 31 (below) shows that the average conversion ratios for subjects taking lower IR CD- LD doses between 400 and 600 mg were slightly higher compared to those taking doses between 600 and 1600 mg. Those taking higher doses of IR had slightly lower conversion ratios. This finding further suggests that patients on lower doses of IR are at risk of developing more adverse events since they will be exposed to a higher levodopa dose. On the contrary,

those who are on higher doses of IR may experience more “off” periods because of lower levodopa exposure.

Table 31: Ratio of IPX066 to Immediate Release (IR) CD-LD as a Function of IR CD-LD Dose for Subjects in Study B09-02 (Sponsor's table).

Adjusted Daily Dose of IR CD-LD (mg LD)	N	IPX066:IR CD-LD Ratio	
		Mean±SD	Median
400 to <600	107	2.30±0.65	2.14
600 to <800	91	1.99±0.46	1.90
800 to <1200	127	1.97±0.49	1.81
1200 to <1600	58	1.92±0.55	1.84
≥1600	10	1.73±0.39	1.57

Abbreviations: IR = immediate release, CD-LD = carbidopa-levodopa, SD = standard deviation

After initial conversion from a stable IR dose to IPX066, the sponsor had to adjust the amount of dose given and dosing frequency to optimize the treatment effect of IPX066 in study B09-02. The sponsor states: “ There was no change in the daily IR CD LD dose in 60.4% of subjects and was adjusted upward by more than 100 mg per day in 15.8% of subjects.” Fewer than 50% of patients who were already stable on their dose of IR needed dose adjustment after the initial conversion to IPX066.

REVIEWER’S COMMENTS:

- *The need for dose adjustments (whether an increase or decrease) of IPX066 using the conversion scheme proposed in both Advanced PD trials proves that that the conversion scheme does not deliver a comparable amount of levodopa.*
- *The conversion scheme also allowed for more levodopa delivery in the IPX066 formulation. The higher levodopa component increases the patient’s risk of developing adverse events such as nausea/vomiting and dyskinesias.*

Aside from dose adjustment, the sponsor allowed dosing frequency changes. In study B09-02, dosing frequency remained the same in 82.4% of patients and was increased in 14.1% of patients. The label states: “ The dosing frequency may be changed from three times a day to a maximum of five times a day if (b) (4)

REVIEWER’S COMMENTS:

For patients who are stable on their dose of IR, the proposed conversion scheme with additional recommendations of allowing changes to dosing frequency may lead to confusion with the amount of dose that they have to take and lead to medication errors. The different IPX066 formulations may further complicate the dosing instructions. In this case, the prescribing physician needs to follow up the patient closely to avoid errors in amount of dose.

Discussion of Persistence of Efficacy and/or Tolerance Effects

The placebo and active comparator trials lasted for only 30 weeks and 22 weeks respectively, to provide a conclusion on persistence of efficacy and tolerance.

The objectives of the Open Label Extension Study (IPX066 B09-03) were to evaluate the long term safety and clinical utility of IPX066 in subjects with PD.

The subjects enrolled into this study had successfully completed the phase 2 study B08-11, or one of the two-phase 3 studies: B08-05 or B09-02. The subjects received individualized dosing regimens of IPX066 (05, 145, 195 or 245 mg capsules for up to 9 months as shown in the figure below.

Figure 7: IPX066 B09-03 Study Design (Source: Sponsor)



Starting dose was determined by the sponsor at Visit 1 (Baseline) and subjects returned to the study site for Visits 2, 3 and 4, at which times IPX066 dose (strength, frequency and total daily dose) was recorded and safety and clinical assessments were performed as shown in the list of assessments performed at scheduled assessment periods:

Table 32: Schedule of Assessments and Procedures for Study IPX066-B09-03 (Sponsor's table).

	Visit 1 Baseline			Visit 2 Month 1	Study Drug Re-supply Months 2-4 ^g	Visit 3 Month 5	Study Drug Re-supply Months 6-8 ^g	Visit 4 Month 9 or Early Discontinuation
	From IPX066- B08-05 ^a	From IPX066- B08-11	From IPX066- B09-02 ^a					
ICF and HIPAA authorization	√	√	√					
Assign subject ID number	√	√	√					
Complete physical exam		√						√
Weight	√	√	√					√
Interim medical event	√ ^b	√	√ ^b					
12-lead or equivalent ECG		√		√				√
Vital signs ^c		√		√		√		√
Clinical laboratory studies		√		√				√
UPDRS ^d		√		√		√		√
PGI				√		√		√
PDQ-39		√		√		√		√
EQ-5D	√	√				√		√
SF-36	√	√				√		√
Dispense study medication	√	√	√	√	√	√	√	
Collect study medication				√	√	√	√	√
Adverse Events	√	√	√	√		√		√
Concomitant Medications	√	√	√	√		√		√
Contact subject	√ ^e			√ ^f		√ ^f		√ ^f

^a Visit 1 is expected to occur on the same day as the End-of Study Visit for protocols IPX066-B08-05 and IPX066-B09-02. After consenting the subject for this study, record the data from the End-of-Study Visit from the previous study as the baseline data for this study. If the study entry is delayed by more than 4 weeks after completion of the previous study, complete all procedures as listed for subjects enrolling from IPX066-B08-11.

^b If the subject is not directly enrolled into the new study on the day of the exit visit from the previous study.

^c Vital signs include blood pressure, heart rate, and respiratory rate.

^d Complete Parts I – IV during the “on” state. For subjects with a score > 0 for Question #39, also complete Part II as in the “off” state.

^e Contact subject approximately every 3 days during titration.

^f Contact subject prior to study visit to bring unused medication and empty medication bottles to the next study visit.

^g Subject may return for study drug re-supply approximately every 1-2 months as needed.

Abbreviations: ICF = informed consent form; HIPAA = Health Insurance Portability and Accountability Act; ID = identification; ECG = electrocardiogram; UPDRS = Unified Parkinson's Disease Rating Scale; PGI = Patient Global Impression Scale; PDQ-39 = Parkinson's Disease Questionnaire-39; EQ-5D = Health Related Quality of Life States; SF-36 = Health Survey Questionnaire.

Key Trial Entry Criteria

Inclusion into the trial required fulfillment of the following criteria:

1. Successful completion of Study B08-05, B08-11 or B09-02
2. In the opinion of the Investigator, the Parkinson's disease diagnosis was still valid and the subject remained eligible for LD therapy

Patients were excluded from the trial mainly if:

1. They received an investigational medication other than IPX066 other than from IPX066 trials mentioned above 4 weeks prior to study participation
2. They received within 4 weeks prior to Baseline Visit or planning to take during study participation nonselective monoamine oxidase (MAO) inhibitors with the exception of rasagiline
3. Anticipation of neurosurgical treatment for PD

Treatment administered was IPX066 capsules that are either swallowed or if subjects had difficulty swallowing, the contents were to be sprinkled in soft food such as applesauce and the entire mixture was to be consumed after sprinkling. The drug was not to be chewed. Subjects can take the drug up to 5 times a day with each medication given 4 hours apart. Dose adjustment was allowed throughout the study.

The following dose strengths administered were:

- IPX066 95 mg: 23.75/95 mg CD-LD caps (blue)
- IPX066 145 mg: 36.25/145 mg CD LD (green)
- IPX066 195 mg: 48.75/195 mg CD-LD (yellow)
- IPX066 245 mg: 61.25-245 mg CD-LD (white)

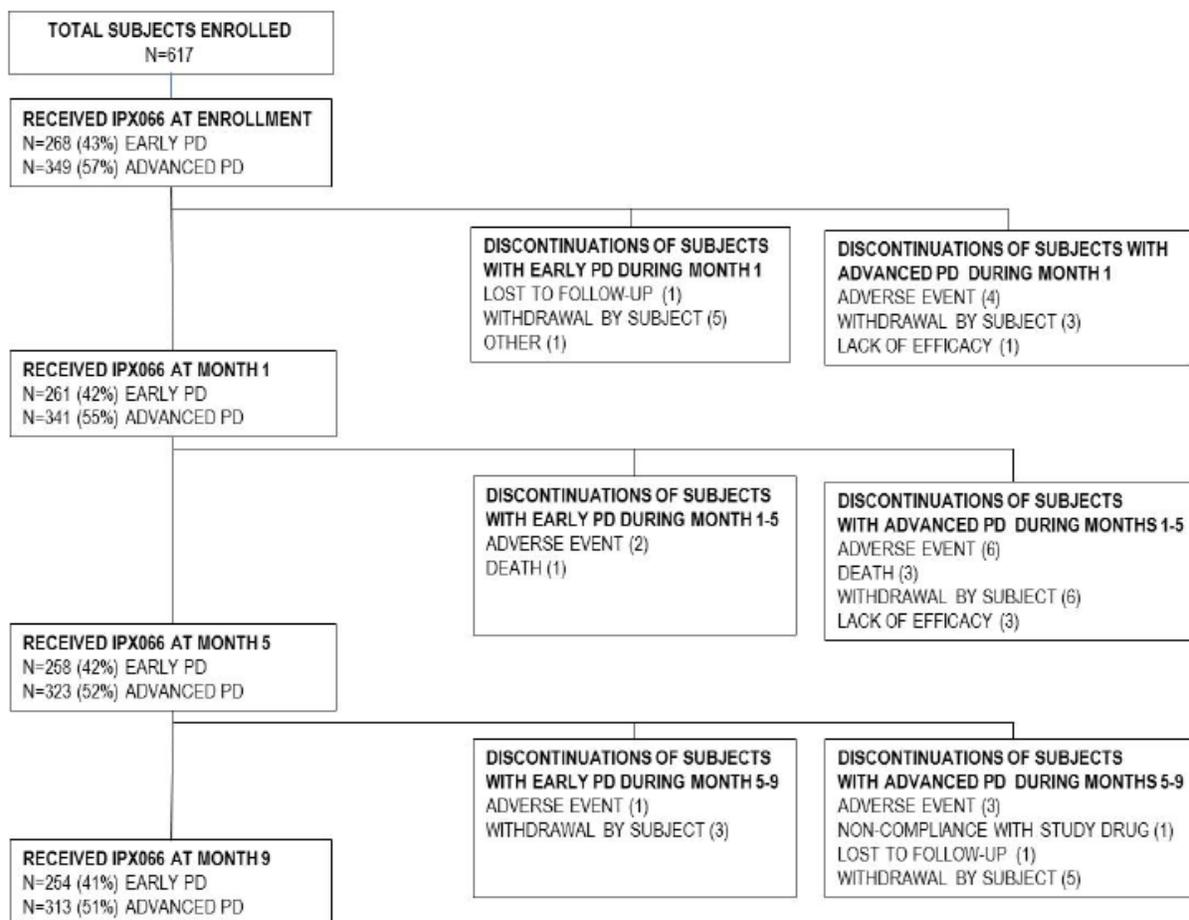
Starting dose was based on previous treatment with IPX066 and optimum daily dose was determined by titration for each subject.

Clinical Utility and Quality of Life Variables that were measured in the study include the UPDRS, Patient Global Impression (PGI), Parkinson's Disease Questionnaire 39 (PDQ 39), and other Quality of Life, Disability and Functional Ability assessment Scales such as the Measure of Health Status from EuroQoL Group, Health Survey Questionnaire (SF 36).

Disposition of Subjects:

From a total of 695 eligible subjects, 617 (88.7%) were enrolled and received 1 dose of IPX066. The flow chart below summarizes subject disposition.

Figure 8: Disposition of Subjects in Study IPX066 B09-03 (Source: Sponsor)



Eighty subjects had 94 protocol deviations and there were no deviations related to exclusion or exclusion criteria. Most frequent cause for deviation in 60/94 (64%) was for visits outside the scheduled window.

Mean age of all treated subjects was 64.1 years. There were more males (383/617=62.1%) who continued into the open label study. Table 34 below shows the distribution of patients according to duration of Parkinson’s disease.

Table 33: Distribution of Duration of PD in Study B09-03 (Sponsor's table).

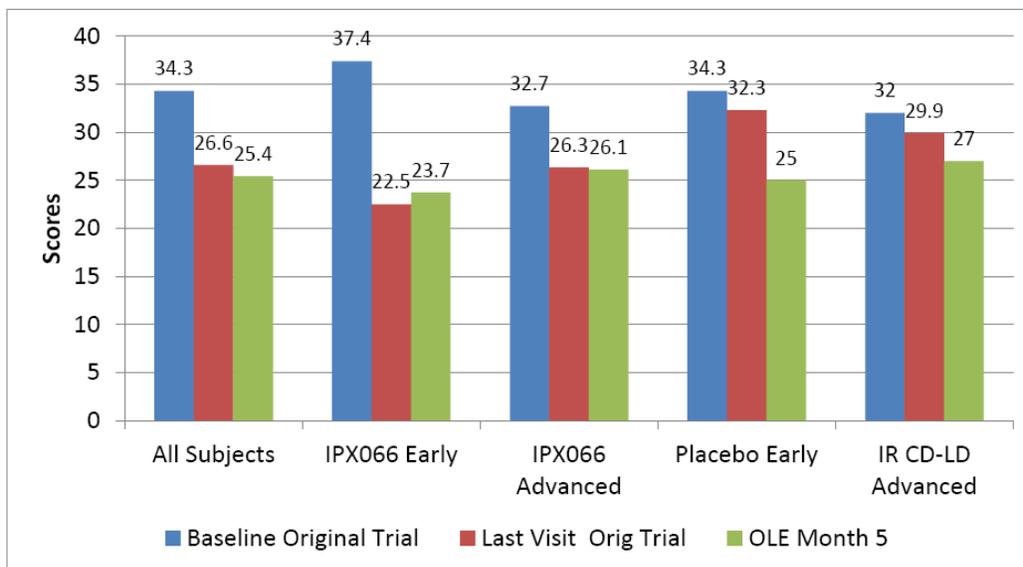
Clinical Review
 Anne E. A. Constantino, MD
 NDA 203312
 Ryтары/IPX066/Carbidopa-Levodopa Extended Release

Duration (Years)	Early Disease (N=268)	Advanced Disease (N=349)	Total (N=617)
< 1	12 (4.5%)	0	12 (1.9%)
1 to < 6	226 (84.3%)	118 (33.8%)	344 (55.8%)
6 to < 11	24 (9.0%)	148 (42.4%)	172 (27.9%)
≥ 11	6 (2.2%)	83 (23.8%)	89 (14.4%)
N (%)	268 (100%)	349 (100%)	617 (100%)
Mean (SD)	2.7 (2.43)	7.9 (4.45)	5.6 (4.53)
Median (Min, Max)	2.0 (1, 19)	7.0 (1, 29)	4.0 (1, 29)

NOTE: Duration = Current age - Age at diagnosis.
 If age at diagnosis and current age are the same, duration is assigned to be 0.5 year.
 % is Percent of Column Total

The primary efficacy endpoint in the long-term PD study (B09-03) was the UPDRS Parts II and III. Figure 10 illustrates that based on the UPDRS Parts II + III scores, patients who continued into the open label extension trial still showed improvement at 5 months from Baseline at entry into the antecedent study. Largest improvement was seen in the early PD patients (from study B08-05) compared to those who were in the advanced PD study (B09-02).

Figure 9: Mean UPDRS Part II + Part III Scores for Study IPX066 B09-03 Month 5 and Original Trial (Source: Sponsor).



The table below summarizes the scores at month 9 in patients who continued into the open label extension study.

Table 34: Summary of Mean UPDRS Part II + III Scores Over Time in Study B09-03 (Sponsor's table).

Disease Stage	Last Previous Treatment	Baseline Previous Trial (N=604)	Final Previous Trial (N=604)	Baseline* (N=213)	Month 1 (N=601)	Month 5 (N=581)	Month 9 (N=567)	Early Termination (N=33)
EARLY	IPX066	37.4 (14.43) N=207	22.5 (12.59) N=207	29.3 (13.69) N=127	24.0 (13.02) N=201	23.6 (12.83) N=200	24.0 (12.90) N=196	41.5 (19.50) N=4
	PLACEBO	34.3 (9.13) N=61	32.3 (12.39) N=61	28.4 (11.87) N=41	25.4 (10.82) N=60	25.0 (10.37) N=58	24.9 (10.37) N=58	21.5 (12.02) N=2
	TOTAL EARLY	36.7 (13.45) N=268	24.7 (13.18) N=268	29.1 (13.24) N=168	24.3 (12.54) N=261	23.9 (12.32) N=258	24.2 (12.35) N=254	34.8 (19.07) N=6
ADVANCED	IPX066	32.7 (14.34) N=173	26.3 (12.54) N=173	32.4 (20.93) N=27	26.2 (13.10) N=174	26.1 (12.76) N=169	28.2 (12.24) N=163	33.1 (8.88) N=11
	IR CD-LD	32.0 (15.43) N=163	29.9 (15.31) N=163	22.7 (11.40) N=18	27.9 (15.59) N=166	27.1 (14.79) N=154	28.1 (15.33) N=150	36.6 (18.89) N=16
	TOTAL ADVANCED	32.4 (14.86) N=336	28.1 (14.05) N=336	28.5 (18.22) N=45	27.0 (14.37) N=340	26.5 (13.75) N=323	28.2 (13.78) N=313	35.2 (15.47) N=27
TOTAL	OVERALL TOTAL	34.3 (14.40) N=604	26.6 (13.76) N=604	29.0 (14.39) N=213	25.9 (13.66) N=601	25.4 (13.19) N=581	26.4 (13.30) N=567	35.1 (15.85) N=33

NOTE: * A Baseline measure in B09-03 was only collected if there were a gap of 4 weeks or more between the Final Previous Trial visit and entry in B09-03.

As in the 5-month period, the numerical change (improvement) in UPDRS scores parts 2 and 3 was among early PD patients. There was persistence of effect at 5 and 9 months in both early and

advanced PD patients although the improvement in the Advanced PD patients at Month 9 was less than the improvement in Early PD patients.

Table 35: Summary of Mean Total UPDRS Score Over Time in Study B09-03 (Sponsor's table).

Disease Stage	Last Previous Treatment	Baseline Previous Trial (N=604)	Final Previous Trial (N=604)	Baseline* (N=213)	Month 1 (N=601)	Month 5 (N=581)	Month 9 (N=567)	Early Termination (N=33)
EARLY	IPX066	39.7 (15.30) N=207	24.4 (13.52) N=207	31.1 (14.75) N=127	25.9 (13.73) N=201	25.6 (13.62) N=200	26.0 (13.65) N=196	44.0 (18.22) N=4
	PLACEBO	36.2 (9.85) N=61	34.5 (13.06) N=61	30.2 (12.39) N=41	27.1 (11.34) N=60	27.1 (11.15) N=58	26.7 (10.91) N=58	23.0 (9.90) N=2
	TOTAL EARLY	38.9 (14.30) N=268	26.7 (14.04) N=268	30.9 (14.18) N=168	26.2 (13.21) N=261	25.9 (13.10) N=258	26.1 (13.06) N=254	37.0 (18.34) N=6
ADVANCED	IPX066	39.7 (15.06) N=173	32.5 (13.36) N=173	38.8 (22.90) N=27	31.9 (14.06) N=174	31.8 (13.69) N=169	34.0 (13.19) N=163	39.5 (10.89) N=11
	IR CD-LD	38.8 (16.08) N=163	36.6 (16.55) N=163	29.1 (12.35) N=18	33.7 (16.80) N=166	32.9 (15.96) N=154	34.2 (16.70) N=150	44.3 (19.94) N=16
	TOTAL ADVANCED	39.3 (15.54) N=336	34.5 (15.12) N=336	34.9 (19.80) N=45	32.8 (15.46) N=340	32.3 (14.80) N=323	34.1 (14.95) N=313	42.4 (16.75) N=27
TOTAL	OVERALL TOTAL	39.1 (14.99) N=604	31.0 (15.14) N=604	31.7 (15.58) N=213	29.9 (14.88) N=601	29.5 (14.41) N=581	30.5 (14.67) N=567	41.4 (16.88) N=33

NOTE: * A Baseline measure in B09-03 was only collected if there were a gap of 4 weeks or more between the Final Previous Trial visit and entry in B09-03.

PGI results showed that majority of patients in the trial were satisfied with IPX066 treatment. (Table 36). The level of satisfaction was consistent until month 9.

Table 36: Distribution of PGI in Study B09-03 (Sponsor's table).

Patient Global Impression	Month 1 (N=599)	Month 5 (N=581)	Month 9 (N=567)	Early Termination (N=32)
Very Much Dissatisfied (1)	1 (0.2%)	5 (0.9%)	3 (0.5%)	2 (6.3%)
Very Dissatisfied (2)	7 (1.2%)	6 (1.0%)	9 (1.6%)	3 (9.4%)
Somewhat Dissatisfied (3)	45 (7.5%)	30 (5.2%)	31 (5.5%)	9 (28.1%)
Neither Satisfied or Dissatisfied (4)	83 (13.9%)	59 (10.2%)	50 (8.8%)	4 (12.5%)
Somewhat Satisfied (5)	212 (35.4%)	191 (32.9%)	193 (34.0%)	6 (18.8%)
Very Satisfied (6)	190 (31.7%)	216 (37.2%)	193 (34.0%)	6 (18.8%)
Very Much Satisfied (7)	61 (10.2%)	74 (12.7%)	88 (15.5%)	2 (6.3%)
N (%)	599 (100%)	581 (100%)	567 (100%)	32 (100%)
Mean	5.2	5.4	5.4	4.1
Std Dev	1.12	1.14	1.16	1.67
Median	5.0	5.0	5.0	4.0
Minimum	1	1	1	1
Maximum	7	7	7	7

Summary of Total PDQ 39 over time were also consistent in showing that there was improvement in the PDQ scores at month 5 and month 9 with IPX066 treatment.

