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APPLICATION NUMBER:

203312Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 203-312 Resubmission/ Amendment -0047	**Reviewer:** Sandra Suarez Sharp, PhD	
Division:	DNP		
Applicant:	Impax Laboratories	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	Rytary®	**Biopharmaceutics Supervisory Lead (acting)**: Paul Seo, Ph.D.	
Generic Name:	Carbidopa+Levodopa fixed dose combination (FDC) extended release (ER) capsules	**Date Assigned:**	Aug 29, 2014
Indication	Treatment of (b) (4) Parkinson's disease	**Date of Review:**	Nov 04, 2012
Formulation/ Strength	Capsule; 23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	Primary Review due in DARRTS
NDA Resubmission - April 9, 2014 NDA Amendment - Aug 29, 2014	Aug 29, 2014	Nov 9, 2014

Type of Submission:	NDA Resubmission/Quality Information Amendment
Type of Consult:	Dissolution acceptance criteria

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Rytary® capsules consist of (b) (4) components (Components (b) (4)). Component (b) (4) contain both CD and LD as active ingredients. Component (b) (4) does not contain active ingredients but includes (b) (4) tartaric acid TA as an (b) (4). The (b) (4) active components of the IPX066 formulation exhibit a combination of immediate release, (b) (4) extended release (ER) (b) (4)

NDA 203-312 for Rytary® was originally submitted on Dec 21, 2011 and was recommended for approval by the Biopharmaceutics review team[1]. However, the submission received a complete response due to deficiencies raised the Office of Compliance (OC). Specifically, OC had concerns that the Applicant withdrawn the Hayward manufacturing site from the application and the approval of the application depended on critical manufacturing data generated at the Hayward facility. In addition, during the inspection of the Taiwan manufacturing site, OC found a deficiency on the validation of the (b) (4)). On Feb 25, 2014, the FDA informed the Applicant that their responses to the inspection related deficiencies adequately addressed the inspectional deficiencies observed during the inspections at the Hayward, CA facility. On April 9, 2014, the Applicant resubmitted the application. From the CMC perspective this included a stability update for the drug product.

[1] Biopharmaceutics review for NDA 203-312 entered in DARRTS by Dr. Sandra Suarez on Aug 2012.

In this amendment to the NDA's resubmission, the Applicant updated the manufacturing information to indicate that only the [redacted] (b) (4) (an [redacted] (b) (4) not covered in the original submission) would be used in the commercial production of Rytary at the Taiwan manufacturing site. Based on Email and phone communications with the CMC Reviewer, Dr. Charles Jewel, the change in equipment is considered minor. Therefore, from the biopharmaceutics perspective and based on SUPAC-ER recommendations, meeting the dissolution acceptance criteria is sufficient to support the proposed equipment change.

Batch Analysis data for [redacted] (b) (4) covering Content Uniformity and Dissolution of levodopa, carbidopa and tartaric acid were provided. Dissolution was tested for one batch per strength for batches manufactured using the new equipment. The following approved dissolution method and acceptance criteria were applied:

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)%

All the batches tested, including stability batches met the approved acceptance criteria for the three components (for details see \\cdsesub1\evsprod\NDA203312\0047\m1\us\12-cov-let).

RECOMMENDATION:

The dissolution information included in Amendment-0047 dated Aug 29, 2014, supports the approval of the proposed manufacturing equipment change.

From the Biopharmaceutics perspective the Resubmission 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 is recommended for APPROVAL.

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cc: PSeo;

Clinical Pharmacology Review

NDA:	203312
PRODUCT (Brand Name):	Rytary™ (IPX066)
PRODUCT (Generic Name):	Carbidopa and Levodopa
DOSAGE FORM:	Extended Release Capsule
INDICATION:	Treatment of (b) (4) Parkinson's disease, postencephalitic parkinsonism and (b) (4) parkinsonism
NDA TYPE:	505(b)(2)
SUBMISSION DATE:	12/21/2011
SPONSOR:	Impax Laboratories Inc.
OCP REVIEWER:	Jagan Mohan Parepally, Ph.D.
PHARMACOMETRICS REVIEWER:	Li Zhang, Ph.D.
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Clinical Pharmacology briefing was held on 11/15/2012.

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1 EXECUTIVE SUMMARY

Rytary (IPX066) is an extended release (ER) capsule formulation of carbidopa-levodopa (CD-LD) in 1:4 ratio. The current 505(b)(2) NDA seeks marketing approval of Rytary, intended for treatment of (b) (4) Parkinson's disease, post-encephalitic Parkinsonism, and (b) (4) Parkinsonism. Levodopa is the metabolic precursor of dopamine, crosses the blood-brain barrier, and is converted to dopamine in the brain thereby relieving symptoms of Parkinson's disease. Carbidopa inhibits the decarboxylation of peripheral levodopa, increasing bioavailability of levodopa. The CD-LD formulations used as reference listed products for this NDA include Sinemet®, Sinemet® CR, and Stalevo®. The proposed dosage strengths of Rytary include 23.75-95 mg, 36.25-145 mg, 48.75-195 mg, 61.25-245 mg. The recommended starting dose is 23.75 mg of carbidopa and 95 mg of levadopa (23.75 mg/95 mg) increased to 36.25 mg/145 mg. If sufficient symptomatic control is not observed, doses may be increased further up to a dose of 97.5 mg/390 mg three times daily.

The sponsor has targeted an exposure profile of levodopa that rapidly reaches an effective level and then maintains that level for duration of about (b) (4) hours. The formulation includes (b) (4) different components which are filled into the capsules to achieve the desired strengths and release/exposure profile. The rationale for development of IPX066 is to provide desired characteristics of initial absorption of LD and stable LD concentrations with reduced maximum observed plasma concentration/minimum observed plasma concentration (Cmax/Cmin) excursions in order to reduce motor fluctuations associated and to reduce the dosing frequency for all stages of the disease.

The pharmacokinetic properties of CD and LD from IPX066 were evaluated in 6 clinical pharmacology studies, including dose proportionality, single and multiple dose pharmacokinetics (PK), food-effect, relative bioavailability (BA) of IPX066 with marketed CD-LD products in healthy subjects, as well as pharmacokinetics and pharmacodynamics of IPX066 in patients with advanced Parkinson's disease. The effectiveness of IPX066 in patients with Parkinson's disease was established in two randomized, double-blind Phase 3 studies – a placebo-controlled study conducted in patients with early Parkinson's disease and a study conducted in patients with

advanced Parkinson's disease compared two different levodopa active comparators Sinemet® and Stalevo®.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP-I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 203312. The submission is acceptable from an OCP perspective. In addition, agreement on the labeling recommendations should be reached between the Sponsor and the Agency.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

General Pharmacokinetic Properties:
Levodopa (LD) is absorbed at fast to moderate rate from IPX066 with a T_{max} ranging from 0.5 to 11 hours after single- or multiple-dose administrations. The initial rise in LD concentration was comparable to the reference drug product for immediate-release (IR) CD-LD (Sinemet® IR). Following multiple-dose administration of IPX066, Q6H, accumulation of LD was comparable to that from IR CD-LD. The peak concentration is approximately 30% and 35% for LD and CD, respectively, relative to IR CD-LD. Following multiple dosing, LD from IPX066 had a lower fluctuation compared to IR CD-LD (fluctuation of 1.51 ± 0.41 and 3.23 ± 1.26 for IPX066 and IR CD-LD, respectively).

Population PK analysis using data from healthy subjects and patients with advanced Parkinson's disease showed that the apparent clearance (CL/F) and volume of distribution (V/F) for LD from IPX066 were 56.8 L/hr and 114.4 L, respectively. Further, intrinsic factors (e.g., age, body weight, gender) and subjects' status (healthy subjects vs. PD patients) had no significant effect on the model parameters.

Relative Bioavailability:
The relative bioavailability (BA) of LD from IPX066 in patients was approximately 70% relative to Sinemet® IR. The relative BA of LD from IPX066 in healthy subjects relative to Sinemet® IR, Sinemet® CR, and Stalevo® was 80.4%, 75.1%, and 56.1%, respectively. Population PK analysis reported that, of the LD absorbed from IPX066, the IR phase contributes 27%, with 48% and 25% contribution from the second and third ER phases, respectively.