REVIEWER'S COMMENTS:

Exposure to IPX066 over a period of at least nine months provided continuous benefit with persistent improvement in UPDRS scores and overall patient satisfaction.

7 Review of Safety

Safety Summary

- There were 11 deaths in 1098 patients (1.0%) reported from all of the studies submitted to this NDA (including the 120 day safety update). The deaths did not appear to be drug related and were mainly due to cardiopulmonary causes which are the most common cause of death among patients with Parkinson's disease.
- Of 849 patients exposed to at least one dose of the study drug in the submitted clinical trials for this study, there were 38 (4.5%) serious adverse events. Adverse events were more frequent in the advanced PD population. Drug related serious adverse events include nausea/vomiting, acute psychosis and disabling dyskinesias.
- In the early PD (B08-05) study, nausea and vomiting is the most common AE occurring in 61 (16%) of subjects on IPX066 and 11 (2.9%) on patients on placebo. They occurred more frequently during the titration phase (12.6%) than during the Maintenance Phase (4.2%). Nausea and vomiting also was the most common adverse event that led to early withdrawals.
- In the advance PD study, there were more frequent cases of dyskinesias (2.5% vs. 1%), nausea and vomiting (4.5% vs. 3.6%), orthostatic hypotension (4.5% vs. 2.6%), hallucinations (1.7% vs. 0.7%) and impulse control behavior disorders (1.4% vs. 0) in the IPX066 treated group than in the IR group.
- The adverse events reported in this clinical development program for IPX066 were similar to the type and frequency of adverse events that were seen in early and advanced PD patients enrolled in PD drug studies.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review analyzed data from 1098 subjects (this includes the 120 day safety update enrollees) who received at least one dose of the study drug IPX066. There were originally 11 studies (2 on-going) submitted to the NDA as of the June 30, 2011 cut-off period. The table below summarizes the design, type of study, number of subjects enrolled and study duration in the Phase 2 and 3 comparator trials.

Table 37: Description of Individual Clinical Studies Submitted to the NDA (Cut-off date: June 30, 2011) (Modified by Reviewer from Sponsor's table 2, p. 33, ISS)

Study ID	Design	Type of Study	# of Subjects per Treatment Arm who Entered/ Completed the Study	Duration
Phase 1 Studies				
IPX-066 B08-08	Open Label Single Dose	PK	21	Stopped Early
IPX-066 B08-09	Open Label Single Dose	Dose Proportionality	31/28	
IPX-066 B08-10	Open Label Single Dose	PK, bioavailability of IPX066 relative to marketed CD_LD	24/22	
IPX-066 B09-01	Open Label Single Dose	PK	21/19	
IPX-066 B09-04	Open Label Single Dose	PK	27/19	
IPX-066 B10-01	Open Label Single Dose	BE	39/34	
Phase 2				
IPX-066 B08-11	Open Label, single and Multiple dose	PK	27	8 days with 7 days between two treatment periods
Phase 3 Comparator Trials				
IPX-066 B08-05	Randomized, Double Blind Placebo Controlled	Evaluate Safety and Efficacy of IPX066 compared to Placebo in Early PD Subjects	145 mg: 87/72 245 mg: 104/83 390 mg: 98/74 Placebo: 92/71 Total Enrolled: 381 Total Completers: 300	30 weeks: Titration: 4 weeks Maintenance: 26 weeks
IPX-066 B09-02	Randomized, double blind, double dummy, active comparator, controlled parallel group	Evaluate safety and efficacy of IPX066 compared to IR CD_LY in treatment of Advanced PD Subjects	Dose Adjustment IR Only: 471/450 Dose Conversion IPX066 Only: 450/393 Maintenance IPX066: 201/186 Maintenance IR: 192/182 Total Enrolled: 471 Completers: 368	22 weeks Dose Adjustment: 3 weeks Dose Conversion: 6 weeks Maintenance: 13 weeks
IPX-066 B09-06 Part 1	Randomized, double blind, double dummy, 2 treatment, 2 period cross-over	Efficacy comparison of IPX066 and CLE and PKE/PD of IPX066 and CLE	Dose Conversion: 110/84 Period 1: 48/45 Period 2: 43/49 Total Enrolled: 10 Completers: 94	11 weeks Dose Conversion: 6 weeks Treatment 1: 2 weeks Treatment 2: 2 weeks

Phase 3 Open Label Long Term Safety Extension				
IPX-066 B09-03	Open label, safety extension study	Evaluate long term safety and clinical utility in subjects with PD	617 ongoing	9 months
IPX-066 B09-06 Part 2	Open label, safety extension study	Evaluate long term safety and clinical utility in subjects with PD	74	6 months

120 Day Safety Update:

Data submitted in the 120-day safety update included safety information from IPX066 clinical studies received as of cut-off date January 23, 2012. All of the patients that entered the long-term trials completed a controlled trial of IPX-066. All new safety information in the 120 day safety update came from the 2 completed open label extension trials: IPX066 B09-03, IPX066 B09-06 Part 2 and one ongoing open label trial: IPX066 B11-01--An Open-Label Conversion Study of Carbidopa-Levodopa Extended-Release (CD-LD ER) taken Alone or in Combination with Carbidopa-Levodopa Immediate Release (CD-LD IR) to IPX066 Followed by an Open-Label Extension Safety Study of IPX066 in Subjects with Advanced Parkinson's Disease. The latter study was initiated after the data cut off for the NDA on June 30, 2011.

The sponsor's table below lists all completed and ongoing open label extension studies that provided additional safety information to the 120 day safety update (SU).

Data from controlled clinical trial were used to describe the frequency of adverse events in the two PD populations studied in clinical trials in patients Parkinson's disease (early and advanced).

Table 38: Completed and Ongoing Open Label, Long Term Extension Studies that Provided New Safety Information to the 120-Day Safety Update (Sponsor's table).

Study Numbers	Study Title	Status	Number of Subjects	
			Enrolled	Completed
Phase 3, Open-Label, Long-Term Safety Extension Studies^b				
IPX066-B09-03	An Open Label Extension Study of the Safety and Clinical Utility of IPX066 in Subjects with Parkinson's Disease	Completed	617 ^b	567
IPX066-B09-06 Part 2	A Study to Compare IPX066 and CD-LD-Entacapone in Advanced Parkinson's Disease	Completed	74 ^c	66
IPX066-B11-01	An Open-Label Conversion Study of Carbidopa-Levodopa Extended Release (CD-LD ER) Taken Alone or in Combination with Carbidopa-Levodopa Immediate Release (CD-LD IR) to IPX066 Followed by an Open-Label Extension Safety Study of IPX066 in Subjects with Advanced Parkinson's Disease	Ongoing	43 ^d	NA
Total Number of Subjects in Long-Term Safety Extension Studies			734	633

7.1.2 Categorization of Adverse Events

The Sponsor used the Medical Dictionary for Regulatory Affairs (MedDRA), Version 12.1 for adverse event coding. Treatment emergent adverse events (AEs), defined as AEs that started after the first dose of study treatment was administered until 72 hours after the last dose of study treatment was administered, were classified by System Organ Class (SOC) and MedDRA Preferred Term. Adverse events were also classified into serious, common and special in its class.

The sponsor's safety coding was reviewed for preferred and verbatim terms that are commonly reported by patients with Parkinson's disease. The datasets were reviewed for consistency of terminologies to ensure that safety signals have been captured. The terminologies will be discussed further in the safety results.

The adverse events from the clinical trials in this submission were compared to FDA approved drugs similar to its class

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the Pre-Phase 3 meeting on August 30, 2011 the pooling strategy was discussed. FDA response to the sponsor's proposed outline of information to be included in the ISS (and ISE) is as follows:

FDA Response to Question 10: Preliminary FDA Response:

In general, we find the organization of the ISS and ISE to be acceptable. We recommend that your safety dataset submission be organized into the following:

Pool 1a: Placebo controlled studies for early PD which includes the following study:

- **IPX066-B08-05 A placebo controlled study of early Parkinson's subjects. This study evaluated the 3 different fixed doses of IPX066 with placebo.**

Pool 1b: All active controlled studies in advanced PD which includes the following studies:

- **IPX-066-B09-02 An active controlled (IR CD-LD) study in advanced PD subjects**
- **IPX-066-B09-06 (part 1) A crossover study that compares IPX066 with a combination of CD-LD and entacapone.**

Pool 1c: Combined data from Pool 1a and 1b

Pool 2a: Uncontrolled, open label safety trials and trial extensions in early PD subjects

- **IPX066-B09-03: Includes subjects who completed IPX066-B08-05.**

Pool 2b: Open label extension study in advanced PD subjects includes the following studies:

- IPX066-B08-11
- IPX066-B09-02
- IPX-066-B09-06 (part 2)

Pool 2c: Safety data from all open label trials involving LD naïve and advanced PD patients and all open label extensions of placebo-controlled trials (pools 2a plus pool 2b). Data from Phase 2 trials.

Study IPX066-B08-11 was an open-label, crossover study in subjects (N=27) with advanced Parkinson's disease with motor fluctuations on levodopa therapy. The objectives of the study were to compare the PK, motor effects, and safety of IPX066, with an immediate-release carbidopa-levodopa formulation in advanced Parkinson's disease.

Data from Phase 1 Trials

Data from trials involving healthy volunteers should be contained in a separate data pool.

The Sponsor and the Agency agree to the safety results for PK studies involving healthy subjects that were designed to explore the PK parameters of different formulations of IPX066.

REVIEWER'S COMMENTS:

The pooling strategy of the safety data that the sponsor submitted in the ISS as presented below is adequate on its classifying the early PD population from the Advanced PD subject according to the following:

- *Overall PD Population - pooled data from all 3 Phase 3 studies*
- *Early PD Population - subjects with early-stage Parkinson's disease who participated in Study IPX066-B08-05*
- *Advanced PD Population - subjects with advanced-stage Parkinson's disease who participated in Studies IPX066-B09-02 or IPX066-B09-06 Part 1*

However, the pooling scheme that is presented in table 39 (below) does not provide separate analyses of adverse events reported in early versus advanced PD subjects who may have different risk for certain adverse events related to their disease severity (e.g., dyskinesia in advanced PD).

Table 39: Sponsor's Plan for Integrating Data from Phase 3 Controlled Studies in Subjects with Parkinson's Disease (Sponsor's table).

Individual Phase 3 Controlled Studies in Subjects with Parkinson's Disease										
Study IPX066-08-05			Study IPX066-09-02			Study IPX066-09-06 Part 1				
Double-Blind IPX066 or Placebo 30 wk			Open-Label Dose Conversion from IR CD-LD to IPX066 6 wk			Double-Blind IR CD-LD or IPX066 13 wk		Open-Label Dose Conversion from CLE to IPX066 6 wk		Double-Blind Alternate CLE or IPX066 2 wk
IPX066 (N = 289)			IPX066 (N = 450)		IPX066 (N = 201)	IPX066 (N = 110)	IPX066 (N = 89)	IPX066	CLE	
Placebo (N = 92)			IR CD-LD (N = 471)	IR CD-LD (N = 192)		CLE (N = 88)		IPX066		

Integrated Analyses of Subjects with Parkinson's Disease									
Number of Subjects in Study IPX066-	IPX066			IR CD-LD			CLE	Placebo	Total Subjects
	Open-Label Period	Double-Blind Period	Total Exposed During Open-Label or Double-Blind Period	Open-Label Period	Double-Blind Period	Total Exposed During Open-Label or Double-Blind Period	Double-Blind Period	Double-Blind Period	
B08-05	—	289	—	—	—	—	—	92	381 ^a
B09-02	450	201	—	471	192	—	—	—	471 ^a
B09-06 Part 1	110	89	—	—	—	—	88	—	110 ^a
Total Subjects	560 ^a	579 ^a	849	471 ^a	192 ^a	471	88 ^a	92 ^a	962 ^a

^aNumber of unique subjects enrolled.

CLE = carbidopa/levodopa/entacapone
 IR CD-LD = immediate-release carbidopa-levodopa
 wk = week

Furthermore, this type of analysis is not informative because it involves comparisons of patients who were compared to different control medications and placebo. —This makes it difficult to interpret differences in the frequency of adverse events in the IPX066 group compared to either the placebo or comparator group. The pooled data in the ISS was evaluated to look at the overall picture of laboratory abnormalities, blood pressure changes and deaths but for the most part of the review, the safety analysis was evaluated by indication: early and advanced PD.

The frequency of adverse drug reactions in the treatment group compared to placebo was analyzed in the study IPX066 B08-05 for the Early PD indication. Study IPX066 B09-02,

which was conducted in advanced PD patients on IR was reviewed to compare the frequencies of adverse events between the patients on IPX066 and patients on IR.

Study B09-06, another advanced PD study with Carbidopa-Levodopa-Entacapone (CLE) as an active comparator, is not useful to make comparisons for both efficacy and safety mainly because the trial design and dosing plan resulted in an unequal comparison of IPX066 and CLE that may bias the results towards IPX066. In the double blind period of the study, the IPX066 group was permitted dose adjustment until they had “minimized off time” while patients assigned to CLE returned to their unoptimized dose without the opportunity for dose adjustment. However, the frequency of adverse reactions in this study can be roughly compared to AES for IPX066 in other controlled trials and the safety data can be examined for rare and uncommon adverse reactions.

Study IPX066 B09-03, an open label study with uncontrolled data was reviewed for rare adverse events that have not reported with long term use of other approved levodopa products. The study also provided information on the time course of adverse events.

7.2 Adequacy of Safety Assessments

In the original NDA submission, a total of 962 (381 Early PD patients and 581 Advanced PD) patients have received at least 1 treatment of IPX066 during the phase 3, controlled studies. While the total patients exposed seem adequate, this absolute number of patients does not translate into the number of patients who have been exposed to clinically relevant doses for at least 6 and 12 months because of the different exposure periods to IPX066 in the design of each study. As discussed in the pre-NDA meeting, the sponsor will submit data from “at least 350 patients with 6 months and 150 patients completing 1 year of continuous exposure to clinical relevant dosages of IPX066 in the NDA”.

Table 40: Cumulative Exposure to IPX066 in Original and Extension Trials in Study IPX066 B09-03 as of 30 June 2011 (Sponsor's table).

Disease State	Duration of Exposure	Number of Subjects
Early and Advanced N=617	Up to 13 Weeks	617
	Up to 26 Weeks	608
	More than 26 Weeks	595
	More than 52 Weeks	279
Early N=268	Up to 13 Weeks	268
	Up to 26 Weeks	266
	More than 26 Weeks	265
	More than 52 Weeks	201
Advanced N=349	Up to 13 Weeks	349
	Up to 26 Weeks	342
	More than 26 Weeks	330
	More than 52 Weeks	78

We requested the sponsor to resubmit their exposure table to include information describing relevant exposure doses and duration of exposure from IPX066 for 6 months and 1 year. The sponsor's table (Table 41) provides the total daily levodopa dose by duration.

Table 41: Exposure for Subjects by Total Daily Dose and by Cumulative Duration (Sponsor's table).

IPX066-ISS: 120-DAY SAFETY UPDATE POST TEXT REPORT

TABLE 15.3.3.1-2 (Page 1 of 1)
Exposure for Subjects on IPX066: Total Daily Dose by Cumulative Continuous Duration (All Subjects Exposed to IPX066)

Dose of IPX066 Received (Total Daily Dose)	Duration of Exposure to IPX066					Total (N=1539)
	<=29 Days (N=285)	30 to 89 Days (N=366)	90 to 179 Days (N=72)	180 to 364 Days (N=624)	>= 365 Days (N=192)	
< 285 mg	72	0	0	3	0	75
285 mg to < 435 mg	56	0	0	24	1	81
435 mg to < 735 mg	53	17	5	144	23	242
735 mg to <1170 mg	29	108	20	202	74	433
1170 mg to <1600 mg	29	89	18	149	40	325
1600 mg to <2400 mg	24	110	21	73	41	269
>=2400 mg	22	42	8	29	13	114

REVIEWER'S COMMENTS:

The sponsor had an adequate number of patients exposed to clinically relevant doses at both 6 months and one year as discussed during the pre NDA meeting.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The demographic distribution has been discussed in detail in the efficacy section of this review. For this submission, the sponsor presented the demographics in the ISS as pooled data for all the Phase 3 controlled studies (table 41). Incidence rates among patients age 65 years and above is higher than among younger individuals making them the most likely group to be exposed to this drug may be at greater risk for adverse events. (Wirdefeldt, 2011)

Table 42: Summary of Age, Sex, Race, Weight and Body Mass Index in Controlled Phase 3 Studies--Overall PD population, All Enrolled Subjects (Sponsor's table).

Demographic / Characteristic	Number of Subjects (%) in Overall PD Population							
	IPX066			IR CD-LD			Double Blind CLE	Double blind Placebo
	Open Label	Double Blind	Total Exposed	Open Label	Double Blind	Total Exposed		
Age								
N (%)	560 (100)	579 (100)	849 (100)	471 (100)	192 (100)	471 (100)	88 (100)	92 (100)
Mean (SD)	63.5 (9.41)	64.0 (9.72)	63.9 (9.48)	63.5 (9.49)	63.4 (8.81)	63.5 (9.49)	63.9 (8.91)	65.4 (9.43)
< 65 years	296 (52.9)	298 (51.5)	431 (50.8)	247 (52.4)	100 (52.1)	247 (52.4)	49 (55.7)	41 (44.6)
≥ 65 years	264 (47.1)	281 (48.5)	418 (49.2)	224 (47.6)	92 (47.9)	224 (47.6)	39 (44.3)	51 (55.4)
Sex								
Male	359 (64.1)	357 (61.7)	519 (61.1)	292 (62.0)	125 (65.1)	292 (62.0)	66 (75.0)	52 (56.5)
Female	201 (35.9)	222 (38.3)	330 (38.9)	179 (38.0)	67 (34.9)	179 (38.0)	22 (25.0)	40 (43.5)
Race								
White	543 (97.0)	568 (98.1)	828 (97.5)	456 (96.8)	186 (96.9)	456 (96.8)	87 (98.9)	90 (97.8)
Black or African American	5 (0.9)	4 (0.7)	7 (0.8)	5 (1.1)	1 (0.5)	5 (1.1)	0	0
Asian	2 (0.4)	2 (0.3)	3 (0.4)	2 (0.4)	1 (0.5)	2 (0.4)	0	1 (1.1)
American Indian or Alaska Native	4 (0.7)	0	4 (0.5)	4 (0.8)	2 (1.0)	4 (0.8)	0	0
Other	5 (0.9)	4 (0.7)	6 (0.7)	3 (0.6)	2 (1.0)	3 (0.6)	1 (1.1)	1(1.1)
Missing	1	1	1	1	0	1	0	0
Weight								
N (%)	558 (99.6)	577 (99.7)	846 (99.6)	469 (99.6)	192 (100)	469 (99.6)	88 (100)	92 (100)
Mean (SD)	80.3 (16.50)	80.0 (16.21)	79.8 (16.23)	79.8 (16.24)	81.5 (16.50)	79.8 (16.24)	83.2 (18.48)	77.9 (15.26)
< 75 kg	206 (36.8)	224 (38.7)	328 (38.6)	179 (38.0)	68 (35.4)	179 (38.0)	31 (35.2)	39 (42.4)
≥ 75 kg	352 (62.9)	353 (61.0)	518 (61.0)	290 (61.6)	124 (64.6)	290 (61.6)	57 (64.8)	53 (57.6)
Missing	2	2	3	2	0	2	0	0

There were more males enrolled in this study. This is expected because epidemiologic studies show a male to female ratio of 1.46 to 1.49 (CI 95%) (Wirdefeldt, 2011) . However, since plasma concentrations of levodopa were reportedly higher in females compared to males. The PK differences were described in IPX066 B08-10, the safety profile differences by subgroups including gender will be discussed in this review.

Disease related differences (UPDRS scores, Hoehn and Yahr stage, duration of levodopa treatment and duration of disease) are more likely to affect the adverse event profile in patients with advanced PD. Previous dose of levodopa treatment and duration of exposure to levodopa are risk factors for developing motor complications such as dyskinesias (Schrag A, 2000) that may be present in up to 28% of patients. Koller et al (1999) commented that dyskinesias are typically seen in patients who have been treated with L dopa for 5 years or more. Tables 43 and 44 below summarizes the characteristics of the advanced PD patients enrolled in the study according to Hoehn and Yahr scores and duration of Parkinson's disease.

Table 43: Distribution and Summary of Hoehn and Yahr Scores in Advanced PD Patients (Sponsor's table)

Hoehn and Yahr	IPX066			IR CD-LD			CLE	Placebo
	Open Label (N=560)	Double Blind (N=290)	Total Exposed (N=560)	Open Label (N=471)	Double Blind (N=192)	Total Exposed (N=471)	Double Blind (N=88)	Double Blind (N=0)
I	15 (2.7%)	7 (2.4%)	15 (2.7%)	13 (2.8%)	7 (3.6%)	13 (2.8%)	3 (3.4%)	-
II	296 (52.9%)	160 (55.2%)	296 (52.9%)	247 (52.4%)	103 (53.6%)	247 (52.4%)	51 (58.0%)	-
III	222 (39.6%)	107 (36.9%)	222 (39.6%)	189 (40.1%)	75 (39.1%)	189 (40.1%)	29 (33.0%)	-
IV	27 (4.8%)	16 (5.5%)	27 (4.8%)	22 (4.7%)	7 (3.6%)	22 (4.7%)	5 (5.7%)	-
N (%)	560 (100%)	290 (100%)	560 (100%)	471 (100%)	192 (100%)	471 (100%)	88 (100%)	-
Mean (SD)	2.5 (0.63)	2.5 (0.64)	2.5 (0.63)	2.5 (0.63)	2.4 (0.63)	2.5 (0.63)	2.4 (0.65)	-
Median	2.0	2.0	2.0	2.0	2.0	2.0	2.0	-
(Min, Max)	(1, 4)	(1, 4)	(1, 4)	(1, 4)	(1, 4)	(1, 4)	(1, 4)	-

Table 44: Distribution and Summary of Pre-Study Duration of Treatment with Levodopa in Advanced PD Patients (Sponsor's table).

Duration on Treatment with Levodopa (in years)	IPX066			IR CD-LD			CLE	Placebo
	Open Label (N=560)	Double Blind (N=290)	Total Exposed (N=560)	Open Label (N=471)	Double Blind (N=192)	Total Exposed (N=471)	Double Blind (N=88)	Double Blind (N=0)
No Prior Treatment	0	0	0	0	0	0	0	-
> 0 to < 8	401 (71.6%)	214 (73.8%)	401 (71.6%)	342 (72.6%)	142 (74.0%)	342 (72.6%)	61 (69.3%)	-
>= 8	159 (28.4%)	76 (26.2%)	159 (28.4%)	129 (27.4%)	50 (26.0%)	129 (27.4%)	27 (30.7%)	-
N (%)	560 (100%)	290 (100%)	560 (100%)	471 (100%)	192 (100%)	471 (100%)	88 (100%)	-
Mean (SD)	6.3 (5.06)	6.3 (5.47)	6.3 (5.06)	6.2 (5.16)	5.8 (3.92)	6.2 (5.16)	6.9 (4.96)	-
Median	5.2	5.2	5.2	5.0	5.0	5.0	6.0	-
(Min, Max)	(0.2, 57.0)	(0.3, 57.0)	(0.2, 57.0)	(0.2, 57.0)	(0.2, 20.0)	(0.2, 57.0)	(0.3, 30.0)	-

The tables above show that subjects with advanced PD exposed to either IPX066 or IR CD-LD had a mean duration of treatment with levodopa of 5.8 to 6.9 years and a Hoehn and Yahr Stage of 2.4 to 2.5. Both groups are comparable in terms of characteristics that could affect treatment related motor and non-motor symptoms in Parkinson's disease (e.g. dyskinesias, hallucinations, orthostatic hypotension, etc).

7.2.2 Explorations for Dose Response

The trial design in the early PD study (B08-05) presented actual dose and duration of exposure for the 145 mg preparation. However, patients on higher doses continued up-titration for at least 4 weeks to 245 mg and 390 mg, patients on higher doses had less

exposure time to the higher doses. The 4-week titration phase provided additional information on tolerability and efficacy of the study drug

Study B09-02 was a flexible dose study that the sponsor did not present an analyses of efficacy or adverse events by actual dose or graduated dose intervals. Instead, adverse events were analyzed by treatment phase with the only analysis of the effects of dose consisted of grouping patients in those who received less than 1600 mg or those receiving IPX066 > 1600 mg. The limitations of the design and analysis methods of reported adverse events do not provide information to permit conclusions about dose response for safety or efficacy.

The Agency requested the Sponsor to provide a list of AEs (SOC and preferred term) and categorized by the total daily levodopa dose used by the Sponsor to convert patients to IPX066. The reanalysis of the adverse event data provided some information regarding dose response and the frequency of adverse events expected to increase with dose such as dyskinesia demonstrated the expected relationship to dose.

7.2.3 Special Animal and/or In Vitro Testing

Results from special animal or in vitro testing were not included in this NDA submission.

7.2.4 Routine Clinical Testing

Abnormalities in liver function tests and blood chemistry have been reported for the reference drugs including Sinemet.. Clinical laboratory samples were drawn at baseline and at end of trial. The tests that were specifically performed include:

Hematology: hematocrit, hemoglobin, erythrocyte count, white blood cell count, platelet count

Serum chemistry: Urea, Uric Acid, Creatinine, Protein, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, sodium, potassium chloride, glucose, total cholesterol, triglycerides.

Vital Signs include systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate was checked for orthostatic changes (supine and standing) only in the pivotal trials: B08-05 and B09-02. Supine and standing blood pressures were not monitored in the open label study B09-03.

Levodopa and other dopaminergic medications may be associated with sleep attacks and psychiatric cases from anxiety to psychosis and impulse control behavior in some patients.

The sponsor conducted formal evaluation for impulse control behavior only in Advanced PD patients. The mMIDI screen that was used to evaluate for impulse control does not capture patients who have binge eating behavior. This review included a search for adverse event terms of ten 61.25-245 mg LD-CD capsules suggesting loss of impulse control. Preferred terms such as binge eating, gambling (pathologic), hypersexuality, “buying sprees” were included in the search terms.

The following are adverse events of special interests for patients treated with dopaminergic medications. Except for Neuroleptic Malignant Syndrome, these events have been reported in patients treated with dopaminergic medications for other indications (i.e. Restless Legs Syndrome).

1. Sleep attacks. Although somnolence and sleepiness have been reported as dose limiting side effects of dopaminergic drugs, cases of sleep attacks (Frucht, 1999) are not as commonly recognized until reports of motor vehicular mishaps have occurred. This phenomenon has been described more commonly in association with dopamine agonists but has also been described in levodopa therapy (Ferreira JJ, 2006) with duration of levodopa therapy as one of the most important factors that can contribute to these sleep attacks. The sponsor tabulated cases of sleep disorders in the adverse event section of each of the clinical trials that they conducted.
2. Neuroleptic Malignant Syndrome. Although the sponsor has not addressed this in detail, my review looked into preferred terms such as fever, hyperthermia, muscle rigidity, autonomic dysfunction and laboratory findings such as creatine phosphokinase elevation, leukocytosis and myoglobinuria and hospitalization.
3. Melanoma. The higher risk of patients with Parkinson’s disease of developing melanoma than the general population is 2 to 6 fold higher. Increased risk of developing melanoma with levodopa treatment has not been established. This review looked at the reports of dermatologic terms especially in the long term studies. However because of the short duration of the conducted studies for this particular dopaminergic agent, it would be difficult (as with other dopaminergic agents) to directly link the drug to the adverse event/dermatologic symptom.

7.2.5 Metabolic, Clearance, and Interaction Workup

The drug relied on the metabolic clearance and interaction of Sinemet. No new information has been developed for this section of the review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor evaluated patients for impulse control behavior using the mMIDI scale among Advanced PD patients. However, this test was not done in the early PD patients. Although the MIDI has been used to assess for impulse control behavior, it is not sensitive to patients who suffer from binge eating or punding.

There are case reports of patients on levodopa who develop sleep disorders and sleep attacks. This risk for sleep disturbances may not be as severe as with patients on dopaminergic agents but they may occur in PD patients. The sponsor did not formally assess for sleep disturbances in their clinical trials.

7.3 Major Safety Results

7.3.1 Deaths

There were a total of 11/1098 deaths reported in the entire NDA—1 death in the placebo controlled trial, 2 in the active control part of the study and 4 additional deaths during the open label portion of the study—a total of 7 deaths at the NDA submission. The Sponsor reported an additional 4 deaths from the open label trials. There were no deaths reported in the phase 1 healthy volunteer studies. There were discrepancies between the numbers of deaths reported from the NDA and the 120 day safety day update. The number of deaths reported in the NDA submission on December 2011 accounted for seven (7) deaths from the following studies:

Study B08-05: 1 death:

Subject 209-006

Study B09-02: 2 deaths:

Subject 175-008

Subject 808-004

Study B09-03: 4 deaths:

Subject 535-001 (501-001 in B09-02)

Subject 630-010 (606-012 in B09-02)

Subject 828-025 (804-012 in B09-02)

Subject 829-021 (205-006 in B08-05)

In the 120-day safety update submitted on April 24, 2012 listed 3 more deaths were reported, all from study B09-06 Part 2:

Subject 376-008

Subject 454-005

Subject 951-023

The sponsor also submitted the table below, which reflects differences between their deaths at the NDA and the 120-day safety update submission.

Table 45: Distribution and Summary of Pre-Study Duration of Treatment with Levodopa in Advanced PD Patients (Sponsor's table).

Table 3: Subject Disposition (Overall PD Population)

	Number (%) of Subjects		
	Reported in NDA	New Information Post NDA	Overall
	IPX066	IPX066	
Number of Subjects Included	691	392	691
Early Discontinuation	45 (6.5%)	13 (3.3%)	58 (8.4%)
Reason for Early Discontinuation			
Adverse event	15 (2.2%)	3 (0.8%)	18 (2.6%)
→ Subject death	4 (0.6%)	1 (0.3%)	5 (0.7%)
Withdrawal by Subject	19 (2.8%)	8 (2.0%)	27 (3.9%)
Lost to Follow up	1 (0.1%)	1 (0.3%)	2 (0.3%)
Other	6 (0.9%)	0	6 (0.9%)

Sources: NDA120 Posttext Tables 14.1.1.2-1, 14.1.1.2-2, and Appendix 16.2.1.1

The clinical review team requested the Sponsor to clarify the inconsistencies in number of deaths reported during their NDA submission and the 120-day safety update. The sponsor responded on May 3, 2012 stating that the “apparent inconsistencies...are an artifact of the variables used in summarizing deaths based on investigator reporting as tabulations of reasons for discontinuation did not have “death” as a primary reason for discontinuation” (those who discontinued due to deaths were not included in the list of deaths). Additionally, the sponsor explained that investigators filling out the adverse event form will often report the adverse events associated with death and not list death as an Adverse Event.

The sponsor’s response to our information request of deaths confirmed the reviewer’s findings. The table below represents the number of deaths in each study and the total number of deaths including the 120-day safety update. A total of 11 deaths have been reported with an additional death in the new open label study B11-01: A Phase 3 open label conversion study from CD LD IR alone or in combination with CD-LD IR products to IPX066. This study commenced on 19 August 2011.

Table 46: Number of Deaths Per Study at the NDA Submission and 120-Day Safety Update (Reviewer's table).

Study	At NDA Submission	120 Day Safety Update	Total
B0805	1		1
B0902	2		2
B09-03	4		4
B09-06 Part 2		3	3
B11-01		1	1
Total	7	4	11

The table below (table 48) summarizes the cause of death in the entire study. These results are almost comparable to what has been reported in the scientific literature as among the most common causes of mortality in Parkinson's disease (Louis ED, 1997, Poewe, 2006, Willis 2012).

Table 47: Causes of Death in NDA 203312 (Reviewer's table).

Cause of Death	Number of Patients
Cardiac	3
Respiratory	2
Sudden Death from Unknown Cause	1
Acute Pancreatitis	1
Stroke	1
Infection	1
Immobility due to Fracture and PD	1

REVIEWER'S COMMENTS:

The conditions listed as the cause of death for patients are similar to the causes of death that have been reported in other published reports of patients with Parkinson's disease-

The table below summarizes the deaths across the entire NDA. The narratives for all patients who died during the clinical trials program are presented in the following table.

Table 48: Deaths from All Studies Submitted to NDA 203312 (Original Submission and 120-Day Safety Update, Cut -off date: January 23, 2012). (Reviewer's table)

APPEARS THIS WAY ON ORIGINAL

Original Submission							
Trial	Subject ID	Age & Gender	H&Y Stage	Levodopa dose at time of death	Days on IPX066	Reported cause of death by sponsor	Reviewer Comment
B08-05	209-006	73 F	II	735 mg	33	Non Hodgkin's Lymphoma	Death not related to medication.
B09-02	175-008	70 M	IV	1365 mg	50	Cardiopulmonary arrest secondary to aortic stenosis	Death not related to medication.
	808-004	74 F	III	3920 mg	30	Autopsy confirmed renal insufficiency from pyelonephritis	Death not related to medication.
B09-03	535-001 (501-001 in B09-02)	75 M		1740 mg	142	Sudden Death due to coronary artery disease.	Death not related to medication.
	630-010 (606-012 in B09-02)	73 M	II	855 mg	43	Sudden Death; unknown cause	Death not related to medication.
	828-025 (804-012 in B09-02)	48	III	2925 mg	121	Autopsy confirmed cause of death as hemorrhagic pancreatitis.	Death not related to medication.
	829-021 (205-006 in B08-05)	68	III	980 mg	82	Hemorrhagic stroke	Death not related to medication.
120 Day Safety Update							
Trial	Subject ID	Age & Gender	H&Y Stage	Levodopa dose at time of death	Days on IPX066	Reported cause of death by sponsor	Reviewer Comment
B09-06 Part 2	376-008	70	IV	1425 mg	218	Pneumonia	Death not related to medication.

	454-005	73	IV	1755 mg	277	Aspiration Pneumonia	Death not related to medication.
	951-023	60	II	2205	187	Autopsy confirmed acute MI secondary to cardiac arrhythmia and hypertensive cardiovascular	Death not related to medication.
B11-01	175014	85	IV	2145 (highest dose; range from 1755 mg to 2145 mg)	41	Poor mobility from fracture and PD	Death not related to medication.

Summaries of Reported Deaths:

IPX066-B08-05: Early PD: One Patient

Subject 209-006 randomized to IPX066 245 mg—total dose 735 mg (one 245 mg cap three times a day) (Country)

This is a 73-year-old woman with H & Y Stage II PD who had a history of cataracts, sclerotic retinopathy and chronic gastroduodenitis choleclytopancreatitis without any pre-study concomitant medications. She received study treatment for a total of 10 days before the onset of SAE. On day 10 (titration phase), she developed moderate periodic nausea and epigastric discomfort that resolved without treatment the same day. Site personnel requested that she come in for an examination and recommended an ultrasound but the subject said she would visit her personal physician. The patient received her last dose of study medication on Day 16. The Subject did not attend study visit 2 (scheduled on Day 29) and did not answer phone calls. On Day 34, family informed site personnel that the subject had died on Day 33 with a diagnosis of non-Hodgkin's lymphoma (NHL). The death certificate confirmed cause of death but the circumstances surrounding death were unknown, including hospital records and autopsy findings. Likewise, NHL was not reported as a concomitant illness by this patient.

IPX066-B09-02: Advanced PD Two Patients

Subject 175-008 received IPX066 1365 mg daily during the Dose Conversion Phase.

This is a 70-year-old man with history PD H & Y Stage IV, aortic stenosis and hypertension, who received 21 days of open label IR CD-LD (1000 mg per day at the end of Dose Adjustment) and 30 days of open label IPX066 during the Dose Conversion phase. He was receiving 1365 mg per day at the time of his last dose of study medication. The patient was in the study for 51 days prior to the onset of SAE. On day 33, the patient reported moderate dizziness that lasted for 1 day. The dizziness was treated with Meclizine also for only 1 day. On day 50 during Visit 4, the subject mentioned lightheadedness and sporadic shortness of breath, especially when climbing the stairs to bed. No medications were changed. That night, the wife recounted that the subject's BP dropped and he began to have chest pain/tightness and shortness of breath. The subject fell to the floor and paramedics were called. The subject was pronounced dead at the hospital. Records state that the subject was asystolic on arrival and could not be resuscitated. The death certificate listed the cause of death as cardiopulmonary arrest and severe aortic stenosis and no autopsy was performed. Concomitant medications at time of death include Baby aspirin, clonazepam, oxybutynin, HCTZ with Losartan, ropinirole, guaifenesin, simvastatin and aspirin.

Subject 808-004 received IPX066 3920 mg daily during the Conversion Phase.

This is a 74-year-old white woman with PD H& Y Stage III, with history of arterial hypertension, chronic pyelonephritis and right nephrectomy due to adenocarcinoma. The patient was on Candesar and Pramipexole. The subject received study treatment which included 23 days of 1800 mg IR CD-LD Dose Adjustment and 6 days of IPX066 3920 mg at Dose Conversion for a total of 29 days of treatment. On Day 14, the patient experienced acute enterocolitis that resolved on Day 24. On Day 29, the patient was admitted to the hospital with aggravated chronic pyelonephritis of the left kidney. On Day 30, she developed erosive esophagitis confirmed by esophago-duodenoscopy. Lab tests showed elevated creatinine (299 mmol/L), urea (22.4 mmol/L) and urine nitrogen (11.2 mmol/L). The subject died on Day 31. Autopsy revealed that the primary cause of death was renal insufficiency aggravated by pyelonephritis.

IPX066-B09-03: Open Label Study: Four Patients

Subject 535-001 (501-001 in B09-02) received IPX066 1740 mg. Died on Day 142 of treatment.

This is a 75-year-old white man with PD H&Y Stage III who was previously enrolled in the Advanced PD trial (B0902) and subsequently enrolled in the Open

Label Phase of the study. His past medical history included hypertension, diabetes, prostate syndrome, myocardial infarction with coronary stent, dyslipidemia, gastric prevention, dopaminergic gastrointestinal side effects prevention, asymptomatic carotid stenosis with the following concomitant medications: enalapril, tamsulosin, alprazolam, aspirin, bisoprolol, metformin, omeprazole, simvastatin, domperidone glicazide and rotigotine. The subject received a total of 1740 mg IPX066 for a total of 142 days prior to onset of SAE. The daughter reported that on Day 142, the subject suddenly fell to the ground as he was going to sleep. Emergency services arrived and detected ventricular fibrillation that did not respond to a defibrillator. The cause of death was coronary disease. No autopsy was performed and paperwork associated with subject's death was lost by the emergency services.

Subject 630-010 (606-012 in B09-02) received a total daily dose of IPX066 855 mg. Died on Day 43 of treatment.

This is a 73-year-old white man with PD (H and Y Stage II) who was previously enrolled in the Advanced PD study. He has a medical history of prostatic hypertrophy and papilloma of the bladder. Concomitant medications include Ropinirole, selegiline and doxazosin. One month prior to entering study B0903 (end of Study B09-02) a high QRS (120 msec) was noted. All other ECG intervals and vital signs were normal except for a heart rate of 101 BPM on a single occasion. Subsequent to baseline, the subject experienced weight loss (unknown onset and amount) and urinary problems. The patient was scheduled to undergo surgery for removal of a bladder papilloma. On day 36, he described as being very weak. On day 39, hematologic results were abnormal. On day 40, the patient's uric acid and calcium were abnormal. On day 42, IPX066 dosing was discontinued. On day 43, subject died at home without being hospitalized. Histopathology exam of the prostate revealed prostate adenocarcinoma, Gleason 8/10. Death certificate cannot be obtained from the family. An autopsy was not performed.

Subject 828-025 (804-012 in B09-02) received a total dose of IPX066 2925 mg. Died on day 121 of treatment.

This is a 48 year old man with PD (H and Y Stage III), and was previously enrolled in the Advanced PD study. He has a history of chronic rhinitis and polyposes of the antrum of Highmore. Concomitant medications included cyclodol (Trihexyphenidylum). The subject received IPX066 for a total of 122 days in B09-03 before the onset of SAE. Previous exams, vital signs, ECG results in B09-02 and B09-03 were unremarkable. Vital signs were normal. The Investigator reported that prior to his death, the subject experienced a very heavy and hectic travel schedule for 3 to 4 days in other regions of Ukraine and possibly

deviated from his normal diet while traveling. Subject died on day 121 (?) in his sleep. Death was due to acute hemorrhagic pancreatitis as described in the translated Certificate of Medical Forensic Investigation Autopsy report. A review of his baseline labs did not show any signs suggestive of alcoholism, liver disease or gallbladder disease.

Subject 829-021 (205-006 in B08-05) received a total dose of IPX066 980 mg. Discontinued treatment on Day 82.

The patient was a 68-year-old white man with PD H and Y Stage III. He was previously enrolled in the Early PD study. Past medical history included atherosclerosis, hypertension, extirpation of lipoma frontalis region, cystopyelonephritis and osteoarthritis of knees. Concomitant medications included trihexyphenidyl, amantadine HCl and enalapril. There were 2 low diastolic readings (106/59 at Week 4 and 109/58 at week 23) and one low PR interval (111 msec at Week 30) during the subject's participation. Creatinine, Glucose and Albumin were at the high end of normal and the specific gravity of urine was at the low end of normal at screening. On Day 82, the patient fainted, vomited and was incontinent of urine and his wife was unable to awaken him. On examination, Glasgow coma scale score was 10 points, Arterial pressure was 140/80 and heart rate was 82 beats per minute. The subject received home care because family refused hospitalization. A neurologist who examined the subject on Day 87 concluded that the patient suffered a hemorrhagic stroke. He subsequently died on day 89. Diagnosis was not confirmed because an MRI, CT and autopsy were not performed. Other reported adverse events in B08-05 and B09-03 included off periods between doses and dyskinesias with no change in IPX066 dosage.