Dose proportionality:
Dose proportionality of LD exposure following administration of single-dose of IPX066 was assessed by dose normalized to IPX066 245 mg LD. The 90% confidence intervals (CIs) for the LD C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, were within 80% to 125% range. The C_{max} and AUC of LD from IPX066 increased in a dose-proportional manner over the LD dose of 95 mg to 245 mg.

Dose Conversion:
Due to the proposed conversion strategy to a IPX066 dose for a range of starting IR LD doses, it was expected that similar Cmax of LD, at all doses, will not be achieved. To overcome this issue, the sponsor proposes that patients can take an additional IPX066 dose during bed time if symptoms are not controlled. The proposed dosing guidelines are reasonable for initial conversion, although in clinical trials the dose of IPX 066 was adjusted further to maximize benefit-risk in each individual patient.

Exposure-Response Relationship:
Population pharmacodynamic modeling was conducted using LD plasma concentration data and pharmacodynamic assessments (tapping, UPDRS Part III scores, and Investigator-rated dyskinesia) from the open-label Phase 2 study in patients with advanced PD (Study IPX066-B08-11, N=27). Pharmacodynamic modeling concluded the following:

- The concentration-effect relationship for IPX066 is comparable to IR CD-LD for tapping and UPDRS Part III.
- The estimated onset of effect for IPX066 as measured by tapping rate and UPDRS Part III occurs within 45 minutes of oral administration. The onset of effect for IPX066 is comparable to that noted with IR CD-LD.
- The duration of effect is approximately 2 hours longer for IPX066 than for IR CD-LD for both tapping and UPDRS Part III. The longer duration of effect is consistent with the sustained LD plasma concentration profile from an extended-release formulation. The longer pharmacodynamic effect translates into the sustained effect noted predose on Day 8.
- The Investigator-rated dyskinesia scores support the observations noted with tapping and UPDRS Part III.

Formulation Bridging:
A bridging crossover BE study (IPX066-B10-01) was conducted to assess bioequivalence of the LD 245 mg strength manufactured in Jhunan (commercial formulation) to IPX066 (clinical formulation) manufactured in Hayward. The 90% CIs of levodopa and carbidopa PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) were within 80 to 125% range.

Food Effect on Bioavailability:
Following administration of IPX066 capsules to healthy subjects in a fed state (standard high-fat, high-calorie), food had no effect on the extent of absorption (AUC_{inf}) of LD. There was a decrease in C_{max} by approximately 21% and a delay in T_{max} by 5.5 hours (from 1.5 to 7 hours) for LD. Sprinkling the IPX066 capsule contents on applesauce did not affect LD PK compared to the intact capsule except for delaying the T_{max} for LD by 2.5 hours (from 1.5 to 4 hours).

IPX066 can be taken with or without food. However, patients should be informed about the possible delay in LD absorption when administered with food. Similar to other CD-LD products, patients should be cautioned that taking IPX066 with foods

rich in proteins or amino acids may interfere with the oral absorption and pharmacological effects of LD.

Effect of Alcohol:
The effect of alcohol co-administration on the PK of IPX066 was determined in a single-dose, three-treatment (0%, 5%, 20% v/v alcohol) crossover study followed by a fixed treatment (40% v/v alcohol). There was a 15% increase, on an average, in LD C_{max} at 5% alcohol co-administration but not at higher concentrations (20% and 40%). There was no change in LD $AUC_{0-\infty}$ at 5% alcohol concentration. However, LD $AUC_{0-\infty}$ at 20% and 40% alcohol concentrations increased by approximately 16% and 23% respectively compared to 0% alcohol.

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2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are therapeutic indication(s) and the mechanisms of action of IPX066?

IPX066 (levodopa + carbidopa) is indicated for the treatment of (b) (4) Parkinson's disease, postencephalitic Parkinsonism and (b) (4) Parkinsonism. Levodopa (LD) is the metabolic precursor of dopamine, crosses the blood-brain barrier, and is converted to dopamine in the brain. This is thought to be the mechanism whereby LD relieves symptoms of Parkinson's disease. When LD is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa (CD) inhibits the decarboxylation of peripheral LD, making more LD available for delivery to the brain. When co-administered with LD, CD increases plasma levels of LD and reduces the amount of LD required to produce a given response by about 75%. Carbidopa prolongs the plasma half-life ($t_{1/2}$) of LD from 50 minutes to 1.5 hours and decreases plasma and urinary levels of dopamine and its major metabolite, homovanillic acid.

2.1.2 What is the proposed dose and dosage form?

The daily dosage of IPX066 is titrated to achieve symptomatic control while closely monitoring during the dose adjustment period, particularly with regard to appearance or worsening of dyskinesia or nausea. The recommended starting dose is one capsule of LD 95 mg three times daily for the first 3 days; this may be increased to 145 mg three times daily from Day 4 of treatment. If sufficient symptomatic control is not observed at a dose of IPX066 LD 145 mg three times daily, doses may be increased further up to a total daily dose of 1170 mg (see Section 2.5.1 for detailed information about the formulation).

IPX066 is an extended release capsule formulation containing dopamine precursor (LD) combined with a decarboxylase inhibitor (CD) in a 4:1 ratio.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The daily dosage of reference listed drugs i.e., Sinemet® IR, Sinemet® CR, and Stalevo®) are determined by titration to achieve optimum therapeutic benefit while closely monitoring during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea.

IPX066 is an extended release formulation intended to provide faster initial absorption of LD comparable to IR CD-LD, decrease fluctuations in maximum

observed plasma concentration/minimum observed plasma concentration, and reduce the dosing frequency compared IR CD-LD for all stages of the disease.

The clinical trials conducted by the sponsor to support the approval of the IPX066 are summarized in the following table:

Table: Clinical studies in support of the IPX066

Type of Study	**Study Title**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects Healthy/**
BA	IPX066-B08-04: A Bioavailability Study of One 2 x 47.5-190 mg Carbidopa-Levodopa Formulation under Fasting Conditions	To compare the bioavailability of one 2 x 47.5-190 test formulation of carbidopa-levodopa capsules with that of one 50-200 mg SINEMET® CR tablet and that of one 25-100 mg SINEMET® tablet in healthy adult subjects administered under fasting conditions.	Randomized, single-dose, three-way, crossover bioavailability study with a 3-day washout between treatment periods	IPX066: 48.75-190 mg (CD-LD) capsules (2 capsules) SINEMET® CR: 50-200 mg tablets 25-100 mg tablets Single-dose Oral	15 Healthy subjects
BA	IPX066-B08-08: Effect of food on the pharmacokinetics of IPX066	To assess the effect of high fat meal on the PK of IPX066. To assess the PK of IPX066 after sprinkling of the capsule contents on applesauce	Randomized, single-dose, open-label, 3-sequence, 3-treatment, crossover bioavailability study with a 6-day washout between treatment periods	IPX066: 61.25-245 mg (CD-LD) capsules (2 capsules) Single-dose: Treatment 1: fed Treatment 2: fasted Treatment 3: sprinkled on apple-sauce	21 Healthy subjects
BA	IPX066-B08-09: Assessment of Dose Proportionality of IPX066	To assess the dose proportionality of four strengths of IPX066 under fasted conditions in healthy subjects.	Randomized, open-label, single-dose, 4-sequence, 4-treatment, crossover bioavailability study with a 6-day washout between treatment periods	IPX066: 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD)	31 Healthy subjects
BA	IPX066-B08-10: Relative Bioavailability of IPX066 to Carbidopa-Levodopa Formulations	To assess the bioavailability of two capsules of IPX066 49.75-195 mg (total dose 97.5-390 mg) CD-LD relative to Sinemet 25-100 mg CD-LD, Sinemet CR 25-100 mg CD-LD, and Stalevo 25-100-200 mg CD-LD-entacapone (CLE) under fasting conditions.	Randomized, single-center, single-dose, open-label, four-sequence, four-treatment, crossover bioavailability study with a 6-day washout between treatment periods	IPX066 : 97.5-390 mg (2 x 48.75-195 mg) (CD-LD) Sinemet®: 25-100 mg (CD-LD) Sinemet® CR: 25-100 mg (CD-LD) Stalevo®: 25-100 mg (CD-LD)	24 Healthy subjects
BA	IPX066-B09-01: Effect Of Food on the Pharmacokinetics of IPX066	To assess the effect of a high-fat, high-calorie meal on the PK of IPX066 and to assess the effect of sprinkling the IPX066 capsule contents on applesauce on the PK of IPX066.	Randomized, single-center, single-dose, open-label, three-sequence, three-treatment crossover bioavailability study with a 6-day washout between treatment periods	IPX066: 61.25-245 mg (CD-LD) capsules (2 capsules) Single-dose: Treatment 1: fed Treatment 2: fasted Treatment 3: sprinkled on apple sauce	21 Healthy subjects

BA	IPX066-B09-04: The Effect of Alcohol on IPX066	To investigate the effect of 240 mL of 0%, 5%, 20%, and 40% v/v alcohol on the IPX066 capsule formulation in healthy volunteers.	Randomized, single-dose, open-label, three-sequence, three-treatment crossover bioavailability study followed by a fixed treatment in period 4 with a 6- day washout between treatment periods	IPX066 : 97.5-390 mg (CD-LD) (2 x 48.75-195 mg) Single dose: •IPX066 with 240 mL of 0% alcohol •IPX066 with 240 mL of 5% alcohol •IPX066 with 240 mL of 20% alcohol •IPX066 with 240 mL of 40% alcohol	21 Healthy subjects
BE	IPX066-B10-01: Assessment of the Bioequivalence of IPX066 Manufactured at Two Sites	• To assess the bioequivalence of IPX066 manufactured in Hayward, CA, USA and in Jhunan, Taiwan. • To assess the dose proportionality between one and two capsules of IPX066 61.25-245 mg CD-LD formulation manufactured in Hayward, CA, USA.	Randomized, single-center, single-dose, open-label, two-sequence, two-treatment crossover study with an additional treatment period after Period 2 with a 6-day washout between treatment periods	IPX066: 61.25-245 mg (CD-LD) capsules (Jhunan, Taiwan) 61.25-245 mg (CD-LD) capsules (Hayward, CA, USA) Single-dose: • IPX066 (1 capsule) (Hayward or Jhunan) • IPX066 (1 capsule) (Jhunan or Hayward) • IPX066 (2 capsules) (Hayward)	39 Healthy subjects
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	• 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 (30 weeks)	IPX066: 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 IPX066 or Placebo: 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	381 Early LD-Naïve PD patients (Hoehn & Yahr Stage I-III)
Phase 2	IPX066-B08-11: A Study to Compare Pharmacokinetics and Pharmacodynamics of IPX066 to Standard Carbidopa-Levodopa	• To compare the single- and multiple-dose pharmacokinetics (PK) of IPX066 capsule formulation with IR CD-LD tablet formulation. • To assess the accumulation of IPX066 at steady state when dosed approximately Q6H. • To examine the efficacy and pharmacodynamics.	Randomized, multicenter, open-label, two-treatment, two-period, crossover study	IPX066: 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD) Sinemet®: 25-100 mg (CD-LD) 7 days of one treatment (IPX066 or IR CD-LD) followed by an approximate 7-day washout period followed by another 7 days of the other treatment (IR CD-LD or IPX066)	27 LD-experienced patients with Parkinson's disease (PD)
Phase 3	IPX066-B09-02 (ADVANCE-PD): A Study to Evaluate the Safety and Efficacy of IPX066 in Advanced Parkinson's Disease	To evaluate the safety and efficacy of IPX066 in the treatment of advanced PD subjects in comparison to IR CD LD. Study Duration: 22 weeks: (3-week dose adjustment, 6-week dose conversion, 13-week double-blind)	Randomized, double-blind, double-dummy, active-control, parallel-group 13-week comparison study	IPX066: 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD) Sinemet®: 25-100 mg (CD-LD) Doses individually titrated during open label, then fixed for double blind phase Dose Evaluated: IR CD-LD: 400 – 2550 mg/day IPX066: 855 – 2940 mg/day	393 patients randomized Advanced PD patients (Hoehn & Yahr Stage I-IV)

Phase 3	IPX066-B09-03: An Open Label Extension Study of the Safety and Clinical Utility of IPX066 in Subjects with Parkinson's Disease	To evaluate the long-term safety and clinical utility of IPX066 in subjects with Parkinson's disease (PD).	Multicenter, open-label safety extension study	IPX066: 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD) Individualized dosing Dose Evaluated: 285 – 2940 mg/day	Early and Advanced PD patients (268 patients with early disease; 349 patients with advanced disease)
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	Part 1: •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. Part 2: •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.	Part 1: Open-label, dose conversion followed by randomized, double-blind, double-dummy, 2-treatment, 2-period (separated by 2-week open-label), crossover study Part 2: 6-month open-label extension	IPX066: 23.75-95 mg (CD-LD) 36.25-145 mg (CD-LD) 48.75-195 mg (CD-LD) 61.25-245 mg (CD-LD) CLE: Sinemet®: 25-100 mg (CD-LD) Comtan®: 200 mg (CD) Individualized dosing. CLE fixed at entry IPX066 fixed after dose conversion	91 patients randomized 84 patients (Advanced PD patients, Hoehn & Yahr Stage I-IV)

2.2.2 What are the clinical endpoints of Phase 3 clinical studies conducted to establish the effectiveness of IPX066?

The effectiveness of IPX066 in patients with Parkinson's disease was established in two randomized, double-blind Phase 3 studies. A placebo controlled study conducted in patients with early Parkinson's disease and another study conducted in patients with advanced Parkinson's disease compared two different levodopa active comparators Sinemet® IR and Stalevo®.

The effects of treatments were measured by Unified Parkinson's Disease Rating Scale [UPDRS], patient diaries, patient and clinical global impressions of change, and quality-of-life questionnaires relating to general health status and PD-associated disability. The UPDRS is a multi-item rating scale evaluating mentation, behavior, and mood (Part 1), activities of daily living (Part II), motor examination (Part III), and complications of therapy (Part IV). Patients recorded the time spent in the "On" and "Off" states in home diaries periodically throughout the duration of the trial. The modified Rankin Scale was used as a measure of disability in daily activities of patients.

2.2.3 Exposure-Response

2.2.3.1 Is there any exposure-effect relationship with IPX066? And how does this relationship compare with IR LD?

Yes, there is an exposure-effect relationship with IPX066. Population pharmacodynamic modeling was performed using LD plasma concentration data and pharmacodynamic assessments (tapping, UPDRS Part III scores, and Investigator-rated dyskinesia) from the open-label Phase 2 study in patients with advanced PD to evaluate exposure-effect relationship (Study IPX066-B08-11). Pharmacodynamic modeling indicated the following:

1) The concentration-effect relationship for IPX066 is comparable to IR CD-LD for tapping and UPDRS Part III.
2) The estimated onset of effect for IPX066 as measured by tapping rate and UPDRS Part III occurs within 45 minutes of oral administration. The onset of effect for IPX066 is comparable to that noted with IR CD-LD.
3) The duration of effect is approximately 2 hours longer for IPX066 than for IR CD-LD for both tapping and UPDRS Part III. The longer duration of effect is consistent with the sustained LD plasma concentration profile from an extended-release formulation. The longer pharmacodynamic effect translates into the sustained effect noted predose on Day 8.
4) The Investigator-rated dyskinesia scores support the observations noted with tapping and UPDRS Part III.

2.2.4 How does the single- and multiple-dose pharmacokinetics of IPX066 capsule formulation compare with IR CD-LD tablet formulation (Sinemet® tablet)?