Since the NDA submission, 4 additional deaths were reported. All patients had advanced Parkinson's disease. Three were enrolled in the extension study B09-06 and one patient was enrolled in the Open Label Conversion Study of Carbidopa-Levodopa Extended Release taken alone or in combination with Carbidopa-Levodopa Immediate Release (B11-01).

IPX066 B09-06 Phase 2: Three Patients

Subject 376-008 (Study B09-06 Part 2) received IPX066 1425 mg. Discontinued treatment on Day 218.

This is a 70-year-old white man with Hoehn and Yahr Stage IV PD. The subject had no relevant medical history. On day 214, subject had a complex focal seizure and developed pneumonia. On the same day, he also had dysphagia, hiccoughs and urinary tract infection. He was treated with antibiotics and respiratory

support. He continued to decline and palliative care was initiated. Subject died of Day 253 of pneumonia.

Subject 454-005 (Study B09-06 Part 2) received a total dose of IPX066 1755 mg daily. Decreased in medication on Day 124. Discontinuation of medication Day 277.

This is a 73-year-old white woman with Hoehn and Yahr Stage IV PD. The patient had a history of ischemic heart disease. She also received amantadine HCl, rotigotine transdermal, escitalopram, aspirin and bisoprolol. On day 124, subject was hospitalized due to severe dyskinesia and her Parkinson's medications were down titrated. It was unclear how much she PD levodopa dose she was on initially. She was discharged on day 129. The investigator assessed the event as severe, ongoing and related to IPX066 but no changes in IPX066 dosage was further initiated. On day 270, patient developed a severe episode of acute respiratory tract infection. On day 277, while eating, the subject aspirated resulting in death.

Subject 951-023 (Study B09-06 Part 2) received IPX066 total dose of 2205 mg daily. Drug was discontinued on Day 187.

This is 60-year-old white man with PD H and Y Stage II with a history of anxiety, depression, hypercholesterolemia and hypertension. Concomitant medications include simvastatin, sertraline and clonazepam. On day 187, the subject demonstrated abnormal behavior with impaired speech and thought processes that required hospitalization for a psychotic episode requiring treatment with haloperidol and lorazepam. IPX066 was discontinued. On day 191, patient suffered cardiopulmonary arrest and died despite resuscitative measures. Autopsy revealed that death was due to cardiac arrhythmia secondary to acute myocardial infarction and hypertensive cardiovascular disease.

IPX066 B11-01 Phase 1 (study ongoing): One Patient

Subject 175-014 received a total dose of 2145 which was later on decreased to 1895 mg. The medication was discontinued on Day 41.

The patient was an 85-year-old white man with PD H and Y Stage IV. The subject had a history of left hip fracture with stabilization surgery. On day 23, the patient's wife noted that his health was declining rapidly due to hip fracture and progression of his underlying PD. The narrative did not elaborate on the symptoms that led to this conclusion. On day 39, patient was admitted to an

inpatient hospice for failure to thrive. On day 45, the patient stopped eating and became less responsive. On day 49, the patient died. Cause of death that was reported was due to complications of Parkinson's disease.

7.3.2 Adverse Events

STUDY B08-05: EARLY PD

1. Summary table of frequencies of adverse events

The table below summarizes the frequencies of treatment emergent adverse events in early PD patients compared to placebo.

Table 49: Treatment Emergent Adverse Events in All Enrolled Subjects with Early PD (Sponsor's table).

Treatment-Emergent Adverse Events	Number of Subjects (%) in Early PD Population ³	
	IPX066 (N = 289)	Placebo (N = 92)
At Least 1 TEAE	194 (67.1)	67 (72.8)
Severe TEAE	14 (4.8)	1 (1.1)
Treatment-Related TEAE	153 (52.9)	44 (47.8)
TE SAE	11 (3.8)	3 (3.3)
Treatment-Related TE SAE	0	0
TEAE Leading to Early Discontinuation by Period at Onset	35 (12.1)	4 (4.3)

³ Received IPX066 or placebo in Study IPX066-B08-05.

Abbreviations: AE = adverse event, PD = Parkinson's disease, SAE = serious adverse event, TE = treatment emergent.

2. Non Fatal Serious Adverse Events

There were 14 (3.7%) in the treatment group and 3 (3.3%) in the placebo group treatment emergent, non-fatal, serious adverse events (TESAE). A summary of the TESAEs is presented in the sponsor's table below.

Table 50: Summary of Serious Adverse Events by Treatment Study IPX066 B08-05 (Sponsor's table).

Clinical Review
 Anne E. A. Constantino, MD
 NDA 203312
 Rytary/IPX066/Carbidopa-Levodopa Extended Release

System Organ Class Preferred Term	IPX066 145 mg (N=87)	IPX066 245 mg (N=104)	IPX066 390 mg (N=98)	Placebo (N=92)	Total (N=381)
N (%) of subjects with At least one serious adverse event	4 (4.6%)	5 (4.8%)	2 (2.0%)	3 (3.3%)	14 (3.7%)
Cardiac disorders	3 (3.4%)	1 (1.0%)	0	0	4 (1.0%)
Acute myocardial infarction	1 (1.1%)	0	0	0	1 (0.3%)
Atrioventricular block complete	0	1 (1.0%)	0	0	1 (0.3%)
Coronary artery disease	1 (1.1%)	0	0	0	1 (0.3%)
Myocardial infarction	1 (1.1%)	0	0	0	1 (0.3%)
Gastrointestinal disorders	0	1 (1.0%)	0	0	1 (0.3%)
Abdominal strangulated hernia	0	1 (1.0%)	0	0	1 (0.3%)
Infections and infestations	1 (1.1%)	0	1 (1.0%)	1 (1.1%)	3 (0.8%)
Escherichia urinary tract infection	1 (1.1%)	0	0	0	1 (0.3%)
Urinary tract infection	0	0	1 (1.0%)	0	1 (0.3%)
Urosepsis	0	0	0	1 (1.1%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	0	1 (1.0%)	0	0	1 (0.3%)
Osteoarthritis	0	1 (1.0%)	0	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.0%)	0	0	1 (0.3%)
Non-Hodgkin's lymphoma	0	1 (1.0%)	0	0	1 (0.3%)
Nervous system disorders	0	0	0	1 (1.1%)	1 (0.3%)
Cerebrovascular accident	0	0	0	1 (1.1%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.0%)	0	1 (0.3%)
Chronic obstructive pulmonary disease	0	0	1 (1.0%)	0	1 (0.3%)
Emphysema	0	0	1 (1.0%)	0	1 (0.3%)
Surgical and medical procedures	0	1 (1.0%)	0	1 (1.1%)	2 (0.5%)
Coronary artery bypass	0	1 (1.0%)	0	0	1 (0.3%)
Prostatectomy	0	0	0	1 (1.1%)	1 (0.3%)

REVIEWER'S COMMENTS:

The Sponsor acknowledged that the cardiovascular events reported during the clinical development program only occurred in patients receiving IPX066. The narratives for patients suffering SAEs classified as cardiovascular events (ischemic and arrhythmia) were reviewed and they did not appear to be related to IPX066. The symptoms of cardiovascular AEs were more the patients who received 145 mg (3=3.1%) and 245 mg (1=1.0%). There were no reported cardiovascular AEs among patients who received 390 mg. The sponsor had the [REDACTED] ^{(b) (4)} Committee evaluate these cases (and other cases that were noted in the study IPX066 B09-02, B09-06 adjudicated in a blinded fashion and the committee warned that the “data should be interpreted with caution because of the small size and the modest number of events”. This finding will be again discussed in Section 7.7.

3. Adverse Events Leading to Withdrawal/Discontinuation

Adverse events were the primary reasons for early discontinuation from the Early PD B08-05 Study. Thirty five patients (9%) of patients treated with IPX066 compared to 4 (1%) of patients on placebo discontinued due to an adverse event as presented in the sponsor’s table below (Table 52).

Table 51: Disposition of Subjects in Early PD Study IPX066 B08-05 by Dose Group. (Sponsor's table).

All Treated Subjects	Number of Subjects (%)				
	Placebo (N = 92)	IPX066 LD Dose Group			Total (N = 381)
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)	
Received Study Treatment	92 (100)	87 (100)	104 (100)	98 (100)	381 (100)
Discontinued Study Treatment	21 (22.8)	15 (17.2)	21 (20.2)	24 (24.5)	81 (21.3)
Primary Reasons for Early Discontinuation					
Adverse Event	4 (4.3)	5 (5.7)	15 (14.4)	15 (15.3)	39 (10.2)
Lack of Efficacy	12 (13.0)	4 (4.6)	0	1 (1.0)	17 (4.5)
Withdrawal by Subject	4 (4.3)	3 (3.4)	1 (1.0)	3 (3.1)	11 (2.9)
Protocol Violation	0	1 (1.1)	0	2 (2.0)	3 (0.8)
Noncompliance	0	0	1 (1.0)	1 (1.0)	2 (0.5)
Lost to Follow-Up	0	1 (1.1)	1 (1.0)	0	2 (0.5)
Death	0	0	1 (1.0)	0	1 (0.3)
Other ^a	1 (1.1)	1 (1.1)	2 (1.9)	2 (2.0)	6 (1.6)

^a Six subjects at Site 202 were removed from the study by the Sponsor because the UPDRS ratings performed at this site indicated that the procedures differed significantly from both the Sponsor's expectations of how these ratings were to be performed and how these ratings were performed at other sites participating in the study.

Source: [Table 14.1.1.1](#).

The sponsor's protocol design up-titrated patients from a dose of 95 mg to the treatment doses of 145 mg, 245 mg and 390 mg as shown in the sponsor's table below.

Table 52: Dose Regimen for Titration Period in Study B08-05 (Sponsor's table).

Treatment	Dose Administered 3 Times Daily, on Days				
	1-3	4-7	8-14	15-21	22-28 ^a
IPX066					
145 mg LD	95 mg LD	145 mg LD	145 mg LD	145 mg LD	145 mg LD + Placebo
245 mg LD	95 mg LD	145 mg LD	195 mg LD	245 mg LD	245 mg LD + Placebo
390 mg LD	95 mg LD	145 mg LD	195 mg LD	245 mg LD	195 mg LD + 195 mg LD
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo + Placebo

^a This is the dose to which the subject was randomized and should have received for the remainder of the study. Abbreviations: LD = levodopa.

Discontinuations were evaluated according to whether the adverse event occurred during the titration or maintenance phase to assess drug tolerability and adequacy of proposed titration scheme. In clinical practice, levodopa naive patients develop more nausea and vomiting during the titration but it usually subsides and may resolve with continued use of levodopa.

The table below summarizes the adverse events that led to early discontinuation, according to treatment arm and whether the adverse event occurred during titration or maintenance phase in study IPX066 B08-05 (early PD). There were no patients in the 145 mg group maintenance phase who discontinued early. In this study, there were 13 patients who discontinued due to nausea and vomiting (12 who received drug and one on placebo). More patients titrated to the higher dose of 390 mg TID developed nausea and vomiting compared patients titrated to lower doses (145 mg and 245 mg). What is interesting though is that there were still 3 patients on the higher doses (1 on 245 mg of IPX066 and 2 on 390 mg of IPX066) who continued to have nausea and vomiting during the maintenance phase—when patients are expected to develop more tolerability for the drug. This also suggests that an initial dose of 390 mg may be too high for some patients. Forced titration at a higher dose led to adverse events but it is important to find that out in a clinical trial.

Table 53: Adverse Events that Led to Withdrawal from the Study According to Dose and Treatment Phase Study IPX066-B08-05. (Reviewer's table).b

	Titration			Maintenance			
	IPX066 145 mg (N=87)	IPX066 245 mg (N=104)	IPX066 390 mg (N=98)	IPX066 145 mg (N=87)	IPX066 245 mg (N=104)	IPX066 390 mg (N=98)	PLACEBO N=92
Nausea and Vomiting	3 (3.4%)	1(0.96%)	5 (5.1%)	0	1(0.96%)	2(2.04%)	1(1.0%)
Dizziness	1(1.1%)	3(2.9%)	2(2.04%)	0	0	1(1.02%)	0
Headache	0	1(0.96%)	2(2.04%)	0	0	0	2(2.1%)
Light-headedness	1(1.1%)	0	1(1.02%)	0		1(1.02%)	0
Hallucinations	0	0	0	0	0	2(2.04%)	0
Dyskinesias	0	1(0.96%)	1(1.02%)	0	0	0	0
Worsening Parkinson's disease	0	0	0	0	0	0	2(2.1%)

Eleven (11) subjects (2.9%) withdrew from the study without any explanation for the reason for withdrawal. Four of these subjects received placebo and seven received the treatment drug. We can only suspect that the four subjects in the placebo group may have withdrawn from lack of effect.

REVIEWER'S COMMENTS:

Titration of IPX066 to higher doses leads to more adverse events. Patients who will need higher doses of IPX066 need to be observed closely for adverse events. Longer titration periods (longer than the 3 week titration period in the protocol) should also be considered when a higher dose is anticipated to allow patients to tolerate the increase in levodopa.

Similarly, with the persistence of some of the symptoms into the maintenance phase at higher doses, it may be safer to maintain patients on 245 mg for longer periods to minimize the potential for nausea and vomiting. As noted from the efficacy review, the treatment effect between 245 mg and 390 mg is not statistically significant.

The other AEs that were reported in this study that led to discontinuation are common AEs seen with the other marketed dopaminergic agents (hallucinations, dyskinesias, postural instability and dizziness. As was the case with nausea and vomiting, the appearance of these dopamine related AEs were reported more commonly during the titration period and were non-existent in patients on 145 mg during the maintenance period.

As expected, majority of patients who withdrew from the placebo group was due to worsening Parkinson's disease.

4. Common Adverse Events

a. Nausea and Vomiting

Nausea and Vomiting has been reported as a common adverse event in other levodopa formulations and other dopaminergic drugs. IPX066, as a levodopa formulation, has caused this adverse event. The table below shows the number and percentage of patients who reported at least one gastrointestinal disorder (SOC) adverse event. Nausea and vomiting (highlighted in yellow) was separated into two categories in the sponsor's table below (table 54).

Table 54: Gastrointestinal Disorders in B08-05 (Sponsor's table).

Preferred Term	IPX066 145 mg N=87	IPX066 245 mg N=104	IPX066 390 mg N=98	Placebo N=92	Total N=381
Gastrointestinal disorders	19 (21.8%)	30 (28.8%)	32 (32.7%)	22 (23.9%)	103 (27.0%)
Nausea	12 (13.8%)	20 (19.2%)	20 (20.4%)	8 (8.7%)	60 (15.7%)
Dry mouth	3 (3.4%)	2 (1.9%)	7 (7.1%)	1 (1.1%)	13 (3.4%)
Vomiting	2 (2.3%)	2 (1.9%)	5 (5.1%)	3 (3.3%)	12 (3.1%)
Constipation	2 (2.3%)	6 (5.8%)	2 (2.0%)	1 (1.1%)	11 (2.9%)
Diarrhoea	1 (1.1%)	3 (2.9%)	3 (3.1%)	2 (2.2%)	9 (2.4%)
Abdominal pain upper	0	1 (1.0%)	1 (1.0%)	4 (4.3%)	6 (1.6%)
Abdominal pain	0	2 (1.9%)	1 (1.0%)	1 (1.1%)	4 (1.0%)
Dyspepsia	1 (1.1%)	1 (1.0%)	1 (1.0%)	1 (1.1%)	4 (1.0%)

b. Dyskinesias

Typically, patients with early PD report a lower frequency of dyskinesia compared to patients with advanced PD. There were eleven (11) patients (2.9%) who developed dyskinesias. All of these patients received IPX066. As expected, the total number of patients reporting dyskinesia among patients with early PD was small although this still demonstrated a relationship to dose.

c. Tabulation of Common Adverse Events in Study B08-05

The sponsor's table below summarizes common adverse events occurring in at least 5% of subjects who received placebo and in the different IPX066 treatment groups.

Table 55: Summary of Adverse Events Occurring in at Least 5% of Subjects in Any Treatment Group in Study B08-05 (Sponsor's table).

Adverse Event Preferred Term	Number of Subjects (%)				
	Placebo (N = 92)	IPX066 LD Dose Group			Total (N = 381)
		145 mg (N = 87)	245 mg (N = 104)	390 mg (N = 98)	
Nausea	8 (8.7)	12 (13.8)	20 (19.2)	20 (20.4)	60 (15.7)
Headache	10 (10.9)	6 (6.9)	13 (12.5)	17 (17.3)	46 (12.1)
Dizziness	5 (5.4)	8 (9.2)	20 (19.2)	12 (12.2)	45 (11.8)
Insomnia	3 (3.3)	2 (2.3)	9 (8.7)	6 (6.1)	20 (5.2)
Abnormal Dreams	0	2 (2.3)	6 (5.8)	5 (5.1)	13 (3.4)
Dry Mouth	1 (1.1)	3 (3.4)	2 (1.9)	7 (7.1)	13 (3.4)
Vomiting	3 (3.3)	2 (2.3)	2 (1.9)	5 (5.1)	12 (3.1)
Constipation	1 (1.1)	2 (2.3)	6 (5.8)	2 (2.0)	11 (2.9)
Dyskinesia	0	2 (2.3)	4 (3.8)	5 (5.1)	11 (2.9)
Anxiety	0	2 (2.3)	3 (2.9)	5 (5.1)	10 (2.6)
Depression	5 (5.4)	1 (1.1)	2 (1.9)	2 (2.0)	10 (2.6)
Orthostatic Hypotension	1 (1.1)	1 (1.1)	1 (1.0)	5 (5.1)	8 (2.1)

Table 56: Most frequent AEs in Study B08-05 (Early PD) in at least 2% of Patients Classified by Treatment Phase and Dose (Reviewer's table)

Preferred Terms	Titration Phase				Maintenance Phase			
	IPX066			Placebo	IPX066			Placebo
	145 mg N=49	245 mg N=75	390 mg N=70	N=67	145 mg N=49	245 mg N=75	390 mg N=70	N=67
# of patients with at least 1 AE	13	29	18	11	36	46	52	56
Nausea and vomiting	12	18	18	7	0	7	8	4
Headache	5	9	12	6	1	5	6	5
Dizziness	7	12	8	3	3	7	3	1
Insomnia	3	5	5	3	3	5	3	2
Daytime Sleepiness	2	2	3	2	1	4	0	0
Abnormal Dreams	2	4	2	0	1	2	2	0
Dry Mouth	3	2	6	0	0	0	2	0
Orthostatic blood pressure changes	1	0	3	1	1	1	4	1
Constipation	1	5	1	0	1	2	1	1
Dyskinesia	1	0	3	0	2	3	1	0
Anxiety	2	1	1	0	0	2	3	0
Depression	1	1	0	1	0	1	2	4
Hallucinations	0	3	0	0	0	2	2	0

REVIEWER’S COMMENTS:

- *By regrouping preferred terms and combining nausea and vomiting and terms that suggest orthostatic hypotension (“dizziness when stands”, “intermittent orthostasis”, “postural dizziness”), the number of reported cases of nausea/vomiting and orthostatic hypotension increased but only modestly. An analysis of the persistence of these AE terms over time suggest nausea and vomiting decrease substantially from the titration to the maintenance phase but persistent use of IPX066 has little effect on the frequency of orthostatic hypotension (see Table 57 above).*

4. Adverse Events of Special Interest in Parkinson’s Disease

These adverse events of special interest were from the placebo-controlled study, IPX066 B08-05 only. This study was conducted in patients who were not exposed to LD or COMT inhibitors for more than 30 days and the exposure was not within 4 weeks prior to study enrollment.

a. Hallucinations

In the early PD study, there were 7 patients on IPX066 (5 subjects in the 245 mg IPX066 group and 2 subjects in the 390 mg IPX066 group), none on placebo, who were reported as having hallucinations. Preferred terms that might suggest “hallucinations” like “illusion” or “psychosis” were searched but there were no reports of these cases. A separate analysis of reports of hallucinations will be discussed in the Advanced PD Study IPX066-B09-02 safety review.

b. Impulse Control Behavior Disorders

A search of AE Preferred terms for gambling, hypersexuality, binge eating-- that may refer to loss of impulse control, was done.

c. Sleep Disorders

The sponsor classified sleep disorders under 2 main system disorders: “Nervous System Disorders”, “Psychiatric Disorders” (Table 58). Preferred terminologies for “sleepiness”, “hypersomnolence” and “drowsiness” were searched and are indicated by the red arrow. Most of these were found under “sleep disorders” which was not very informative. There were 14 (3.7%) cases of somnolence/hypersomnia more in the treatment group (12 cases) than in the Placebo group (2 cases) but this did not seem to follow a dose response pattern nor were there any severe cases that were reported.

Table 57: Frequency Distribution by Treatment Arm of Preferred Terms for Sleep (Sponsor’s table).