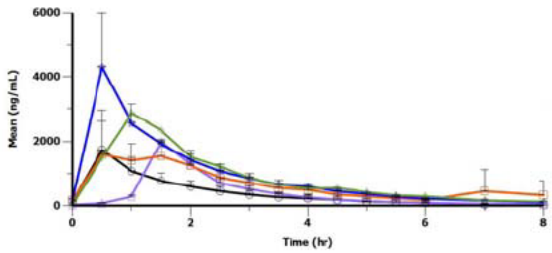
Single- and multiple-dose PK of IPX066 test capsule formulations (48.75-195 mg and 61.25-245 mg CD-LD) were compared with reference IR CD-LD tablet formulation (Sinemet® 25-100 mg CD-LD) in Study IPX066-B08-11. This study was a randomized, multicenter, open-label, two-treatment, two-period, crossover study in LD-experienced subjects with Parkinson's disease. The reference and test treatments were administered every 6 hours (Q6H) for 7 days.

LD is absorbed at fast to moderate rate from IPX066 with a T_{max} ranging from 0.5 to 11 hours after single- or multiple-dose administrations. Compared to levodopa, carbidopa (CD) was absorbed at slower rate with a T_{max} ranging from 1.5 to 12 hours. The initial rise in LD concentration was comparable to that for immediate-release carbidopa-levodopa (IR CD-LD) (Sinemet® IR). 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 Q6H was comparable to IR CD-LD. The peak concentration is approximately 30% and 35% for LD and CD, respectively, relative to IR CD-LD. Following multiple dosing, IPX066 had a lower fluctuation compared to IR CD-LD (fluctuation of 1.51 ± 0.41 and 3.23 ± 1.26 for IPX066 and IR CDLD, respectively). The fluctuation in CD plasma concentrations following IPX066 was 1.19 ± 0.49, less than that noted for IR CD-LD treatment (1.54 ± 0.45) as shown in the figures and tables below.

Figure: Mean (SD) LD Plasma Concentration-Time Profiles Following Single-Dose and Multiple-Dose Sinemet® IR Administration

Single Dose (Day 1)



Multiple Dose (Day 8)

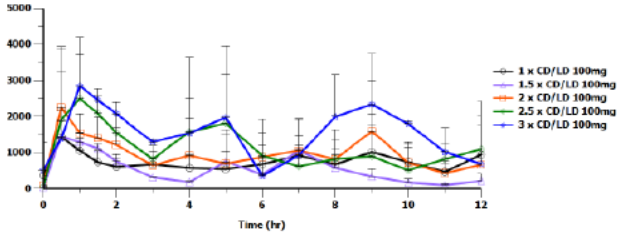
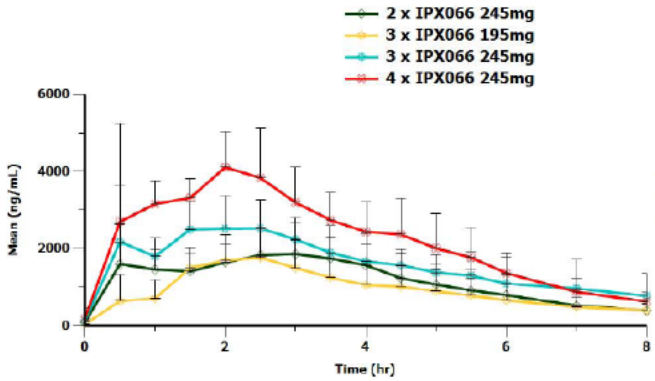


Figure: Mean (SD) LD Plasma Concentration-Time Profiles Following Single Dose and Multiple Dose IPX066 Administration

Single Dose (Day 1)



Multiple Dose (Day 8)

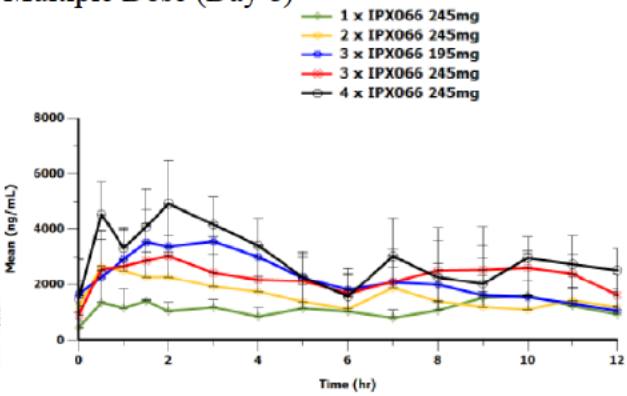
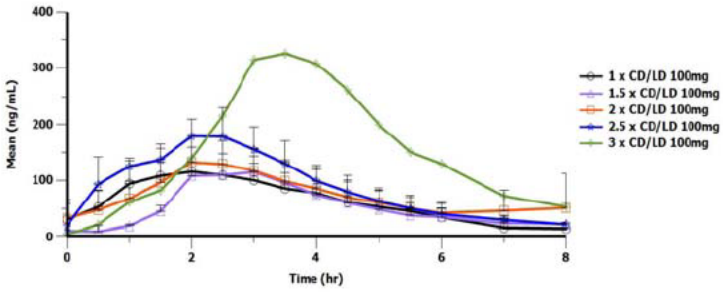


Figure: Mean (SD) CD Plasma Concentration-Time Profiles Following Single-Dose and Multiple-Dose Sinemet® IR Administration

Single Dose (Day 1)



Multiple Dose (Day 8)

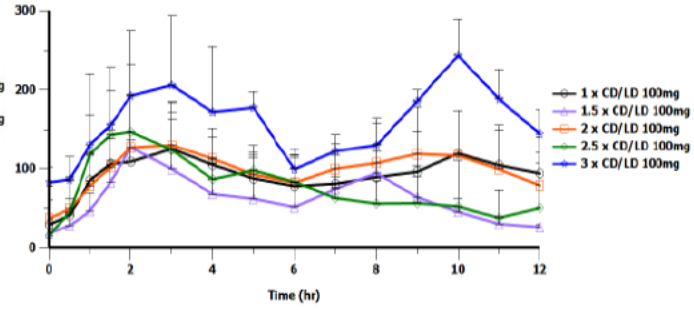
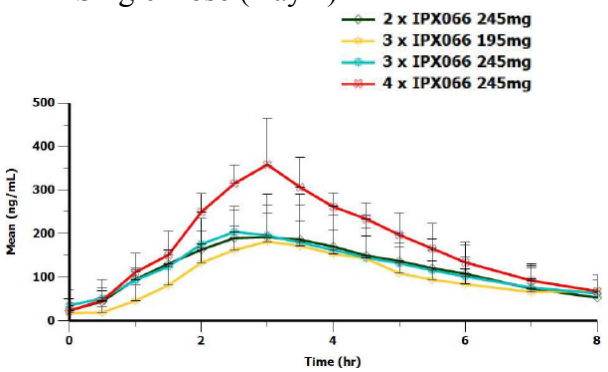


Figure: Mean (SD) CD Plasma Concentration-Time Profiles Following Single-Dose and Multiple-Dose IPX066 Administration

Single Dose (Day 1)



Multiple Dose (Day 8)

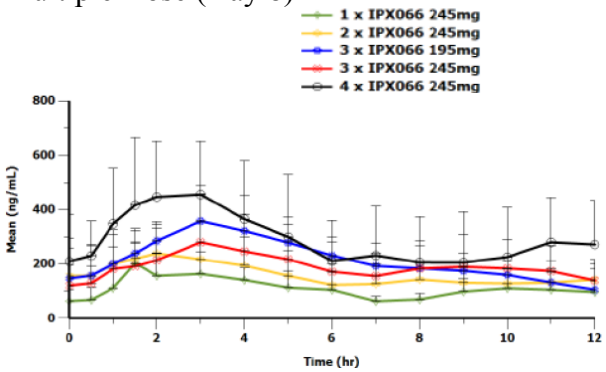


Table: Summary of Levodopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate-Release CD-LD

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 $AUC_{0-\tau}$ on Day 8/$AUC_{0-\tau}$ 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: Summary of Carbidopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate-Release CD-LD

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 $AUC_{0-\tau}$ on Day 8/$AUC_{0-\tau}$ 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.

Of note, a population PK analysis was conducted by the Sponsor using data from healthy volunteers (Studies IPX066-B08-10 and IPX066-B09-01) and from patients with advanced Parkinson's disease (Study IPX066-B08-11). It was concluded that:

- IPX066 PK can be adequately described by a one-compartment model with first-order absorption and elimination, and a lag time for the IR and two ER components of the IPX066 formulation.
- Relative BA for LD from IPX066 compared to IR LD was 85%. Of the LD absorbed from IPX066, the IR phase contributes 27%, with 48% and 25% contribution from the second and third ER phases, respectively.
- Apparent clearance (CL/F) was 56.8 L/hr and apparent volume of distribution (V/F) was 114.4 L.
- Age, body weight, gender, and subjects' status (healthy volunteer vs. PD patient) had no significant effect on the model parameters.

(See Section 4.2 Pharmacometrics Review for details)

2.2.5 Do different strengths of IPX066 show dose proportionality in terms of carbidopa and levodopa PK parameters?

Dose proportionality of LD PK parameters following administration of IPX066 was assessed by dose normalized to IPX066 245 mg LD. The 90% CI for the PK parameters Cmax, AUC0-t and AUC0-∞ were with 80% to 125% range. The Tmax of LD ranged from 2.75 to 4 hours. The half-life of LD ranged from 1.44 to 1.53

hours. The Cmax 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 figure and table below.

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

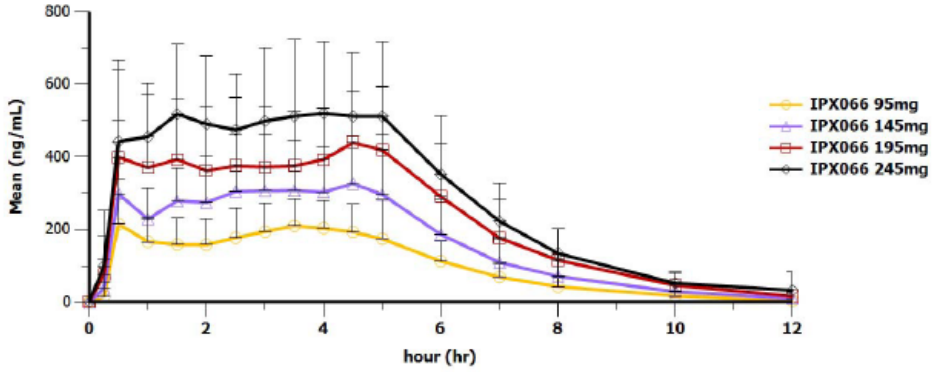


Table: Statistical Analysis of the Log-Transformed Pharmacokinetic Parameters for LD in Study IPX066-B08-09, Mean ± SD, (N=28)

PK Parameters	Contrast IPX066 Dose (mg)	Ratio (%)	90% Confidence Interval	
			Lower	Higher
Cmax	95/245	105.30	96.86	114.47
AUC0-t	95/245	89.57	83.07	96.57
AUC0-∞	95/245	89.95	83.93	96.41
Cmax	145/245	107.83	99.17	117.24
AUC0-t	145/245	94.52	87.65	101.92
AUC0-∞	145/245	94.41	88.08	101.19
Cmax	195/245	101.84	93.68	110.71
AUC0-t	195/245	98.22	91.10	105.89
AUC0-∞	195/245	97.74	91.20	104.76

Figure: Mean (SD) Carbidopa Plasma Concentration-Time Profiles

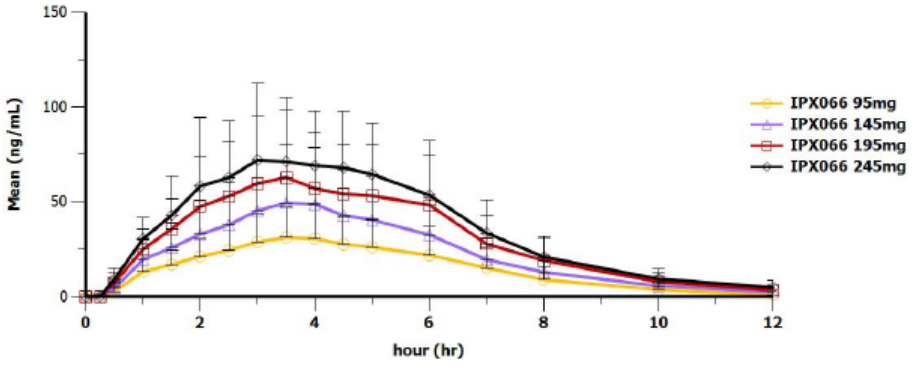


Table: Statistical Analysis of the Log-Transformed Pharmacokinetic Parameters for CD in Study IPX066-B08-09, Mean ± SD, (N=28)

PK Parameters	Contrast IPX066 Dose (mg)	Ratio (%)	90% Confidence Interval	
			Lower	Higher
Cmax	23.75/61.25	104.03	88.83	121.83
AUC0-t	23.75/61.25	98.67	87.60	111.15
AUC0-∞	23.75/61.25	100.25	89.33	112.50
Cmax	36.25/61.25	99.83	85.22	116.95
AUC0-t	36.25/61.25	98.43	87.36	110.91
AUC0-∞	36.25/61.25	99.05	88.25	111.18
Cmax	48.75/61.25	101.86	86.98	119.29
AUC0-t	48.75/61.25	102.28	90.79	115.21
AUC0-∞	48.75/61.25	101.71	90.64	114.13

2.2.6 What is the Dose/Dosing Regimen for Initial Conversion from Immediate-Release Levodopa (IR LD) Product to IPX066 in Parkinson's disease Patients?

The dose/dosing regimen for initial conversion from IR LD to IPX066 in Parkinson's disease patients is shown in the table below.

Table: Guidelines for Initial Conversion from IR Levodopa Product to IPX066 in Parkinson's Disease Patients.

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	[TRADE NAME] 95	4 capsules
750 to	[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
(b) (4)		

The proposed conversion is verified by a simulated model using mean LD concentration time profile when patients were initially treated with IR LD for one week and switched to IPX066 for another week. The simulation was to characterize the mean PK of IPX066 in healthy volunteers and in patients with PD when they were treated with IR and IPX066.

The simulation model was based on the Sponsor's PK model with 85% bioavailability. The PK model that described the data for IR LD was a one-compartment model with first-order absorption, first-order elimination, and an absorption lag time. The PK model that described the data for IPX066 included

three-phase absorption corresponding to the IR component and the two ER components in addition to first-order elimination.

Due to the proposed conversion strategy to a IPX066 dose for a range of starting IR LD doses, it is expected that similar Cmax of LD, at all doses, will not be achieved. To overcome this issue, the Sponsor proposes that patients can take an additional IPX066 dose during bed time if symptoms are not controlled. The proposed dosing guidelines are reasonable for initial conversion, although in clinical trials the dose of IPX066 was adjusted further to maximize benefit-risk in each individual patient.

2.2.7 What is the inter- and intra-subject variability in IPX066 LD PK parameters in healthy subjects and patients?

Intersubject and intrasubject variability in LD PKs was estimated in healthy volunteers using log-transformed AUCinf and Cmax data from Studies IPX066-B08-09 and IPX066-B10-01 following dose-normalization to 245 mg LD. Intersubject and intrasubject variability was 62.0% and 38.0% respectively for LD AUCinf. Intersubject and intrasubject variability accounted for 52.5% and 47.5% for LD Cmax, respectively (table below).

Table: Analysis of Variance of Log-transformed Dose-normalized PK Parameters for Healthy Subjects

Analyte	PK Parameter	Between Subject Covariance Parameter Estimate	Within Subject Covariance Parameter Estimate	Total Estimate of Variability	Between Subject Variability (%)	Within Subject Variability (%)
Carbidopa	ln(AUCinf)	0.1252	0.0594	0.1847	67.81	32.19
	ln(Cmax)	0.1279	0.0965	0.2244	57.01	42.99
Levodopa	ln(AUCinf)	0.0479	0.0293	0.0772	62.04	37.96
	ln(Cmax)	0.0383	0.0346	0.0729	52.51	47.49

NOTE: Dose normalized to 245 mg.