Clinical Review

Anne E. A. Constantino, MD

NDA 203312

Rytary/IPX066/Carbidopa-Levodopa Extended Release

System Organ Class Preferred Term	IPX066 145 mg (N=87)	IPX066 245 mg (N=104)	IPX066 390 mg (N=98)	Placebo (N=92)	Total (N=381)
Psychiatric disorders	11 (12.6%)	23 (22.1%)	22 (22.4%)	11 (12.0%)	67 (17.6%)
Insomnia	2 (2.3%)	9 (8.7%)	6 (6.1%)	3 (3.3%)	20 (5.2%)
Abnormal dreams	2 (2.3%)	6 (5.8%)	5 (5.1%)	0	13 (3.4%)
Anxiety	2 (2.3%)	3 (2.9%)	5 (5.1%)	0	10 (2.6%)
Depression	1 (1.1%)	2 (1.9%)	2 (2.0%)	5 (5.4%)	10 (2.6%)
Sleep disorder	2 (2.3%)	2 (1.9%)	2 (2.0%)	0	6 (1.6%)
Initial insomnia	1 (1.1%)	1 (1.0%)	1 (1.0%)	2 (2.2%)	5 (1.3%)
Hallucination	0	3 (2.9%)	1 (1.0%)	0	4 (1.0%)
Hallucination, visual	0	2 (1.9%)	1 (1.0%)	0	3 (0.8%)
Nightmare	1 (1.1%)	0	1 (1.0%)	0	2 (0.5%)
Rapid eye movements sleep abnormal	0	1 (1.0%)	1 (1.0%)	0	2 (0.5%)
Psychiatric disorders (Continued)					
Restlessness	1 (1.1%)	0	1 (1.0%)	0	2 (0.5%)
Bradyphrenia	1 (1.1%)	0	0	0	1 (0.3%)
Bruxism	0	0	0	1 (1.1%)	1 (0.3%)
Confusional state	0	1 (1.0%)	0	0	1 (0.3%)
Nervousness	0	0	0	1 (1.1%)	1 (0.3%)
Panic reaction	0	1 (1.0%)	0	0	1 (0.3%)
Sleep talking	1 (1.1%)	0	0	0	1 (0.3%)
Somnambulism	1 (1.1%)	0	0	0	1 (0.3%)
Nervous system disorders	23 (26.4%)	41 (39.4%)	37 (37.8%)	28 (30.4%)	129 (33.9%)
Headache	6 (6.9%)	13 (12.5%)	17 (17.3%)	10 (10.9%)	46 (12.1%)
Dizziness	8 (9.2%)	20 (19.2%)	12 (12.2%)	5 (5.4%)	45 (11.8%)
Somnolence	3 (3.4%)	5 (4.8%)	3 (3.1%)	2 (2.2%)	13 (3.4%)
Dyskinesia	2 (2.3%)	4 (3.8%)	5 (5.1%)	0	11 (2.9%)
Parkinson's disease	1 (1.1%)	1 (1.0%)	1 (1.0%)	4 (4.3%)	7 (1.8%)
Restless legs syndrome	2 (2.3%)	3 (2.9%)	1 (1.0%)	0	6 (1.6%)
On and off phenomenon	0	3 (2.9%)	2 (2.0%)	0	5 (1.3%)
Tremor	4 (4.6%)	0	0	1 (1.1%)	5 (1.3%)
Dizziness postural	1 (1.1%)	0	2 (2.0%)	1 (1.1%)	4 (1.0%)
Balance disorder	0	1 (1.0%)	0	1 (1.1%)	2 (0.5%)
Carpal tunnel syndrome	0	1 (1.0%)	0	1 (1.1%)	2 (0.5%)
Dysgeusia	0	2 (1.9%)	0	0	2 (0.5%)
Nervous system disorders (Continued)					
Dystonia	0	1 (1.0%)	0	1 (1.1%)	2 (0.5%)
Hypoaesthesia	0	1 (1.0%)	1 (1.0%)	0	2 (0.5%)
Myoclonus	0	1 (1.0%)	1 (1.0%)	0	2 (0.5%)
Paraesthesia	0	1 (1.0%)	1 (1.0%)	0	2 (0.5%)
Poor quality sleep	1 (1.1%)	0	0	1 (1.1%)	2 (0.5%)
Amnesia	0	0	0	1 (1.1%)	1 (0.3%)
Bradykinesia	0	0	1 (1.0%)	0	1 (0.3%)
Carotid artery stenosis	0	0	0	1 (1.1%)	1 (0.3%)
Cerebrovascular accident	0	0	0	1 (1.1%)	1 (0.3%)
Coordination abnormal	0	0	1 (1.0%)	0	1 (0.3%)
Decreased vibratory sense	0	0	0	1 (1.1%)	1 (0.3%)
Disturbance in attention	0	0	1 (1.0%)	0	1 (0.3%)
Hypersomnia	0	1 (1.0%)	0	0	1 (0.3%)
Hypotonia	0	1 (1.0%)	0	0	1 (0.3%)
Intercostal neuralgia	0	0	1 (1.0%)	0	1 (0.3%)
Migraine	0	0	0	1 (1.1%)	1 (0.3%)

d. Orthostatic Hypotension

Orthostatic hypotension occurred in 8 (2.1%) of patients in the placebo-controlled study in the sponsor's table 59. The sponsor's table classified Orthostatic hypotension under SOC Vascular Disorders.

Table 58: Frequency Distribution by Treatment Arm of Vascular Orders Preferred Term (Sponsor's table).

System Organ Class Preferred Term	IPX066 145 mg (N=87)	IPX066 245 mg (N=104)	IPX066 390 mg (N=98)	Placebo (N=92)	Total (N=381)
Vascular disorders	4 (4.6%)	6 (5.8%)	6 (6.1%)	3 (3.3%)	19 (5.0%)
Orthostatic hypotension	1 (1.1%)	1 (1.0%)	5 (5.1%)	1 (1.1%)	8 (2.1%)
Hypertension	2 (2.3%)	3 (2.9%)	0	0	5 (1.3%)
Hot flush	1 (1.1%)	1 (1.0%)	0	0	2 (0.5%)
Hyperaemia	0	0	1 (1.0%)	0	1 (0.3%)

Additional verbatim and preferred terms that may represent orthostatic hypotension were searched. The results of the search are tabulated in Table 60 below. Table 60 contains the results of this reviewer's search for additional verbatim and preferred terms that are likely to represent symptomatic orthostatic hypotension. The table shows that orthostatic hypotension has been coded under different AEDECOD (dizziness postural and orthostatic hypotension) and AEBODYSYS (Nervous system disorders, vascular disorders).

Table 59: Preferred Terms Searched That May Correspond to Orthostatic Hypotension (Reviewer's table created with JMP from sponsor's dataset).

AETERM	AEDECOD	AEBODYSYS
INTERMITTENT ORTHOSTASIS CONFIRM ORTHOSTASIS REFERENCE DUE TO SUBJECTIVE DIZZINESS UPON STANDING	Dizziness postural	Nervous system disorders
ORTHOSTATIC HYPOTENSION	Orthostatic hypotension	Vascular disorders
DIZZINESS WHEN STANDS	Dizziness postural	Nervous system disorders
INCREASE ORTHOSTATIC HYPOTENSION	Orthostatic hypotension	Vascular disorders
ASYMPTOMATIC ORTHOSTATIC HYPOTENSION	Orthostatic hypotension	Vascular disorders
ASYMPTOMATIC ORTHOSTATIC HYPOTENSION	Orthostatic hypotension	Vascular disorders
POSTURAL DIZZINESS	Dizziness postural	Nervous system disorders
ORTHOSTATIC HYPOTENSION	Orthostatic hypotension	Vascular disorders

Reanalysis of the cases of orthostasis which included the preferred terms and verbatim terms in the table above increased the frequency of cases of orthostasis from the sponsor's 8 to a re-analyzed result of 12 cases as shown in the table below. These cases were more frequent in the patients who had received 390 mg suggesting a dose response attributable to drug.

Table 60: Frequency of Orthostatic Hypotension During Maintenance and Titration Phase in IPX066 Treatment and Placebo Groups, Study B08-05 (Reviewer's table).

	Titration Phase				Maintenance Phase				Total
	IPX066			PBO	IPX066			PBO	
Preferred Term	145 mg N=49	245 mg N=75	390 mg N=70	N=67	145 mg N=49	245 mg N=75	390 mg N=70	N=67	381
Orthostatic blood pressure changes	1	0	3	1	1	1	4	1	12 (3.1)

PBO = Placebo

e. Falls

This is a special event not only because of the vulnerability of patients with PD to falls due to disease (balance and coordination problems) but also because of lack of drug effect (freezing and off periods). There were no cases of falls in the early PD study.

STUDY B09-02: ADVANCED PD STUDY

The study design of IPX066 B09-02 begins with a one week IR adjustment phase followed by a 3 week dose conversion phase. The table below shows the frequencies of serious adverse events, treatment related SAEs and Early Termination due to AEs during the 6 week conversion period.

Table 61: Adverse Events During Dose Conversion Phase (Sponsor's table).

Adverse Events	AEs Starting during IPX066 Dose Conversion (n = 450)
	Number of Subjects (%)
Any AE	206 (45.8%)
Treatment-related AEs	148 (32.9%)
Deaths	2 (0.4%)
Serious AEs	
-- Any SAE	14 (3.1%)
-- Treatment-related SAE	4 (0.9%)
Early Termination due to AEs	23 (5.1%)

Abbreviations: AE = adverse event; IR CD-LD = immediate release carbidopa-levodopa.
 Source: Tables 14.3.1.1-1, 14.3.1.1-2, 14.3.1.1-4, 14.3.1.2-1, 14.3.1.2-2, 16.2.7.3.

REVIEWER'S COMMENTS:

The information in the conversion phase of this study is important because the patients were converted from a stable dose of IR to a dose of IPX066 using the conversion scheme that the sponsor had proposed. This conversion scheme attempted to convert patients to what would have been a comparable dose of IR. The AEs that are seen in the conversion phase confirm the limitations of the conversion scheme (discussed earlier in the efficacy portion of the study)—mainly, that patients were exposed to relatively higher doses of levodopa and that IPX066 dose has to be adjusted.

A 13-week double blind maintenance phase follows the conversion phase. Patients are randomized to either IPX066 or IR during the Maintenance Phase. Table 64 is a summary of the adverse events during the Maintenance Period.

Table 62: Overall Summary of Adverse Events During the Maintenance Period in All Randomized Subjects, B09-02 (Sponsor's table)

Adverse Events	Number of Subjects (%)	
	AEs Starting During Maintenance (All Randomized Subjects)	
	IPX066 (n = 201)	IR CD-LD (n = 192)
Any AE	87 (43.3%)	76 (39.6%)
Treatment-related AEs	46 (22.9%)	39 (20.3%)
Deaths	0	0
Serious AEs		
-- Any SAE	11 (5.5%)	5 (2.6%)
-- Treatment-related SAE	1 (0.5%)	1 (0.5%)
Early Termination due to AEs (by Termination Period)	3 (1.5%)	3 (1.5%)

1. NON FATAL SERIOUS ADVERSE EVENTS

The table below summarizes the **serious adverse events** that were reported during the conversion phase that are related to levodopa. The adverse events related to levodopa were more frequent during the six week dose conversion period than the 13 week maintenance period.

Table 63: SAEs During the Different Treatment Periods That Are Likely Related to Drug in Advanced PD Patients, Study B09-02 (Reviewer's table).

System Organ Class Preferred Term	Six week Dose Conversion (from CDLD to IPX066) (N=450)	Double Blind Maintenance	
		IPX066 (N=201)	IR CDLD (N=192)
Nausea and Vomiting	2 (0.2%) (405-001)		
Acute Psychosis	1 (0.2%) 804-008	1 (0.5%) 606-005	
Anxiety	1 (0.2%) 139-003	1 (0.5%) 606-005	
Dyskinesia	2 (0.4%) 166-003 804-008		
PreSyncope	1 (0.2%) 175-010		

The sponsors conclude that cases of dyskinesia and acute psychosis during the conversion period are related to IPX066.

Other AEs that led to discontinuation during the maintenance phase are discussed below. Most of these cases occurred in the open label conversion period and in two cases, the patients were converted to higher doses of IPX066 compared to their IR CD-LD dose.

One patient who developed psychosis during the six-week dose conversion period received 2940 mg of IPX066 but was initially on a dose of 1800 mg IR by the end of the IR dose adjustment phase. Although the converted IPX066 dose was within the 30% increase needed when converting IPX066 from IR CD-LD, the case illustrated the need for monitoring following dose conversion.

Similarly, dyskinesias were reported in 2 subjects during the conversion period. The first subject received 1300 mg IR for 21 days with mild dyskinesias 26-50% of the day; on day 22, the patient took 4 capsules of 195 mg IPX066 three times a day and experienced severe dyskinesias in her left arm and jaw with biting her tongue and cheeks and difficulty talking. IPX066 was decreased to 2040 mg.

Subject 804-008 received 1800 mg IR for 21 days and was instructed to take 2340 mg of IPX066 at the dose conversion phase but mistakenly took 195 mg 12 caps

5x a day but went back to the originally prescribed dosage of 3 caps 4x a day. On day 25, the patient developed hyperactivity, hallucinations, sleep disturbance and dyskinesias. The psychotic episode and dyskinesias resolved on day 26. Although this latter AE report was clearly drug related but it was not due to the prescribed dose but patient's misunderstanding of the amount of drug that he should take which led to overdosing.

2. ADVERSE EVENTS LEADING TO DISCONTINUATION/WITHDRAWAL

During the 6-week Dose Conversion period, 14 subjects (3.1%) reported 22 SAEs including the two deaths. The sponsor's table (Table 65 below) showed only 20 SAEs because 2 subjects had more than one event during dose conversion—2 events of dyskinesia which occurred 1 month apart occurred in 1 patient and two consecutive events which were considered as “overdose” in another subject.

Table 64: Summary of Serious Treatment Emergent AEs Starting During IPX066 Dose Conversion Classified by System Organ Class and Preferred Term, Study B09-02 (Sponsor's table).

System Organ Class Preferred Term	Number of Subjects (%) Subject ID Number
	SAEs Reported during IPX066 Dose Conversion (n = 450)
At least 1 SAE	14 (3.1%)
Gastrointestinal Disorders	
Constipation	1 (0.2%) 170-011
Gastric Ulcer	1 (0.2%) 405-004
Nausea	1 (0.2%) 405-001
Vomiting	1 (0.2%) 405-001
General Disorders and Administration Site Conditions	
Gait Disturbance	2 (0.4%) 127-010 ^a 405-001 ^{a,b}
Non-cardiac Chest Pain	2 (0.4%) 101-005 606-015
Sudden Death	1 (0.2%) 175-008 ^c
Hepatobiliary Disorders	
Cholecystitis	1 (0.2%) 128-008 ^b
Infections and Infestations	
Sepsis	1 (0.2%) 128-008 ^b
Injury, Poisoning and Procedural Complications	
Overdose	1 (0.2%) 804-008 ^{a,d}

System Organ Class Preferred Term	Number of Subjects (%) Subject ID Number
	SAEs Reported during IPX066 Dose Conversion (n = 450)
Nervous System Disorders	
Dyskinesia	2 (0.4%) 166-003 ^{a,b,e} 804-008 ^a
Presyncope	1 (0.2%) 175-010
Psychiatric Disorders	
Acute Psychosis	1 (0.2%) 804-008 ^a
Anxiety	1 (0.2%) 139-003 ^b
Renal and Urinary Disorders	
Nephrolithiasis	1 (0.2%) 150-001
Renal Failure	1 (0.2%) 808-004 ^c
Respiratory, Thoracic and Mediastinal Disorders	
Pulmonary Embolism	1 (0.2%) 405-004

^a SAE was related to study treatment (unlikely, probably, or related) per Investigator.

^b Subject terminated early due to SAE.

^c SAE was fatal.

^d Two consecutive adverse event entries (representing a single clinical episode) were mapped to the preferred term "overdose" for subject 804-008.

^e Two events of dyskinesia were reported during Dose Conversion for subject 166-003.

Abbreviations: SAE = serious adverse event.

The table below lists the adverse events that led to early termination during the conversion phase.

Table 65: Adverse Events Leading to Early Termination During the Conversion Phase, B09-02 (Reviewer's table).

Preferred Term	Number of Subjects N=450 (%)
Nausea and Vomiting	3 (0.6)
Dyskinesia	5 (1.1)
Somnolence	1 (0.2)
Hallucinations	3 (0.6)

The reported serious adverse events and those leading to discontinuation are similar those reported in other approved dopaminergic drugs.

The reasons given for patients that discontinued prematurely during the maintenance phase are similar to the reasons for early discontinuation during the conversion phase, as shown below in Table 67.

Table 66: Summary of Treatment-emergent AEs Leading to Early Termination from Maintenance in Study 09-02, by System Organ Class and Preferred Term (Sponsor's table).

System Organ Class Preferred Term	Number of Subjects (%) Subject ID Number	
	Maintenance Period (All Randomized Subjects)	
	IPX066 (n = 201)	IR CD-LD (n = 192)
Early Termination due to any Adverse Event	3 (1.5%)	3 (1.5%)
Early Termination due to Non-serious Adverse Events	2 (1.0%)	2 (1.0%)
Early Termination due to Serious Adverse Events	1 (0.5%)	1 (0.5%)
Gastrointestinal Disorders		
Dyspepsia	0	1 (0.2%) 302-001 ^a
Nausea	1 (0.5%) 205-003 ^b	0
Injury, Poisoning and Procedural Complications		
Subdural Haematoma	0	1 (0.5%) 114-003 ^c
Psychiatric Disorders		
Acute Psychosis	1 (0.5%) 606-005 ^c	0
Anxiety	1 (0.5%) 127-006 ^d	0
Delusion	0	1 (0.5%) 603-001
Obsessive-Compulsive Disorder	1 (0.5%) 127-006	0

^a AE of dyspepsia for subject 302-001 started during Dose Adjustment but subject discontinued during Maintenance.

^b AE of nausea for subject 205-003 started during Dose Conversion but subject discontinued during Maintenance.

^c Serious adverse event.

^d AE of anxiety for subject 127-006 started during Dose Conversion but subject discontinued during Maintenance.

Abbreviations: IR CD-LD = immediate release carbidopa-levodopa

The frequency of patients who terminated early from the study due to any AE were the same for the IPX066 and IR treatment groups.

Narrative Summaries of Patients Who Discontinued Prematurely in Study IPX066 B09-02

- Subject 606-005 in the IPX066 group developed psychosis during this treatment period. The patient received 1000 mg IR at the end of the dose adjustment phase, 1755 mg IPX066 at the end of the dose conversion phase and during the double blind randomization. The patient started developing visual hallucinations and anxiety on day 146. Study treatment drug was withdrawn on day 147 and on day 150, the patient's condition

improved. The narrative mentioned that the subject “continued to respond to the gradual reduction of psychotic disorder medication and increased doses of Parkinson disease medication, obtaining improvement of motor efficiency” but the narrative was unclear whether the patient was maintained on IPX066.

- Subject 127-006 was another early termination. This 64-year-old male received 1400 mg of IR during the dose adjustment and 2730 mg IPX066 at dose conversion and during the double blind randomization. On day 56, the patient experienced anxiety and on day 67 (double blind randomization), he experienced a gambling compulsion. The subject also had developed “occasional dizziness upon standing” on day 29.

REVIEWER’S COMMENTS:

The AEs leading to early termination for IR and IPX066 were similar for the two groups and they were also similar to adverse events that are reported with other dopaminergic agents.

3. COMMON ADVERSE EVENTS

The common adverse events are presented separately for the conversion phase and for the maintenance phase. The similarities and differences in the adverse events that may be seen during these two phases can be attributed mainly to the difference in the duration of the treatment phases. The conversion phase is similar to the titration phase in the Early PD study where IPX066 is optimized to an effective dose. It is also the “open label” portion of the study and any adverse event that occurs here cannot be directly compared to adverse events that occur with other levodopa preparations.

The maintenance phase however will allow comparison of adverse events and since this is the longer period of the study, patients would have been “stabilized” and optimized on their doses of IPX066.

Table 68 is the sponsor’s table of treatment emergent adverse events during the conversion phase.

Table 67: Treatment Emergent Adverse Events by Preferred Term in the Dose Conversion Phase of IPX066 Study B09-02 (Sponsor's table).

Adverse Event Preferred Term	Number of Subjects (%)
	Adverse Events during IPX066 Dose Conversion (N = 450)
At least 1 AE	206 (45.8%)
Dyskinesia	25 (5.6%)
Nausea	24 (5.3%)
Headache	19 (4.2%)
Dizziness	17 (3.8%)
On and Off Phenomenon	14 (3.1%)
Fall	12 (2.7%)
Dry Mouth	11 (2.4%)
Anxiety	11 (2.4%)
Insomnia	11 (2.4%)
Constipation	9 (2.0%)
Back Pain	8 (1.8%)
Hallucination	8 (1.8%)
Vomiting	7 (1.6%)
Abdominal Pain Upper	6 (1.3%)
Tremor	6 (1.3%)
Oedema Peripheral	5 (1.1%)
Upper Respiratory Tract Infection	5 (1.1%)
Balance Disorder	5 (1.1%)
Somnolence	5 (1.1%)
Depression	5 (1.1%)

REVIEWER'S COMMENTS:

The appearance of adverse events such as nausea, vomiting, hallucinations, and dyskinesias suggests that the conversion scheme results in a higher dose of levodopa than their optimized IR dose .

Table 69 is the reviewer's summary table of treatment of emergent adverse events during the conversion phase. In this table, reports of nausea and vomiting were combined. The table below shows the results for combined terms for nausea and vomiting, orthostasis and dyskinesias.

Table 69. Summary of Treatment Emergent Adverse Events During Conversion Phase-Combination of Preferred Terms (Reviewer's table).