In subjects with PD the intersubject variability in LD Cmax and AUCinf as measured by %CV using the pooled data from Studies IPX066-B08-11 and IPX066-B09-06 was 40.1% and 44.2%, respectively.

2.3 Intrinsic Factors

2.3.1 Did population PK analysis identify the need for dose adjustment with regard to intrinsic factors?

No. Population PK analysis did not identify the need for dose adjustment with regard to intrinsic factors (e.g., age, gender, and body weight).

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 PK model utilized was a one-compartment model with first-order absorption and elimination. For IPX066, three first-order absorption rates, each with a lag time, were incorporated corresponding to the IR and two ER components of the IPX066 formulation. Age, body weight, gender and population status (healthy volunteer versus PD patient) were tested as covariates in the PK model. Based on the population PK analysis from healthy volunteers and patients with PD:

- Age, body weight, gender, and subjects' status (healthy volunteer versus PD patient) had no significant effect on the model parameters.
- IPX066 PK can be adequately described by one-compartment model with first-order absorption and elimination, with lag times for the IR and two ER components of the IPX066 formulation.
- Apparent CL/F was 56.8 L/hr and apparent V/F was 114.4 L.

2.4 Extrinsic Factors

2.4.1 Is there any drug-drug interaction involving carbidopa or levodopa with the concomitant medications?

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 review for NDA 19-856).

2.4.2 Is there an excipient (b) (4)-drug interaction potential with drugs co-administered with IPX066 in PD patients?

(b) (4) co-polymers of (b) (4) and the metabolite (b) (4) of IPX066. These polymers dissolve at different pH (b) (4) drugs (b) (4)

At the maximum recommended human dose (MRHD) per day of 612.5-2450 mg (CD-LD) from the IPX066 formulation, the intake of (b) (4) will be (b) (4) mg/day and (b) (4) mg/day, respectively. The Agency's non-clinical review team notes that the total daily dose of (b) (4) at MRHD per day in IPX066 exceeds products containing (b) (4), approved for regimens up to 6 weeks, by (b) (4)-fold. The total daily dose of (b) (4) in IPX066 at MRHD per day was (b) (4)-time lower than the approved drugs containing (b) (4). Given that, the intake of total (b) (4) would be comparable to the approved formulations. There are no known excipient-drug interactions reported in the literature to date. Therefore, the potential for excipient (b) (4) in IPX066 to interact with concomitant medications can be ruled out.

2.5 General Biopharmaceutics

2.5.1 What is the formulation of IPX066?

Rytary (IPX066) is an ER capsule formulation of CD-LD. The capsules are available in four CD-LD dosage strengths 23.75 mg/ 95 mg, 36.25 mg/145 mg, 48.75 mg/195mg, and 61.25 mg/245 mg (all strengths with the fixed dose ratio of CD/LD being 1:4).

To achieve an exposure profile that rapidly reaches an effective level and then maintains that level for the duration of (b) (4) hours. The Sponsor developed a formulation that involves (b) (4) different components which are filled into the ER capsules to achieve the desired strengths and release/exposure profile. (b) (4) of the components contain CD and LD (albeit each component demonstrates a different release profile driven by its formulation) (b) (4)

Each capsule also contains TA (b) (4) excipient. (b) (4)

The formulation itself is not particularly sensitive to the amount of TA. The table below shows some of the key attributes of each of the components:

Table: key Attributes of Each of the Component of IPX066 Formulation

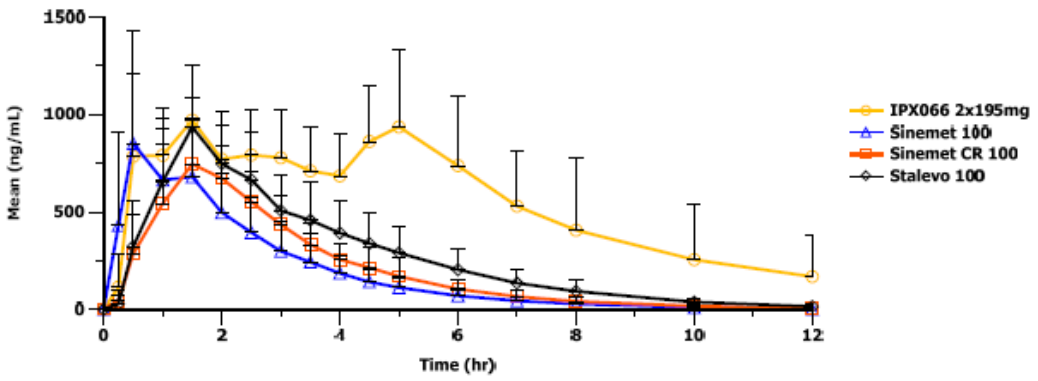
Component ID	Attributes
(b) (4)	

2.5.2 How does the bioavailability of carbidopa and levodopa from IPX066 capsule compare with reference formulations (Sinemet® tablet, Sinemet® CR tablet and Stalevo®)?

Relative bioavailability of Rytary (CD-LD, 97.5-390 mg) to other CD-LD formulations including Sinemet® 25-100 mg, Sinemet® CR 25-100 mg, and Stalevo® 25-100-200 mg -entacapone was assessed in a single-dose, open-label, randomized, four-sequence, four-treatment crossover study (IPX066-B08-10) in healthy volunteers.

Following SD administration of IPX066 the initial increases in LD plasma concentrations were similar to Sinemet® at about 0.5 hours. The first peak appeared at approximately1.5 hours. There was a similar second peak in LD concentration at approximately 5 hours. In between the two peaks there was sustained LD concentration which was comparable to initial peak LD concentration at 0.5 hours. The bioavailability of LD from IPX066 relative to Sinemet, Sinemet CR, and Stalevo was 80.4%, 75.1%, and 56.1%, respectively. IPX066 produced more sustained LD plasma profile than Sinemet, Sinemet CR, and Stalevo as shown in the figure below.

Figure: Mean (SD) LD Plasma Concentration-Time Profiles Following Administration of IPX066, Sinemet, Sinemet CR, and Stalevo



The relative bioavailability for CD to the reference drug products (Sinemet® 25-100 mg CD-LD, Sinemet® CR 25-100 mg CD-LD, and Stalevo® 25-100-200 mg CD-LD-entacapone) was 47.5%, 57.0%, and 55.0%, respectively, as shown in the figure below. Summary of the key PK parameters of LD and CD are presented in the tables below.

Figure: Mean (SD) CD Plasma Concentration-Time Profiles Following Administration of IPX066, Sinemet, Sinemet CR, and Stalevo.

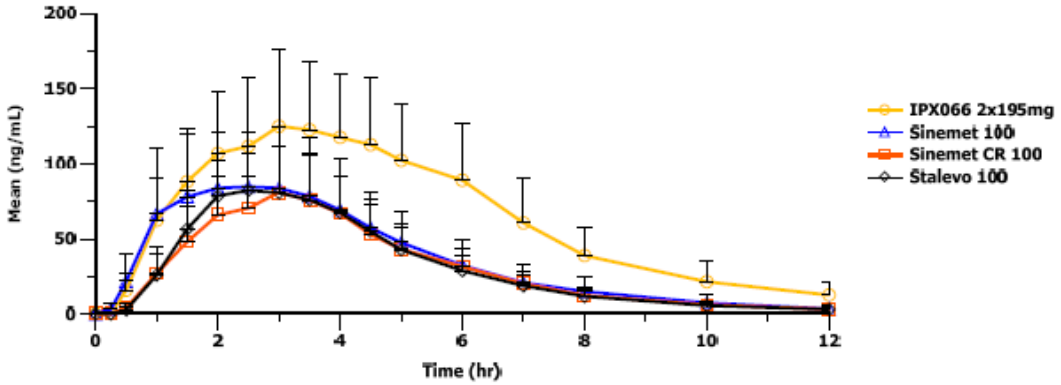


Table: Summary of Levodopa Pharmacokinetics Following a Single Dose of IPX066 97.5-390 mg CD-LD, Sinemet® 25-100 mg CD-LD, Sinemet® CR 25-100 mg CD-LD or Stalevo® 25-100-200 mg CD-LD-entacapone in Study IPX066-B08-10, Mean ± SD, (N = 22).

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**
Tmax (h) (median)	4.50 (0.5-8.0)	1.00 (0.50-2.00)	1.50 (1.00-2.00)	1.50 (1.00-2.00)
Cmax (ng/mL)	1325.64 ± 267.88	1094.36 ± 401.14	854.96 ± 299.28	1026.77 ± 284.29
AUC0-t (ng·hr/mL)	6752.81 ± 2086.16	2215.35 ± 665.20	2372.43 ± 682.29	3250.82 ± 1135.40
AUC0-∞ (ng·hr/mL)	7243.98 ± 2553.23	2250.63 ± 664.36	2403.06 ± 679.99	3290.75 ± 1149.47
t1/2 (h)	1.91 ± 0.66	1.55 ± 0.17	1.55 ± 0.20	1.57 ± 0.19
Bioavailability of LD Relative to IPX066	Reference	80.4% (74.30, 86.89)	75.1% (69.45, 81.22)	56.1% (51.90, 60.69)
Bioavailability of LD Relative to Sinemet®	80.4% (74.30, 86.89)	Reference	107.0% (98.93, 115.69)	143.2% (132.39, 154.83)

Table: Summary of Carbidopa 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**
Tmax(h) (median)	3.50 (1.50 - 6.00)	2.50 (1.00 - 5.00)	3.00 (2.00 - 4.50)	2.50 (2.00 - 4.00)
Cmax (ng/mL)	147.89 ± 49.45	106.39 ± 42.90	85.87 ± 31.96	92.47 ± 29.50
AUC0-t (ng·hr/mL)	769.12± 250.98	437.11± 155.33	361.50±114.54	371.62 ± 109.97
AUC0-∞ (ng·hr/mL)	822.40 ± 275.67	447.86 ±157.38	372.76±117.05	380.74 ± 11.52
t1/2 (h)	2.54 ± 1.10	1.84 ± 0.24	2.04 ± 0.42	1.82 ± 0.31
Bioavailability of CD Relative to IPX066	Reference	47.5% (42.25, 53.46)	57.0% (50.69, 64.15)	54.9% (48.85, 61.82)
Bioavailability of CD Relative to Sinemet	47.5% (42.25, 53.46)	Reference	83.3% (74.08, 93.75)	86.5% (76.88, 97.29)

2.5.5 What is the effect of food on the bioavailability of IPX066?

The effects of a high-fat, high-calorie meal and sprinkling the IPX066 capsule contents on applesauce on the PK profiles of CD and LD from IPX066 were determined in a single-dose, open-label, randomized, three-sequence, three-treatment crossover study in healthy subjects (IPX066-B09-01).

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 (AUCinf). There was a delay in LD absorption to reach the secondary peak plasma concentration (Tmax) by 5.5 hours (from 1.5 hours to 7 hours) and a decrease in LD Cmax 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, as well as the Forest Plot presentation of statistical analysis are shown in the figure below.

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

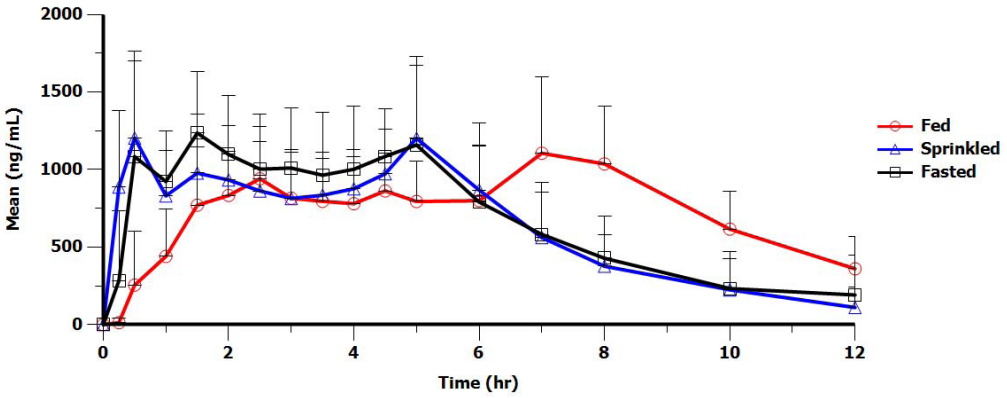
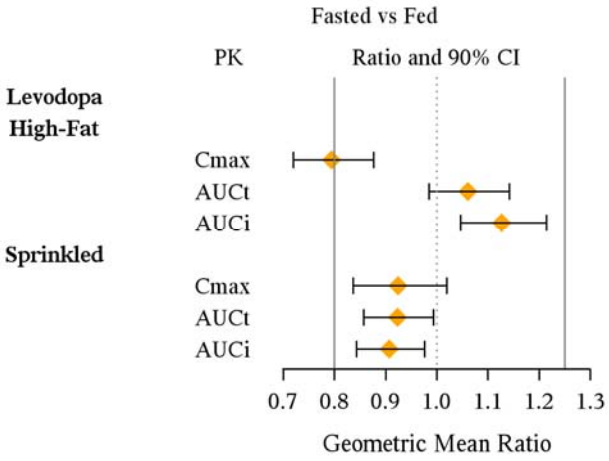
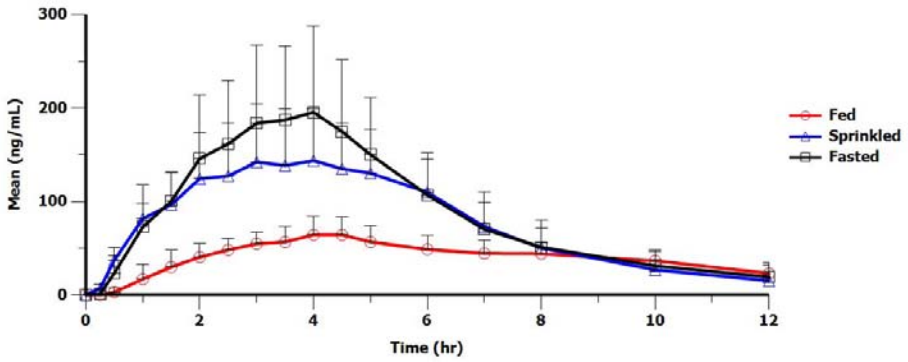


Figure. Forest Plot: Summary of 90% CI Assessment for Levodopa in Study IPX066-B09-01, (N = 19)



Carbidopa AUC and Cmax values, on the other hand, were decreased by 40% and 50%, respectively, with a delay in reaching peak concentration by approximately 1 hour in the presence of high fat and high calorie food when compared to the fasted state as shown in the figure below. It is noted that the peripheral dopa decarboxylase is saturated by carbidopa at approximately 70~100 mg a day, and thus the observed decrease in CD exposure by food is not likely to have adverse impact on availability of LD to the site of action (see approved labels for Stalevo®, Sinemet®, and Sinemet®CR).

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

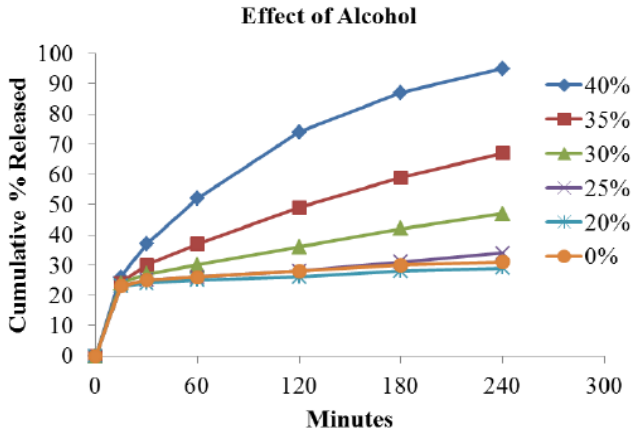


In the Phase 2 and Phase 3 clinical studies with IPX066, subjects were allowed to take IPX066 with or without meals. There were no adverse events noticed when IPX066 was administered with food. IPX066 can be taken with or without food. However, patients should be informed about the possible delay in LD absorption when administered with food. Similar to other CD-LD products, patients should be cautioned that taking IPX066 with foods rich in proteins or amino acids may interfere with the oral absorption and pharmacological effects of LD.