Adverse Event Preferred Term	Number of Subjects (%)
	Adverse Events During IPX066 Dose Conversion (N-450)
Dyskinesias	40 (8.8%)
Nausea and Vomiting	36 (8.0%)
Orthostatic Hypotension, Postural Dizziness	26 (5.8%)

Table 70: Adverse Events Reported by at least 1% of subjects in IPX066 or IR CD-LD treatment during Maintenance Phase, Study B09-02 (Sponsor's table).Table

Adverse Event Preferred Term	Number of Subjects (%)	
	Adverse Events during Maintenance	
	IPX066 (N = 201)	IR CD-LD (N = 192)
At least 1 AE	87 (43.3%)	76 (39.6%)
Insomnia	7 (3.5%)	2 (1.0%)
Nausea	6 (3.0%)	3 (1.6%)
Fall	6 (3.0%)	4 (2.1%)
Dizziness	5 (2.5%)	2 (1.0%)
Dyskinesia	5 (2.5%)	2 (1.0%)
Diarrhoea	4 (2.0%)	1 (0.5%)
Oedema Peripheral	4 (2.0%)	4 (2.1%)
Upper Respiratory Tract Infection	4 (2.0%)	4 (2.1%)
Urinary Tract Infection	4 (2.0%)	4 (2.1%)
Sleep Disorder	4 (2.0%)	4 (2.1%)
Weight Decreased	4 (2.0%)	0
Bronchitis	3 (1.5%)	2 (1.0%)
Back Pain	3 (1.5%)	4 (2.1%)
Constipation	2 (1.0%)	2 (1.0%)
Arthralgia	2 (1.0%)	4 (2.1%)
Headache	2 (1.0%)	3 (1.6%)
On and Off Phenomenon	2 (1.0%)	2 (1.0%)
Anxiety	2 (1.0%)	3 (1.6%)
Orthostatic Hypotension	2 (1.0%)	2 (1.0%)
Vomiting	1 (0.5%)	4 (2.1%)
Nasopharyngitis	1 (0.5%)	3 (1.6%)
Muscle Spasms	1 (0.5%)	3 (1.6%)
Depression	1 (0.5%)	5 (2.6%)
Gait Disturbance	0	3 (1.6%)
Rash	0	3 (1.6%)
Arthropod Bite	0	2 (1.0%)
Skin Laceration	0	2 (1.0%)

REVIEWER'S COMMENTS:

Nausea was more frequent among patients on the study drug, compared to IR. Combining nausea and vomiting increased the number of cases for IPX066 (9=4.5%) and for IR CD_LD (7=3.6%). There were no unusual AEs that were not already noted with the other levodopa nor dopaminergic agents although for patients previously exposed to levodopa, the frequency of AEs more commonly experienced by levodopa naïve patients (nausea, dizziness), persisted into the maintenance phase on patients who had levodopa treatment.

There were 393 patients who entered the Maintenance Phase of the study which is a decrease of 57 patients from the 450 subjects who entered the conversion phase. 23 (5.1%) withdrew because of adverse events. 13 patients withdrew due to lack of efficacy (2.9%) and another 12 patients (2.7%) withdrew and the reasons for withdrawal were not mentioned in the protocol.

4. ADVERSE EVENTS OF SPECIAL INTEREST in Study IPX066 B09-02: Advanced PD Patients

The following AEs have been reported in the Advanced PD Patients.

a. Hallucinations

There were 8 (1.8%) cases of hallucinations reported during the conversion phase. In the maintenance phase, the sponsor did not report any cases of hallucinations. In my review of the sponsor's datasets, I was able to identify 5 cases (1.7%).

b. Impulse Control Behavior Disorders

The m-MIDI was administered in the advanced PD patients. Four cases of Impulse Control Disorder (ICD) were identified in the IPX066 group compared to 0 in the IR group.

Compulsive gambling behavior was reported in one patient during the dose conversion phase. Although the mMIDI was negative at screening, the woman reported a history of compulsive gambling, anxiety and depression 6 years prior to entry into the study. During the Maintenance Phase, 3 additional cases of impulse control disorders were reported in patients who were only on IPX.

c. Sleep Disorders

Insomnia was more common in the IPX066 group (7=3.5%) than in the IR group (2=1.0%). "Sleep Disorders" were also reported with an equal frequency in both treatment groups but there were no specific terminologies to identify the nature of the sleep disorder. On further review of the AEs, there was one patient who

complained of somnolence and withdrew from the study. There were no cases of sleep attacks or hypersomnias identified in the Maintenance Phase of the advanced PD study. Somnolence usually occurs in patients who report sleep attacks.

d. Orthostatic Hypotension

The preferred terms that suggest orthostatic hypotension were combined as was done in the early PD review. Nine (4.5%) patients on IPX066 and 2 (1.0%) of IR complained of orthostasis or postural dizziness in the Maintenance part of the study.

e. Falls

Falls were frequent in both comparator groups in Advanced PD patients. Although falls has been one of the more frequently reported AEs in the Advanced PD population, it cannot be solely attributed to the treatment drug.

REVIEWER'S COMMENTS:

The AEs of special interest seen in study B09-02 conducted in advanced PD patients are similar in the early PD patients.

5. DOSE AND CONVERSION

The adverse event information for study B09-02 did not report the dose when the particular adverse event occurred. We asked the sponsor to resubmit their AE data with the corresponding dose range of IPX066, IR CD-LD (or CLE) dose range based on their conversion table providing shell tables as to how data should be presented. This would provide some insight into the comparison of adverse event rates in the flexible dose design trial.

The following table lists the most common adverse events in levodopa treatment (nausea/vomiting and dyskinesias). The first column lists the adverse events (presented by preferred term) that were reported by patients who were exposed to the comparator IR CD-LD or IPX066 during the Maintenance Phase. The rows (purple) are the doses of IR that the subject received when the AE occurred. The corresponding IR doses are highlighted in the green row. For example, for the preferred term "nausea and vomiting", 1 patient received 400 to 550 mg IR and 1 patient received 855-1140 mg of IPX066. The 400 to 550 mg dose of IR corresponds to 855 mg to 1140 mg of IPX066. The 551 mg-750 mg of IR corresponds to 1141 mg to 1305 mg of IPX066 and so forth. The IPX066 doses were computed using the sponsor's conversion table.

Table 68: Comparison of Frequency of Adverse Events Related to IR CD-LD or IPX066 by Dose Following the Conversion Table Proposed in Study B09-02 (Reviewer's table).

COMPARATOR: IR CD-LD							
Preferred Term	400 mg to 550 mg (N=88)	551 mg - 750 mg (N=70)	751 mg - 950 mg (N=55)	951 mg - 1250 mg (N=42)	1251 mg - 1650 mg (N=22)	>1650 mg (N=3)	Any dose IR CD-LD (N=280)
Nausea and Vomiting	1 (1.1%)	2 (2.9%)	2 (3.7%)	2 (4.8%)	0	0	7 (2.5%)
Dyskinesia	1 (1.1%)	0	2 (3.6%)	0	0	0	3 (1.1%)
Hallucination	0	2 (2.9%)	0	0	0	0	2 (0.7%)
ICBD	0	0	0	0	0	0	0
STUDY DRUG: IPX066							
Preferred Term	855 mg - 1140 mg (N=79)	1141 mg - 1305 mg (N=40)	1306 mg - 1755 mg (N=80)	1756 mg - 2340 mg (N=50)	2341 mg - 2940 mg (N=21)	>2940 mg (N=15)	Any dose PX066 (N=290)
Nausea and Vomiting	1 (1.3%)	3 (7.%)	1 (1.3%)	3 (6.0%)	1 (4.8%)	0	9 (3.1%)
Dyskinesia	0	1 (2.5%)	3 (3.8%)	1 (2.0%)	3 (14.3%)	1 (6.7%)	9 (3.1%)
Hallucination	1 (1.3%)	0	4 (5.0%)	0	0	0	5 (1.7%)
ICBD	0	0	1 (1.3%)	1 (2.0%)	1 (4.8%)	1 (6.7%)	4 (1.4%)

REVIEWER'S COMMENTS:

On an expected comparable dose of IR, the adverse events that are commonly reported (the highlighted frequencies and percentages are > 2%) with use of dopaminergic drugs are higher in the IPX066 exposed group suggesting that the conversion scheme proposed had exposed the IPX066 group to higher doses of levodopa.

STUDY B09-06 ADVANCED PD

IPX066 B09-06 is a phase 3 randomized, double blind, double dummy, two treatment, two period crossover study in which the double blind crossover portion included two two- week treatment periods separated by a one week washout period of IPX066 treatment. Upon entry into the study, subjects were to be converted from stable doses of CLE (Carbidopa-Levodopa-Entacapone) to open- label IPX066 over a 6- week period. Following dose conversion the patients were to be randomized into a 1:1 ratio to one of two treatment sequencies and treated with either IPX066 or CLE under double blind conditions for 2 weeks. -The conversion scheme shown in the table below is different from the conversion table that was proposed in IPX066-B09-02

Table 69: Dose Conversion Scheme of CLE to IPX066 in Study B09-06 in Patients with Advanced PD (Sponsor's table).

Total Daily LD Dose (mg)	Suggested Initial IPX066 Dose (LD in mg) ^a		
	Morning Dose	Midday Dose	Evening Dose
(b) (4)	4 capsules x 95	4 capsules x 95	4 capsules x 95
(b) (4)	2 capsules x 245	2 capsules x 245	2 capsules x 245
(b) (4)	3 capsules x 195	3 capsules x 195	3 capsules x 195
(b) (4)	3 capsules x 245	3 capsules x 245	3 capsules x 245
(b) (4)	4 capsules x 245	4 capsules x 245	4 capsules x 245

Abbreviations: LD=levodopa; CLE=carbidopa/levodopa/entacapone

^aEach dose approximately 6 hours apart during waking hours

Source: [Appendix 16.1.1, section 7.6](#).

1. Summary table of frequencies of adverse events

The table below provides an overall summary of the treatment emergent adverse events defined as AEs that started after the first dose of study treatment was administered until 72 hours after the last dose of the study was administered in Advanced PD Study B09-06. All these tables are from the sponsor's report.

Table 72 included the treatment emergent adverse events during dose conversion for 6 weeks.

Table 70: Overall Summary of TEAEs in Enrolled Subjects in the IPX066 Dose Conversion Period in Study B09-06 (Sponsor's table).

Adverse Events	Number of Subjects (%) with AEs Starting during IPX066 Dose Conversion (N = 110)
Any AE	34 (30.9%)
Treatment-related AEs	18 (16.36%)
Deaths	0 (0%)
Serious AEs	
-- Any SAE	2 (1.8%)
-- Treatment-related SAE	0
Early Termination due to AEs	1 (0.9%)

Ninety-one patients entered the randomized crossover study. Table 73 provides a summary of all AEs that started during this portion of the study.

Table 71: Overall Summary of TEAEs during Randomized Cross Over Period in Study B09-06 (Sponsor's table)Table

Adverse Events	Percent of Subjects with AEs Starting During Crossover (All Randomized Subjects)		
	Double-Blind IPX066 (N = 89)	Double-Blind CLE (N = 88)	Open-Label Washout IPX066 (N=89)
Any AE	18 (20.22%)	12 (13.64%)	12 (13.48%)
Treatment-related AEs	15 (16.85%)	5 (5.68%)	5 (5.62%)
Deaths	0 (0%)	0 (0%)	0 (0%)
Serious AEs			
-- Any SAE	1 (1.1%)	0 (0%)	1 (1.1%)
-- Treatment-related SAE			
Early Termination due to AEs (by Termination Period)	0 (0%)	0 (0%)	1 (1.1%)

2. Serious Adverse Events

There were 4/91 (4.4%) patients who reported 6 SAEs on treatment with IPX066 in Study IPX066-B09-06. The following SAEs were reported: atrial fibrillation, constipation, chemical gastroenteritis, hypercalcemia, sciatica-- none of which were drug related. One patient had an SAE of “dehydration”. The same patient also developed hallucinations and agitation. The same report also mentions that he took a higher dose of IPX066 while still taking Stalevo. The patient’s treatment was interrupted because of this adverse event once his symptoms resolved, he resumed IPX066 without additional levodopa. It was unclear why the case was labeled as an SAE of “dehydration”. The occurrence of hallucination and agitation can be attributed to IPX066 because of an “overdose” of levodopa (Stalevo and IPX066 combination).

3. Adverse Events Leading to Discontinuation in Study IPX066 B09-02

One patient in the IPX066 group was reported to have withdrawn from the study. The patient received IPX066 for 2 days prior to developing indigestion. The subject’s initial dose was IPX066 was 1470 mg and the dose was increased to 2940 mg on day 12. On day 17, the patient started experiencing vomiting and on days 1 to 29, the patient experienced nausea. The Investigator withdrew the patient from the study. The AE is related to treatment.

Another patient withdrew early because of excessive dyskinesias on day 1 of the washout period. The patient received 40 days of IPX066 and 12 days of CLE. It was unclear from the narrative when the dyskinesias started as it implies in the

report that the excessive dyskinesias did not occur till the 1st day of the washout period. The patient received 2450 mg of IPX066, 1000 mg of CLE and started on 2450 mg of IPX066 during the washout period.

REVIEWER'S COMMENTS:

The reported adverse events occurred when patients were receiving high doses of IPX066. Adverse events described above are common adverse reactions reported in patients taking levodopa especially at high doses.

4. Common Adverse Events

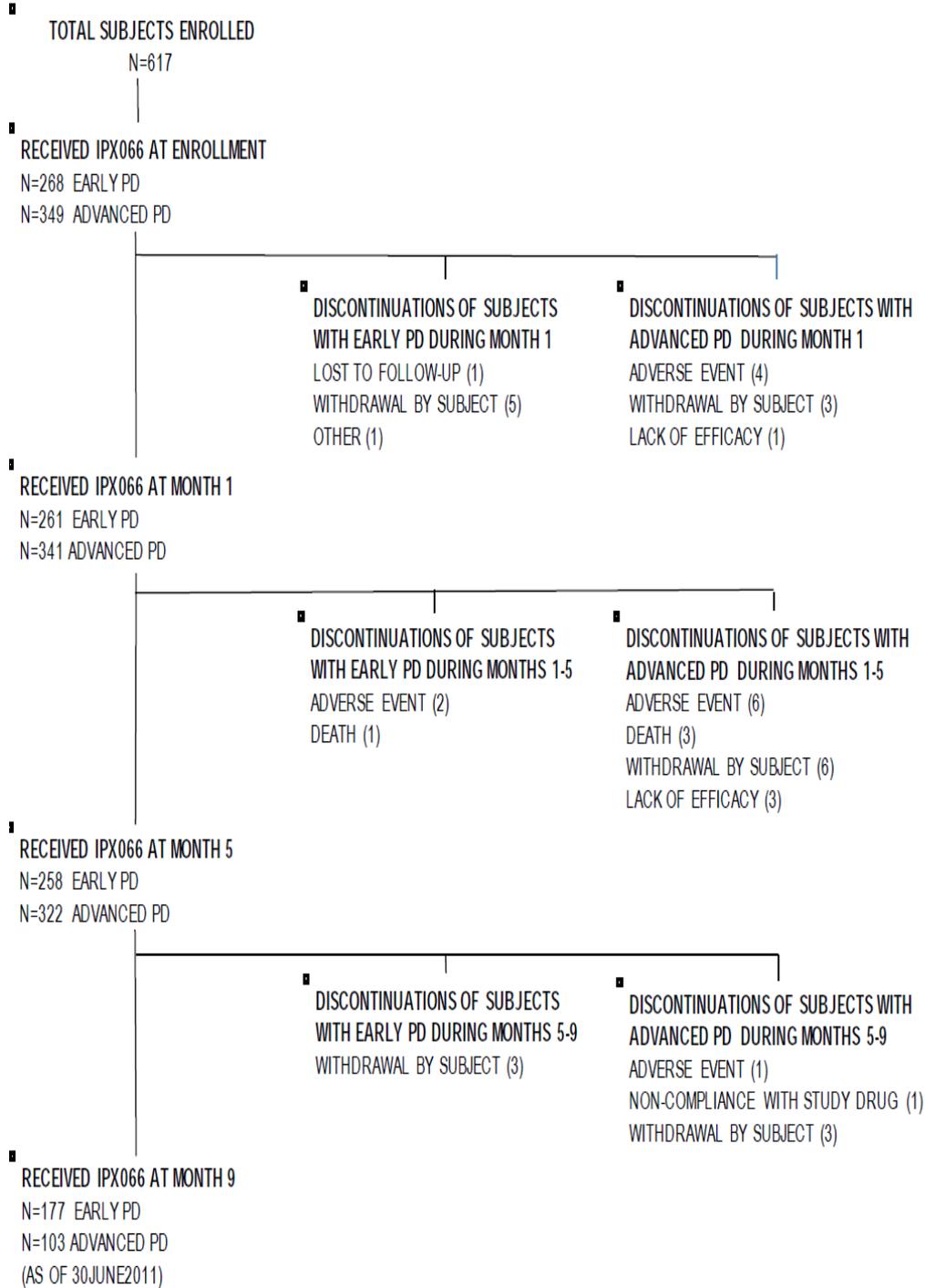
Adverse events were reported by 20.2% of all randomized subjects with IPX066 treatment compared to 13.6% in the CLE treatment. The most commonly reported individual AE were dyskinesias (4 subjects, 4.5%), confusional state (3 subjects, 3.4%) and insomnia (3 subjects, 3.4%).

STUDY B09-03 : OPEN LABEL EXTENSION STUDY

Study B09-03 is a multicenter, open label study of IPX077 in subjects with Parkinson's disease who successfully completed 1 of the following studies: IPX066-B08-11, IPX066-B08-05 or IPX066-B09-02. The objectives were to evaluate the long-term safety and clinical utility of IPX077 in subjects with Parkinson's disease. Subjects received IPX066 in an open label manner. Safety assessments included AEs, ECGs, clinical laboratory tests (chemistry, hematology, urinalysis, vital signs), physical examination and concomitant medications during study. The safety database includes patients exposed to IPX066 for at least 9 months.

The completed trial data for this study was presented in the 120-day safety update and provided safety data for patients treated with IPX066 for at least 9 months. The subject disposition for this study is summarized in the subsequent figure 11.

Figure 10: Disposition of Subjects in Study B09-03 (Source: Sponsor)



1. Serious Adverse Events

Table 72: Serious Adverse Events Reported in Study B09-03 (Sponsor's table).

Subject ID	Dose of IPX066	MedDRA Preferred Term
Other SAEs Occurring During B09-03		
332-003	725	Syncope, 2 episodes
332-005	1110	Fall; concussion
332-006	1450	Femoral neck fracture
335-007	855	Hyponatraemia
630-004	1755	Loss of consciousness
631-005	1415	Gastritis
634-001	1715	Atrial fibrillation
635-008	855	Intervertebral disc disorder; spondylolisthesis
650-002	1170	Sinus bradycardia
828-005	725	Femoral neck fracture
836-003	1305	Femoral neck fracture
900-003	2030	Wound infection; spinal column stenosis
902-017	1950	Confusional state
905-009	285	Small intestinal obstruction
912-005	1960	Hallucination; paranoia
914-003	1140	Volvulus; hypotension
915-007	2940	Spinal osteoarthritis
916-003	585	Pelvic prolapse
917-007	4900	Knee arthroplasty; neuropathy peripheral
918-009	3500	Cellulitis
919-001	580	Hip fracture
922-018	870	Sick sinus syndrome
922-028	480	Calculus ureteric
922-035	1155	Back pain
923-003	2320	Bladder cancer
924-002	2450	Convulsion; scapula fracture
924-005	1950	Atrial fibrillation; gastritis
926-001	870	Renal failure; hyponatraemia; inflammatory bowel

		disease
926-004	1755	Atrioventricular block
932-002	2340	Cerebrovascular accident
932-003	1140	Humerus fracture; fall
934-013	950	III rd nerve paralysis
937-001	1235	Non-cardiac chest pain
938-003	1170	Foot deformity

Forty three (7.0%) subjects reported 64 SAEs during the study. The reported SAEs were events associated with dopamirgic medications. One patient who developed excessive somnolence that led to early withdrawal.

2. Adverse Events Leading to Discontinuation

The table below summarizes the AEs leading to discontinuation. Sixteen patients discontinued due to AEs. The table below lists the 14 patients. There was one patient who was listed under SAE that was not included in this list of early discontinuations.

Table 73: Summary of Patients Who Discontinued Early due to SAEs (Sponsor's table).

Subject ID	Dose of IPX066	MedDRA Preferred Term
252-004	3675	Freezing phenomenon
829-044	2205	Femur fracture
251-002	435	Insomnia
256-026	1140	Photosensitivity reaction
633-003	1305	Musculoskeletal pain
827-006	190	Tachycardia
828-009	870	Head discomfort
837-001	585	Asthenia
902-001	760	Nausea; dizziness
917-005	770	Constipation
925-001	2940	Dysarthria; muscle twitching
925-008	3920	Nausea; dizziness
727-001	720	Hepatic enzyme increased
931-009	870	Homicidal ideation; suicidal ideation

Treatment emergent adverse events that led to discontinuation were more frequent in patients with advanced PD compared to early PD patients. One patient received a very high dose of IPX066 5390 mg/day levodopa component and developed hallucinations, the dose was reduced to 5145 mg and the symptoms disappeared. (915-009).

REVIEWER'S COMMENTS:

Consistent with what is known about dopaminergic treatment, hallucinations may occur with long-term disease and is dose related. In patients where the dose was reduced, the hallucinations disappeared.

A total of 22/617 (3.6%) subjects who withdrew consent without any clear explanation on the reason for withdrawal. Among patients who withdrew consent, four patients had decreased their dose of IPX066 prior to the early termination visit. Although the reasons for withdrawing consent are not documented, it is reasonable to believe these patients may have withdrawn because of adverse event from the high dose of IPX066.

3. Common Adverse Events

Of the three hundred fifty three (57.2%) subjects who reported AES that started in the long term study B09-03, the most frequent adverse event was fall (32=5.2%), followed by dyskinesia (29=4.7%) and nausea (25=4.1%). The table below from the Sponsor lists down the most frequently reported AEs in > 2% of subjects

Table 74: Most Frequently Reported AEs (>2%) in Study B09-03, Open Label Study (Sponsor's table).

	All Enrolled N=617	Subjects with Early PD N=268	Subjects with Advanced PD N=349
Fall	32 (5.2%)	9 (3.4%)	23 (6.6%)
Dyskinesia	29 (4.7%)	5 (1.9%)	24 (6.9%)
Nausea	25 (4.1%)	15 (5.6%)	10 (2.9%)
Insomnia	24 (3.9%)	15 (5.6%)	9 (2.6%)
Back Pain	19 (3.1%)	9 (3.4%)	10 (2.9%)
Dizziness	17 (2.8%)	9 (3.4%)	8 (2.3%)
Headache	18 (2.9%)	10 (3.7%)	8 (2.3%)
Urinary Tract Infection	15 (2.4%)	4 (1.5%)	11 (3.2%)
Pain in Extremity	15 (2.4%)	2 (0.7%)	13 (3.7%)
Hypertension	15 (2.4%)	11 (4.1%)	4 (1.1%)
Hallucination	14 (2.3%)	2 (0.7%)	12 (3.4%)
Constipation	16 (2.6%)	7 (2.6%)	9 (2.6%)
Arthralgia	16 (2.6%)	5 (1.9%)	11 (3.2%)
Depression	12 (1.9%)	4 (1.5%)	8 (2.3%)
Dry mouth	11 (1.8%)	4 (1.5%)	7 (2.0%)
Anxiety	10 (1.6%)	3 (1.1%)	7 (2.0%)
Upper Respiratory Tract Infection	9 (1.5%)	6 (2.2%)	3 (0.9%)
Respiratory Tract Infection	7 (1.1%)	0	7 (2.0%)
Worsening PD	8 (1.3%)	6 (2.2%)	2 (0.6%)
Tremor	12 (1.9%)	8 (3.0%)	4 (1.1%)
Muscle Spasms	7 (1.1%)	0	7 (2.0%)
Weight decreased	7 (1.1%)	0	7 (2.0%)

REVIEWER’S COMMENT:

The adverse events in the long term study are consistent with what was observed in the early and advanced PD studies. More common are adverse events reported in levodopa preparations: nausea and vomiting, dyskinesias, hallucinations.

“Falling a common adverse event. Because of the numerous clinical conditions associated with “falls” especially in the elderly and in Parkinson’s disease, this cannot be solely attributed to the drug.

7.4 Supportive Safety Results

7.4.1 Laboratory Findings

Laboratory analyses were conducted by (b) (4) (located in (b) (4) and in (b) (4)). Reference values for the laboratory results followed FDA standards. The approach to the review included the review of the central tendency for each laboratory parameter, the shift tables and a discussion of cases of outliers (for single cases identified) and “clustering” of abnormal cases if any. The laboratory shift tables are presented for both the Phase 3 controlled and long term extension studies.

A. Hematology

a. Mean Hematology Values

Table 77 below summarizes the mean hematology values among all patients exposed to the different treatment arms and placebo in all the conducted clinical studies for IPX066.

Table 75: Hematology Values mean, Median and Standard Deviation in All Comparator Studies (Summarized from Sponso's table)

	IPX066		IR CD-LD		CLE		Placebo	
	Baseline	End of Study						
HGB								
Mean	14.12	13.95	13.9	13.98	14.15	13.82	14.04	13.89
HCT								
Mean	42.17	41.64	41.74	41.55	42.07	41.58	41.87	41.49
RBC								
Mean	4.51	4.43	4.46	4.44	4.5	4.42	4.48	4.42
PLT								
Mean	221.5	223.4 1	220.56	219.73	226.82	230.47	226.96	224
WBC								
Mean	6.62	6.49	6.49	6.33	6.86	6.88	6.34	6.23

HGB=Hemoglobin, HCT=Hematocrit, RBC=Red Blood Cell, PLT=Platelets, WBC=White Blood Cell

REVIEWER'S COMMENTS:

There was no significant change from baseline mean values at the end of study in all treatment and placebo groups.

b. Hematology Values Outside Reference Ranges Post Baseline

The subsequent table summarizes the hematology values outside the reference range.

Table 76: Hematology Values Outside the Reference Range at Post Baseline Assessment in study B09-03 (Reviewer's table).

Parameter	Category	Placebo 85 (100%)	IPX066 581 (100%)	IR 198 (100%)	CLE 45 (100%)
Hemoglobin	High	1 (1.2%)	5 (0.9%)	1 (0.5%)	1 (2.2%)
	Low	1 (1.2%)	7 (1.2%)	5 (2.5%)	1 (2.2%)
Hematocrit	High	1 (1.2%)	16 (2.8%)	5 (2.5%)	1 (2.2%)
	Low	0	4 (0.7%)	5 (2.5%)	0
RBC	High	0	5 (0.9%)	3 (1.5%)	0
	Low	1 (1.2%)	5 (0.9%)	7 (3.5%)	1 (2.2%)
WBC	High	2 (2.4%)	10 (1.7%)	2 (1.0%)	1 (2.2%)
	Low	3 (3.5%)	12 (2.1%)	6 (3.0%)	
Platelets	High	0	2 (0.3%)	0	0
	Low	1 (1.2%)	9 (1.5%)	3 (1.5%)	1 (2.2%)

REVIEWER'S COMMENTS:

The shift tables likewise did not show a percentage difference in patients with abnormal hematology values (high or low) at the end of the study.

c. Review of Outliers

- Patient (subject 109-004) received IPX066 145 mg and their absolute neutrophil count dropped from 3.55 at baseline screening and to 1.99 at the end of study. The patient is a 61-year-old woman with no family history except that she is postmenopausal and has no concomitant meds. This patient was not listed in the sponsor's list of patients having abnormal findings.
- Subject 804-003, exposed to IPX066 in the Advanced PD study, had a baseline platelet count of 209,000 and end of study platelet count of 122,000. The patient reported an adverse event of diarrhea.
- There was one patient (452-005) who had dropped both Hgb and Hct from baseline to final visit. The patient had no complaints that were due to anemia.
- In the open label long-term extension study, there was one patient (174-005) who fell to Hct < 22 because of NSAID induced UGIB. The patient however completed the long-term study.
- One subject had a lymphocyte count of 12.21 due to chronic lymphocytic leukemia

B. Clinical chemistries

a. Mean Clinical Chemistry Values

Table 79 summarizes the means of the clinical chemistry values for IPX066, IR, CLE and Placebo at baseline and end of study.

Table 77: Clinical Chemistry Values Mean, Median and Standard Deviation in All Studies (Reviewer's table).

	IPX066		IR CD-LD		CLE		Placebo	
	Baseline (N=612)	End of Study (N=612)	Baseline (N=213)	End of Study (N=213)	Baseline (N=45)	End of Study (N=45)	Baseline (N=92)	End of Study (N=92)
Glucose								
Mean	101.7	100.8	100.7	99.7	105.0	105.9	103.3	106.8
BUN								
Mean	18.0	18.2	19.0	18.2	18.2	19.3	17.1	17.0
Creatinine								
Mean	0.815	0.769	0.814	0.798	0.818	0.833	0.869	0.836
Total Bilirubin								
Mean	0.53	0.49	0.45	0.46	0.45	0.44	0.53	0.52
Alkaline Phosphatase								
Mean	75.1	76.7	76.2	75.0	76.9	78.1	68.7	68.4
ALT, SGPT								
Mean	18.2	17.5	17.0	14.0	17.8	17.6	21.3	19.3
AST, SGOT								
Mean	21.0	20.5	20.4	19.0	20.2	20.3	21.4	20.0
GGT								
Mean	24.3	24.6	21.3	20.6	24.3	26.8	23.3	23.1
Sodium								
Mean	323.662	323.87	323.74	323.83	323.65	324.16	324.56	324.42
Potassium								
Mean	16.989	16.950	16.833	16.880	16.743	17.009	17.174	16.800
Calcium								
Mean	9.47	9.39	9.43	9.41	9.30	9.32	9.52	9.43
Creatine Kinase/Creatine Phosphokinase								
Mean	115.0	116.5	134.4	123.0	125.9	128.3	103.8	106.4

b. Clinical Chemistry Values Outside Reference Ranges Post Baseline

Table 80 summarizes the frequency of patients who shifted from a normal blood chemistry parameter (first column) to either a higher or lower value than the reference range (category column). The reference ranges for the clinical parameters are as follows:

Table 78: Clinical Chemistry Values Outside the Reference Range at Post Baseline Assessment in the Safety Population Classified According to Treatment Groups (Reviewer's table).

Parameter	Category	TREATMENT ARMS			
		Placebo N=86	IPX066 N=585	IR N=199	CLE N=43
Total Bilirubin	High	1 (1.1%)	8 (1.4%)	0	0
AST (SGOT)	Low	0	0	8 (1.4%)	0
	High	0	8 (1.4%)	2 (1.0%)	0
ALT (SGPT)	High	0	8 (1.4%)	0	0
Alkaline Phosphatase	High	0	2 (0.3%)	0	0
	Low	0	23 (3.9%)	19 (9.3%)	3 (6.8%)
Creatinine	High	0	5 (0.8%)	3 (1.5%)	0
Blood Urea Nitrogen	High	4 (4.6%)	20 (3.4%)	9 (4.4%)	1 (2.3%)
Sodium	High	0	2 (0.3%)	0	0
	Low	0	5 (0.8%)	3 (1.5%)	0
Potassium	High	0	3 (0.5%)	1 (0.5%)	0
	Low	0	3 (0.5%)	2 (1.0%)	0
GGT	High	2 (2.3%)	6 (1.0%)	2 (1.0%)	
Glucose	High	13 (15.1%)	91 (15.6%)	36 (18.1%)	11 (25.6%)
	Low	0	5 (0.9%)	2 (1.0%)	
Calcium	High	0	2 (0.3%)	0	0
	Low	0	2 (0.3%)	1 (0.5%)	2 (4.5%)
Creatine Phosphokinase	High	3 (3.4%)	33 (5.6%)	14 (6.9%)	3 (6.8%)
	Low	0	1 (0.2%)	0	0

Reviewer's Comment:

Review of the shift tables (above) did not find any difference among the treatment and placebo groups in the percentage of patients who had abnormal values (high or low) at the end of the study.

c. Review of Outliers

Hepatic: Elevated AST and ALT

- Only one patient (patient 221-007) had elevated AST and ALT > 3x ULN however, his bilirubin was not elevated to even 1.5 x Normal. This patient enrolled in the Open Label Long Term Safety Extension and continuously had an elevated AST and ALT.

REVIEWER'S COMMENTS:

There were no cases of Hy's Law following the sponsor's criteria of:

Increase in ALT or AST of > 3 × ULN and increase in total

*bilirubin of $>2 \times ULN$ and alkaline phosphatase activity
 $<2 \times ULN$*

Renal: Elevated Creatinine

- One patient who had received a dose of IPX066 from 570 to 870 mg in the B09-03 study had a recorded creatinine of 2.29 mg/dl and was hospitalized for renal insufficiency. Patient was diagnosed with colitis 7 days prior to entry into the study

Abnormal Sodium:

- One patient on IPX066 (405-004) who had low Na (129 at end of visit which was a discontinuation visit—from a baseline of 133). This patient developed arrhythmias, had a pulmonary embolism, gastric ulcer and cerebral infarction.

High CK:

- There were 33 (5.6%) patients in the IPX066 group who had Creatine Phosphokinase (CK) values above normal but only one patient with high CK was reported as an adverse event. The case described was of Patient 807-011 (randomized to IR), who had severely elevated CK of 2233 at Visit 5 from a screening CK level of 60 U/L. The CK was repeated after one week and it went down to 130 U/L.
- Although most patients who had abnormal elevations in CK had no complaints and there were no other reason that could explain their elevated CK. There were 4 patients with elevated CK who discontinued from the study. Three patients were on IPX066 and one patient was on IR. The three patients on IPX066 who discontinued from the study and who had elevated CK at termination had the following clinical issues:
 - Patient 475-001 had dyskinesias
 - Patient 952-003 fell and had a contusion
 - Patient 958-001 fell and hand pain in the upper extremity

7.4.3 Vital Signs

Vital sign monitoring, especially for orthostatic changes, has been given more focus in this review—not only because of the risk for orthostatic hypotension due to disease but also because of reports of dizziness leading to falls in patients who take dopaminergic agents.

The sponsor's criteria for evaluating markedly abnormal vital sign results are shown in the table below. These are acceptable parameters.

Table 79: Sponsor's Criteria for Evaluating Markedly Abnormal Vital Signs (Sponsor's table).

Vital Sign (unit)	Reference Range	Criteria for Markedly Abnormal Values ^{a,b}	
		Blood Pressure or Pulse Change	Orthostatic Change (Decrease)
Systolic Blood Pressure (mmHg)	90-140	≥ 40 increase or decrease and outside normal reference range	Systolic BP > 20 or Diastolic BP > 10
Diastolic Blood Pressure (mmHg)	50-90	≥ 20 increase or decrease and outside normal reference range	
Pulse (bpm)	60-100	≥ 30 increase or decrease outside normal reference range	NA

Abbreviations: bpm= beats per minute, NA = not applicable

^a Changes in supine, standing or unspecified blood pressure and/or pulse are identified if either a markedly abnormal increase or markedly abnormal decrease relative to baseline is observed.

^b Orthostatic changes in blood pressure (standing - supine) are identified only if a decrease is observed.

A. BLOOD PRESSURE

Review of the blood pressure results show that there were 10 patients who had a significant orthostatic drop in diastolic and systolic blood pressure in the treatment group. The sponsor documented only 1 patient who reported orthostatic hypotension (patient 135-001 who received 245 mg of IPX066). On further analysis of patients who had an SBP drop of more than 20, there were 10 patients who discontinued early, one patient on 145 mg discontinued for nausea and dizziness and another patient on 390 mg discontinued for nausea and dizziness. It is hard to correlate the symptoms of dizziness to orthostatic blood pressure changes or whether the blood pressure drop had led to the discontinuation. However, it may be important to evaluate patients more closely for orthostatic blood pressure changes especially if they were to be started on higher doses because this may be underreported especially if the supine to standing blood pressures are not checked routinely.

Advanced PD patients Study 09-02

Patients with adverse events reporting preferred terms such as “dizziness”, “orthostatic hypotension”, “hypotension”, “fainting”, “syncope” with a corresponding diastolic or systolic blood pressure change were identified. Only one patient on IPX066 (Patient 104-022) complained of symptomatic orthostatic hypotension compared to five patients on IR CD-LD who had symptomatic

orthostatic hypotension. The number of patients who had complaints suggestive of orthostatic hypotension is small compared to those who were asymptomatic.

Long Term Study B09-03

- The sponsor's datasets did not provide information about orthostatic blood pressure change.
- There were 12 patients who were reported to have had symptoms of orthostatic hypotension but only 3 patients had narratives. Three patients (presented below) had other medical reasons that may explain the hypotension.
 - Patient 909-004: patient was coded to have an Acute Myocardial Infarction but upon clarification with the site, the subject did not have a myocardial infarction and the event was then coded to left atrial dilatation. Hypotension in this case could be cardiac related.
 - Patient 914-003 had a history of a surgically corrected inguinal hernia. He underwent exploratory laparotomy with a left colectomy for sigmoid volvulus. He developed dehydration and had dizziness hypotension. The hypotension is not likely drug related.
- Concomitant medications that could potentially drop blood pressure were also reviewed. Three of the patients were on anti-hypertensives (103-004, 122-005, 205-015) that could cause a drop in blood pressure. One patient (112-006) might have orthostatic hypotension prior to enrollment as he was treated with Midodrine ®.

B. HEART RATE

An analysis of Heart Rate in the Pooled Study that included all Phase 3 Controlled Studies was performed. In the over-all study, there were no significant mean differences in the mean heart rates among between IPX066 and placebo (in early PD patients), IR CD-LD and CLE (in advanced PD patients as reported in the sponsor's table below).

Table 80: Distribution and Summary of Ventricular Rate in All Phase 3 Controlled Studies (Sponsor's table).

Ventricular Rate (BEATS/MIN)	IPX066		IR CD-LD		CLE		Placebo	
	Baseline (N=612)	End of Study (N=612)	Baseline (N=213)	End of Study (N=213)	Baseline (N=45)	End of Study (N=45)	Baseline (N=92)	End of Study (N=92)
< 60	127 (20.8%)	104 (17.6%)	35 (16.4%)	28 (14.0%)	8 (17.8%)	10 (22.7%)	16 (17.4%)	12 (13.8%)
60 - 100	477 (77.9%)	481 (81.5%)	177 (83.1%)	172 (86.0%)	37 (82.2%)	34 (77.3%)	75 (81.5%)	75 (86.2%)
> 100	8 (1.3%)	5 (0.8%)	1 (0.5%)	0	0	0	1 (1.1%)	0
Missing	0	22	0	13	1	1	0	5
N (%)	612 (100%)	590 (96.4%)	213 (100%)	200 (93.9%)	45 (97.8%)	44 (97.8%)	92 (100%)	87 (94.6%)
Mean	69.4	69.4	70.4	70.8	69.6	68.5	69.7	69.7
Std Dev	12.05	11.15	11.14	10.15	12.46	11.19	11.71	11.18
Median	69.0	68.0	70.0	70.0	68.0	67.0	68.0	68.0
(Min, Max)	(37, 124)	(39, 105)	(48, 109)	(49, 100)	(47, 98)	(49, 91)	(42, 103)	(43, 98)

Reviewer's Comments:

The mean heart rate of patients who received IPX066, IR, CLE and placebo was 68 to 71.

Outliers:

- Patient 204-007, enrolled in the early PD study (08-05) had a heart rate of 124 beats per minutes. His heart rate was persistently above 110 beats per minute and had complained of angina.
- Patient 112-002, enrolled in the long-term open label study, had a heart rate of 39 beats/minute. The patient is a 74-year-old man who was also on Artane, Cymbalta, Levitra, Requip, Zolpidem and Clonazepam. The patient was asymptomatic. Specific cause of the bradycardia was undetermined.

7.4.4 Electrocardiograms (ECGs)

There were no additional QTc clinical studies conducted in support of this NDA because a thorough QTc study was not required in this 505(b)(2) application. The ECG's were performed for screening and routine safety and were not defined specifically to detect a change in QTc. The sponsor's ECG parameters and reference intervals were acceptable. The sponsor calculated the corrected QT interval using both the QTcF and Bassett's method (for completion) but their reports only discussed the QT interval correction using QTcF. The results using this method did not provide additional information from what was already concluded using Federicia's method.

Early PD Study B08-05

The table below summarizes number of subjects in each treatment and placebo group whose QT interval (uncorrected, and with correction using Federicia's and Bassett's method) met the outlier criteria for change from baseline. There was no significant differences in the QTcF and QTcB intervals among the treatment groups as shown in the table below.

Table 81: QT Interval Meeting Outlier Criteria in Study B08-05 (Reviewer's table).

ECG Parameter	Change from Baseline (msec)	Placebo N= 87	IPX 145 mg N= 84	IPX 245 mg N= 101	IPX 390 mg N= 97
Uncorrected QT	> 30	18	7	14	9
	> 60	5	1	4	0
	> 500	3	1	2	0
QTcB	> 30	17	7	16	10
	> 60	4	3	4	1
	> 500	3	1	2	0
QTcF	> 30	11	5	12	5
	> 60	4	2	4	0
	> 500	2	0	1	0

There was no dose related prolongation of the QT interval detected during routine ECG monitoring. However, there were three patients (two subjects on treatment, compared to 1 subject on placebo), who had cardiac AEs. These three subjects that had ECG abnormalities considered as AEs are described below:

1. Subject 224-015. Arm: LD 245 mg. This patient had signs of myocardial ischemia starting Study Day 208 and Ending Day 239. On Day 210 (Week

- 30), an abnormal ECG showed an RR interval of 1,040. All the other ECG parameters were normal. This was the only AE reported for that subject and the investigator did not mark it as “serious”. Treatment outcome is unknown.
2. Subject 224-001. Arm: LD 390 mg. Verbatim term for AE: “microvoltage QRS in all leads”. This reading was recorded on Day 30 during the titration period and until patient’s discontinuation from the study. The patient also complained of moderate nausea on Days 25 through 29, moderate dizziness and gait disorder from days 25 to 32 and moderate vomiting from day 28 to 29. It appears that the patient withdrew mainly because of the clinical side effects and the low voltage ECG was an incidental finding.
 3. Subject 224-005. Arm: Placebo. The patient had a prolonged QT interval starting at Day 119 and ending on Day 162. BP was also noted to have elevated BP at screening which remained high during the study (range 140/100 to 170/95). QTcF was reported to be 413 ms at screening, 466 ms at Week 16 and 432 ms at Week 30. The Investigator thought that the Week 16 QTcF interval was significant. This was not related to drug.

Advanced PD Study B09-02

Similarly, for study 09-02, there two patients who met the outlier criteria for having a prolonged QT interval from baseline. One patient in each treatment group —IPX (Subject 114-002) and IR comparator (Subject 602-015) met criteria for QTcB>500 (also meeting criteria for QTcF > 500). Both patients had QT increase from baseline of more than 60 as shown in the table below.

Table 82: QTC>500 and QTC change from baseline in patients on IPX066 and IR CD-LD, Study B09-02 (Reviewer's table).

	IR CD-LD	IPX066
QT interval		
QTcB interval >500		
Increase from baseline		
> 30 to 60 ms	1	1
> 60 ms	1	1
QTcF interval > 500	1	1
Increased from baseline		
>30 to 60 m	1	1
> 60 ms	1	1

Subject 602-015 was developed depression that was reported as an AE. There were no narratives alluding to any cardiac problems. Subject 114-002 was flagged as an early discontinuation and further analysis of the case reveal that at the time of enrollment, he has atrial flutter and was taking Levothyroxine, Modafanil and Aspirin aside from his PD drugs. He continued until the

Maintenance Phase of the study but subsequently withdrew from the study for reasons that were not stated in the report.

Advanced PD Study B09-06

In this study with CLE as a comparator, the sponsor did not report any subjects who had a QTcF >500. A reanalysis of the datasets for patients with QTcF and QTcB >500 was performed. There were 3 patients who were exposed to IPX066 who had corrected QT intervals >500 as shown in the table below.

Table 83: QTc >500 and QTC Change from Baseline in Study B09-06 (Reviewer's table).

	IPX066	CLE [®]
QTcB interval > 500	2 (375-003 375-004)	None
QTcF interval > 500	1 (376-003)	None

Patients 375-003 and 375-004 were assigned to the IPX066 treatment group but were dispensed placebo instead of the drug. Both subjects withdrew from the study due to lack of efficacy.

Patient 376-003 developed hypercalcemia (a serious adverse event) 4 days after being exposed to IPX066 1140 mg. The patient was admitted to the hospital with nausea and recurrent vomiting for 2 to 3 days prior to hospitalization. ECG done on admission showed a heart rate of 73 bpm. The patient was also diagnosed with H. pylori during this admission. An ultrasound scan of the neck during admission revealed struma multinodosa on the thyroid gland with no definitive evidence of parathyroid adenoma. The physical examination during enrollment did not report any abnormalities in neck area suggestive of thyroid enlargement. During the time of hospitalization, patient's IPX066 treatment was decreased from 1140 mg to 855 mg. Patient was discharged on Day 13 with resolution of the hypercalcemia. On day 76, the subject returned to her original daily dose of IPX066, 1140 mg. There were no cardiac sequelae reported.

REVIEWER'S COMMENTS:

This single case of thyroid abnormality occurred at a dose of 1140 mg of IPX066 for 3 days and was found to have struma multinodosa on hospitalization. The datasets did not report any prior history of thyroid disease.

The sponsor also presented the cases with QTcF changes > 30 and >60 between Baseline and End of the Study in IPX066 (Table 95). Subject 454-006 had a history of ischemic heart disease and showed a “left anterior fascicular block”. The patient was given CLE and a repeat ECG done on the medication showed an “anterior infarction, stabilized, fascicular anterior block”. The patient completed the study without any reports of any sequelae.

Table 84: QTcF changes > 30 and > 60 at Baseline Screening and End of Study in B09-02 (Sponsor's table).

Subject Number	Screening QTcF (msec)	End of Study QTcF (msec)	Change (msec)	Screening VR (bpm)	End of Study VR (bpm)
Increase in QTcF >30 msec					
450-011	399	431	32	74	76
455-002	313	347	34	56	60
456-001	408	464	56	50	50
952-005	387	420	33	87	91
955-001	384	421	37	58	71
Increase in QTcF >60 msec					
455-003	240	312	72	60	52
376-004	324	474	150	57	84

Long Term Safety Study B09-03

There were 3 patients in the long term study who had QTcB/QTcF interval greater than 500 by visit 9 (end of the long term study). There were no narratives provided for any of these patients who did not meet criteria for providing a narrative. All the patients listed below were study completers.

Table 85: Frequency of Patients who had Prolonged QTcB/QTcF > 500 in Study B09-03 (Reviewer's table).

QTcB interval > 500	2 <ul style="list-style-type: none"> • 210-011 • 802-023
QTcF interval > 500	2 <ul style="list-style-type: none"> • 102-012 • 802-023

Patient 802-203 had prolonged QT using both correction methods.

Past medical history, concurrent illnesses and concomitant drugs were reviewed to explain the cardiac abnormalities. Two of these patients had heart disease and

were taking medications for ischemic heart disease. The cases are presented below:

- Patient 210-011 is a 46 year old man with PD, memory complaints and B12 deficiency. He also takes Rasagiline, Ropinirole and Sinemet for PD, Trazodone, and vitamin supplements.
- Patient 802-023 is an 81 year old woman with diabetes, ischemic heart disease and hypertension. Concomitant drugs include Amaryl, Cardiomagnyl, Diaformin, Tonorma.
- Patient 102-012 is a 56 year old woman with heart disease, open angle glaucoma, vertigo and hypertension. She takes Aspirin, Paxil for anxiety, hydrochlorothiazide and lisinopril.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials conducted or designed to evaluate a specific safety concern.

7.4.6 Immunogenicity

There were no immunogenicity issues related to the drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Early PD Study B08-05 looked at dose response for 145 mg, 245mg and 390 mg. There appears to be a dose response for nausea and vomiting, dyskinesias and orthostatic hypotension. Although the Advanced PD Study (B09-02) did not evaluate a fixed dose, we reviewed the dose given when an AE occurred. Dyskinesias and hallucinations appeared at higher doses of IPX066. This has been discussed in the section on Major Safety Results.

7.5.2 Time Dependency for Adverse Events

This review showed that nausea and vomiting was the most frequent adverse event in early PD can occur immediately, as early as a day after exposure with symptoms lasting to about a 6 to 7 weeks. Nausea and vomiting was more common during the titration period which suggesting that the study is too short to allow the patient to accommodate to higher doses (above 245 mg).

Dyskinesias were frequently reported by patients taking IPX066 and can occur as early as one day after taking IPX066 and is most frequent at 3 weeks after exposure and in some

patients, persisted up to 20 weeks. It commonly resolves at nine weeks with continued treatment.

Hallucinations were also common adverse events in the pooled studies. The onset was as early as 16 days after starting medications, but more commonly occur around 8 weeks of treatment.

7.5.3 Drug-Demographic Interactions

Of the total 849 subjects treated with IPX066 in the overall PD population, 519 (61.1%) were male and 330 (38.9%) were female. TEAEs that occurred in at least 2% of patients by gender distribution are presented in the table below.

Table 86: Occurrence of Nausea, Vomiting and Dyskinesias in Males and Females (N (%)), (Reviewer's table).

Preferred Term	Males	Females
Nausea and Vomiting	38 (7.3%)	69 (20.9%)
Dyskinesias	21 (4.0%)	25 (7.6%)

There is a higher rate of nausea and vomiting, and dyskinesias among females, suggesting the possibility of a higher plasma concentration of the drug in the females that may predispose them to frequent adverse events. Body weight can also influence plasma concentrations and in this NDA, the mean body weight of females (71-73 kg) is less than mean body weight of males (85-87 kg), making females more susceptible to more adverse reactions. Similarly, adverse reactions such as nausea, vomiting and dyskinesias were reported in patients with lower weights.

There was no difference in the occurrence of adverse events according to age.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were reported.

7.5.5 Drug-Drug Interactions

No new drug-drug interaction studies were performed during development of IPX066. The label for Sinemet advised that caution should be exercised when the following drugs are administered concomitantly with Sinemet. These drug-drug interactions were also included in the IPX066 label:

- (b) (4) Selegiline (b) (4) may be associated with postural hypotension (b) (4)

- Nonselective MAO inhibitors are contraindicated for use with Sinemet. Patients taking MAO B Inhibitors need to be monitored because of orthostatic hypotension that may occur with combination of MAO B Inhibitors and levodopa.
- Dopamine D2 receptor antagonists and isoniazid may reduce the therapeutic effects of levodopa
- There are rare reports of hypertension and dyskinesia with tricyclic antidepressants and carbidopa-levodopa
- Iron salts such as multivitamin tablets may reduce the amount of levodopa available to the body
- Foods rich in protein or amino acids may decrease the absorption of levodopa
- High fat, high calorie meal may delay onset of action of levodopa for 2 to 3 hours.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa. These bioassay studies were done in the reference drug, Sinemet.

The label for Sinemet states that “Epidemiological studies have shown that patients with Parkinson’s disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson’s disease or other factors, such as drugs used to treat Parkinson’s disease, is unclear.” The development program for IPX066 did not do any dermatologic studies to assess for melanoma.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred during the studies in IPX066.

7.6.3 Pediatrics and Assessment of Effects on Growth

The pediatric studies are not required because Parkinson’s disease is rare in the pediatric population and clinical trials are not feasible. The sponsor requested for a waiver with the justification that the prevalence and incidence of Parkinson’s disease in the pediatric population is sufficiently low. The FDA granted the sponsor waiver from PREA requirements.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was one report of a patient overdose.

Subject 804-008 enrolled in B09-02 was prescribed a daily dose of IPX066 2340 mg per day (195 mg capsules 4 times per day which he took for 4 days during Dose Conversion but then inadvertently took 11700 mg per day (12 capsules 5 times per day) for one and a half days (total of 8 doses of 12 capsules). On the following evening, the subject experienced changes in motor behavior, hallucinations, and sleep disturbances. Study Treatment was interrupted and subject was hospitalized overnight due to worsening dyskinesia. The symptoms resolved the next day and the originally prescribed dose of 2340 mg per day was resumed and well tolerated. The subject completed dosing in the study.

REVIEWER'S COMMENTS:

Although there was only one case of overdose in the study, there is a risk that patients will be combine CD/LD preparations increasing the risk for medication error and the label should contain a statement advising prescribers to warn patients about this risk..

No studies were conducted to evaluate the abuse potential, tolerance or physical dependence of IPX066 on animals or humans.

7.7 Additional Submissions / Safety Issues

SUICIDALITY

A retrospective search for events on suicidality using FDA Guidance (Refer to meeting minutes on September 28, 2011) was performed on the two double blind, phase 3, controlled studies. The search criteria used to identify possibly suicide related adverse events was reviewed. Narrative summaries were prepared for all possibly suicide related adverse events. The narratives were prepared by searching the electronic data for any information that might be considered possibly relevant to suicidality. Other relevant sources of information like hospital records, consults, questionnaire responses were used to prepare the narrative summaries. Once the narratives were prepared, they were blinded to details that might bias their assessment. These blinded narratives for suicidality review were sent to Dr. Kelly Posner at the Center for Suicide Risk Assessment at Columbia University. The search identified 68 subjects with 87 possible suicide related terms that were provided for classification utilizing the Columbia Classification Algorithm for Suicide Assessment (C-CASA). Fifty five subjects had a single possible suicide related AE and thirteen subjects had more than one term (range of 2 to 5) suicide related AEs.

The narratives of these cases were reviewed and a rational classification of all the narratives was provided by the Center for Suicide Risk Assessment. There were no cases that were categorized by the C CASA as suicide, suicide attempt, suicidal ideation or self injurious behavior.

CARDIOVASCULAR DISEASE

The Sponsor identified events that were believed to be ischemic in nature. The sponsor reports that 12 of 849 subjects (1.4%) exposed to IPX066 during the controlled phase 3 studies experienced cardiac or neurologic ischemic events. In 8 of the 12 subjects, the events were TE SAEs but none were considered as related to study drug. Since the cardiovascular events occurred only in the IPX066 treated patients (none in the comparator and placebo group), the adverse events were reviewed and adjudicated in a blinded fashion by the [REDACTED] (b) (4) [REDACTED] Committee. The adjudicators classified the cardiovascular and cerebrovascular events into composite endpoint categories. All analyses were performed using the safety population that included 960 patients.

There were 15 ischemic events in 11 patients. There were 4 cases of myocardial infarctions, 1 cardiovascular death, 1 unstable angina event, 4 angina/chest pain events, 1 transient ischemic attack, 1 ischemic stroke, 2 percutaneous coronary interventions and 1 patient required coronary artery bypass surgery. The adjudication committee warned that the data should be interpreted with caution because of the small sample size and the modest number of events. I agree with the sponsor that although the cardiovascular AEs were only noted in the IPX066 treated population, there is no dose relationship of this adverse events. Likewise, the presence of pre-existing cardiovascular risk factors and age of the PD population, make it difficult to identify whether these cardiovascular and cerebrovascular events were solely due to the treatment drug.

8 Postmarket Experience

No postmarketing experience exists with IPX066.

9 Appendices

9.1 Literature Review/References

- Allison W, S. M. (2012). Predictors of Survival in Patients with Parkinson's Disease. *Arch Neurol*.
- Driver, J. K. (2008). Parkinson disease and risk of mortality. *Neurology*, 1423-1430.
- Fahn, S. (2008). The History of Dopamine and Levodopa in the Treatment of Parkinson's Disease. *Movement Disorders*, S497-S508.
- Ferreira JJ, T. C.-C. (2006). Levodopa monotherapy can induce "sleep attacks" in Parkinson's disease patients. *J Neurol*, 460-2.
- Frucht, S. R. (1999). Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology*, 1908-10.
- Kohler WC, H. J. (1999). Immediate release and controlled release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. *Neurology*, 1012-9.
- Louis ED, M. K. (1997). Mortality from Parkinson disease. *Arch Neurol*, 260-4.
- Poewe, W. (2006). The natural history of Parkinson's disease. *J Neurol*, VII/2-VII/6.
- Schrag A, Q. N. (2000). Dyskinesias and motor fluctuations in Parkinson's disease. A community based study. *Brain*, 2297-2305.
- Toth C, B. M. (2008). Neuropathy as a potential complication of levodopa use in Parkinson's disease. *Mov Disord*.
- Weintraub d, H. H. (2007). Presentation and management of psychosis in Parkinson's disease and dementia with lewy bodies. *Am J Psychiatry*, 1491-8.
- Wirdefeldt, K. A. (2011). Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol*, S1-S58.

9.2 Labeling Recommendations

At this time, there is no Medication Guide recommended.

9.3 Advisory Committee Meeting

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

/s/

ANNE E CONSTANTINO
01/18/2013

GERALD D PODSKALNY
01/18/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203312

Applicant: IMPAX

Stamp Date: 12/21/2011

Drug Name: IPX066

NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: IPX066-B08-09 Study Title: Assessment of Dose Proportionality of IPX066 Sample Size: 24 Arms: Open Label, 4 Sequence, 4 Treatment Cross-over Study Location in submission: Mod 5.3.3.1 Study Number: IPX066-B08-11 Study Title: A Study to Compare Pharmacokinetics and Pharmacodynamics of IPX066 to Completed Standard Carbidopa Levodopa Sample Size: 27 Arms: Open	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Label Two Treatment, Two Period Crossover Study Location in submission: 5.3.4.2				
EFFICACY primary efficacy check with stats to see if they can recreate datasets					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study IPX066-B08-05: Placebo Controlled Study to Evaluate the Safety and Efficacy of IPX066 in Subjects with Parkinson’s Disease Randomized, double blind, placebo controlled, fixed dose, parallel group study of three doses of IPX066 (145 mg LD, 245 mg LD, 390 mg LD) vs placebo in EARLY PD Duration: 30 weeks Primary Endpoint: Change from Baseline in sum of UPDRS Part II and Part III and EOS (Week 30) Indication: Parkinson’s Disease</p> <p>Pivotal Study IPX066 B09 02: A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson’s Disease Randomized, double blind, double dummy, active control, parallel group study to compare efficacy and safety of IPX066 to that of IR CD-LD in subjects with ADVANCED PD Duration: 22 Weeks (Adjustment IR: 3 weeks; IPX066: 6 weeks; Randomization: 13 weeks) Primary Endpoint: Baseline adjusted “off” time as a percentage of waking hours at the end of study. Indication: Parkinson’s Disease</p>	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses	x			Requested clarification from sponsor regarding

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	available and complete?				exposure table. Additional information on independent doses for a particular duration was also requested. Shell tables were provided for the sponsor to complete (see comment below)
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information? **make sure the investigators who filed and who has disclosable relationship—data influence	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

The comments/requests (quoted below) which were sent to the Sponsor are NOT FILING ISSUES.

Please clarify whether the data in Table 17 (below) from the Interim Study Report for IPX066-B09-03 (open label), represents cumulative exposure in subjects who have completed continuous treatment with IPX066 at the listed duration of treatment (as of the June 30, 2011 cut-off date) or does the table reflect the projected number of patients that will have completed the listed duration of exposure by the end of the trial.

The ISS should include a cumulative exposure table for all completed patients from all clinical trial.

Table 17: Cumulative Exposure to IPX066 in Original and Extension Trials -- All Study IPX066-B09-03 Data at Impax as of 30 June 2011

Disease State	Duration of Exposure	Number of Subjects
Early and Advanced N=617	Up to 13 Weeks	617
	Up to 26 Weeks	608
	More than 26 Weeks	595
	More than 52 Weeks	279
Early N=268	Up to 13 Weeks	268
	Up to 26 Weeks	266
	More than 26 Weeks	265
	More than 52 Weeks	201
Advanced N=349	Up to 13 Weeks	349
	Up to 26 Weeks	342
	More than 26 Weeks	330
	More than 52 Weeks	78

Source: Table 14.3.1.13-1, 14.3.1.13-4, 14.3.1.13-7, 14.3.1.14-1, 14.3.1.14-4, 14.3.1.14-7, 14.3.1.15-1, 14.3.1.15-4, 14.3.1.15-7

Please populate exposure table 1 below with the number of subjects/patients who have completed each respective cumulative continuous exposure period for each total daily dose range listed in the table. Include the exposure information for all studies in the development program that administered the same formulation of IPX066 used in the pivotal clinical trials. In trials that involved dose titration, list exposure by the patient's maintenance dose. For patents who were allowed to change their dose, report their exposure at

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

their modal dose. For example, patients who were started on 285 mg/day for 10 days but they were increased to 435 mg/day for 10 days and then returned to 285 mg/day for 70 days should be reported in this table as 285 to 435 mg for 90 days.

Table 1 Exposure for Completed Patients: Total daily dose by cumulative continuous duration (days) for all clinical studies.

Dose of IPX066 Received (Total Daily Dose)	Duration of Exposure to IPX066				
	≤29 days	30 to 89 days	90 to 179 days	180 to 364 days	≥365 days
<285 mg					
285 mg to < 435 mg					
≥435 mg to < 735 mg					
≥735 mg to < 1170 mg					
≥1170 mg					
Total					

Please populate exposure 2 table (below) with the number of subjects/patients who have completed the each cumulative continuous exposure range list in the table, at each at the total daily dose range listed in the table, by the June 30, 2011 cut-off date for each individual trial. Please indicate whether the trial was conducted in healthy volunteers, early or late Parkinson's disease patients. Include the exposure information for all studies in the development program that administered the same formulation of IPX066 used in the pivotal clinical trials. In trials that involved dose titration list exposure by the patient's maintenance dose. For flexible dose trials or for patients who were allowed to change their dose, report their exposure at the modal dose. For example, patients who were started on 285 mg/day for 10 days but they were increased to 435 mg/day for 10 days and then returned to 285 mg/day for 70 days should be reported in this table as 285 to 435 mg for 90 days.

Table 2 Exposure for Completed Patients: Total daily dose by duration for each individual study

Trial Number (i.e. IPX006-B09-01) Healthy Subjects	Dose Received (Total Daily Dose)	Duration of Exposure				
		≤29 days	30 to 89 days	90 to 179 days	180 to 364 days	≥365 days
	<285 mg					
	285 mg to < 435 mg					
	≥435 mg to < 735 mg					
	≥735 mg to < 1170 mg					
	≥1170 mg					
	Total					

Trial Number (i.e. IPX006-B09-02 Early PD)	Dose Received (Total Daily Dose)	Duration of Exposure				
		≤29 days	30 to 89 days	90 to 179 days	180 to 364 days	≥365 days
	<285 mg					
	285 mg to < 435 mg					
	≥435 mg to < 735 mg					
	≥735 mg to < 1170 mg					
	≥1170 mg					
	Total					

The 120 day Safety Update should also include an updated version of the tables above or a similar table that summarizes total number of cumulative patient exposure for each dose (or dose range) for non-overlapping periods of time (in days) that clearly identifies patients with completed continuous exposure for 3, 6 and 12 months.

Anne E. A. Constantino, MD
 Reviewing Medical Officer

February 2, 2012
 Date

Clinical Team Leader

Date

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

/s/

ANNE E CONSTANTINO
05/14/2012

GERALD D PODSKALNY
05/14/2012