2.5.6 What are the effects of concomitant alcohol ingestion with IPX066 capsule formulation on bioavailability of carbidopa and levodopa?

The effects of alcohol on in vitro dissolution profile of LD from IPX066 were first evaluated in the presence of various concentrations of alcohol (20%, 25%, 30%, 35% and 40% v/v). As shown in the figure below, alcohol concentrations above 25% v/v in dissolution media resulted in concentration-dependent increases in the LD release from IPX066.

Figure: Effect of Alcohol on the In Vitro Release of LD from IPX066



Subsequently, the effects of alcohol co-administration 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). The concentration-time profiles of LD and CD in the presence of alcohol are presented in the figures below.

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

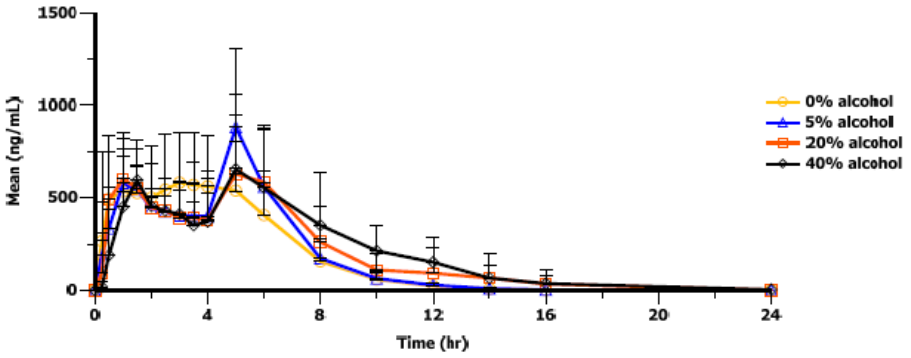
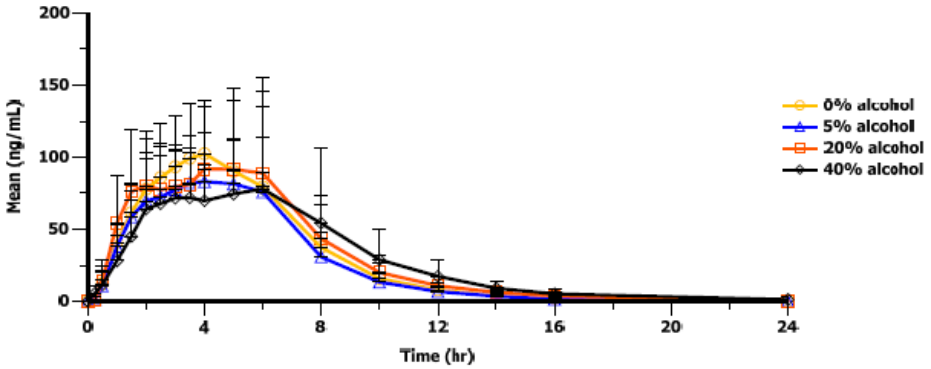
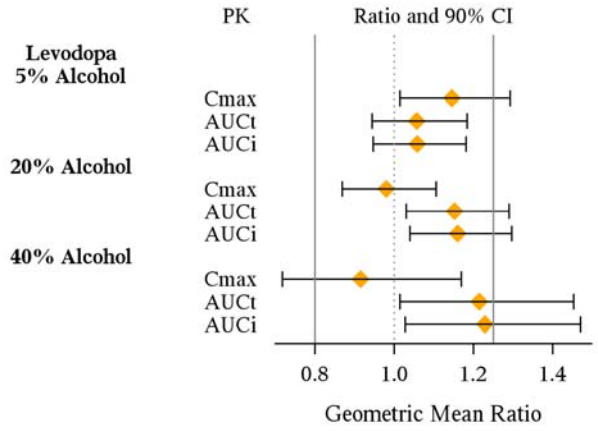


Figure: Mean (SD) Carbidopa Plasma Concentration-Time Profiles



There was a 15% increase in LD C_{max} on average with the 5% alcohol co-administration. However, with higher alcohol concentrations (20% and 40%) there was no change in LD C_{max}. There was no change in LD $AUC_{0-\infty}$ at 5% alcohol concentration. However, LD $AUC_{0-\infty}$ with 20% and 40% alcohol ingestion were increased by 16% and 23%, respectively, compared to 0% alcohol co-administration. Unlike Cmax, the increases in LD $AUC_{0-\infty}$ were concentration-dependent with the alcohol concentrations greater than 5%. No significant effects by alcohol on Tmax and t1/2 of LD or CD were observed. Results of the statistical analysis to show the impact of various alcohol contents on absorption of LD are illustrated in the Forest Plot presentation.

Figure. Forest Plot: Summary of 90% CI Assessment for Levodopa in Study IPX066-B09-04, (N = 15)



Reviewer's Comment: Most of the adverse events including dykinesias and hallucinations were related Cmax concentration. It is noted that the observed mean changes in Cmax and $AUC_{0-\infty}$ are within the intra-individual variability for C_{max} and $AUC_{0-\infty}$ (47% and 37%, respectively). While most of the adverse events, including dykinesias and hallucinations, were related peak plasma LD concentration, the increases in overall exposure (AUC) in the presence of high alcohol concentrations observed in this study are not likely to lead to significant clinical consequence.

As indicated by the Medical review team, alcohol use is contraindicated in PD patients. Therefore, details of this study and the lack of PK interaction will not be described in the Clinical Pharmacology section of the labeling (section 12.3) concerning the potential misinformation for patients, physicians and pharmacists.

2.5.6 Is the IPX066 clinical formulation manufactured at Hayward, CA bioequivalent to the commercial formulation manufactured in Jhunan, Taiwan?

A single-dose, two-treatment, crossover bridging study (IPX066-B10-01) was conducted to assess bioequivalence of the IPX066 clinical formulation (the highest 61.5-245 mg strength) manufactured at Hayward, CA to the commercial formulation of the same strength manufactured in Jhunan, Taiwan, based on the relative bioavailability of LD. In this study the sponsor also assessed the dose linearity comparing administration of one or two capsules of IPX066 245 mg LD. The LD and CD concentration-time profiles of clinical formulation and commercial formulation were essentially superimposable as shown in the figures below.

Figure: Mean (SD) LD Plasma Concentration-Time Profiles (Study IPX066-B10-01)

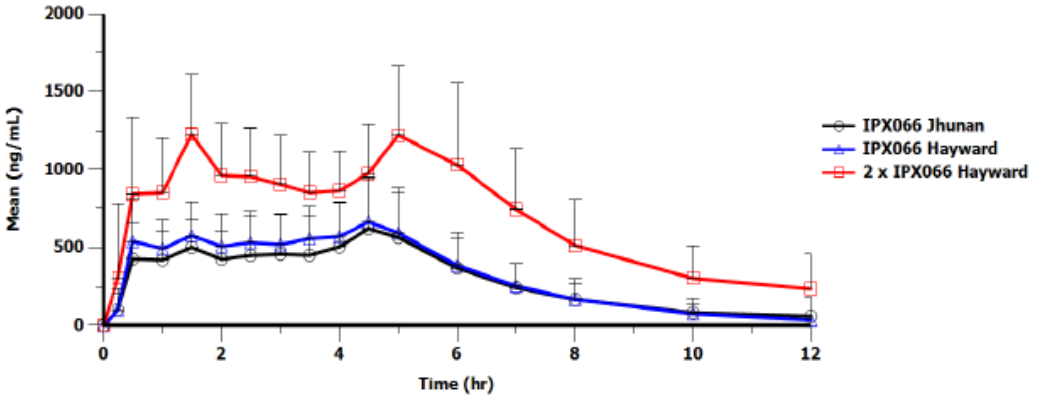
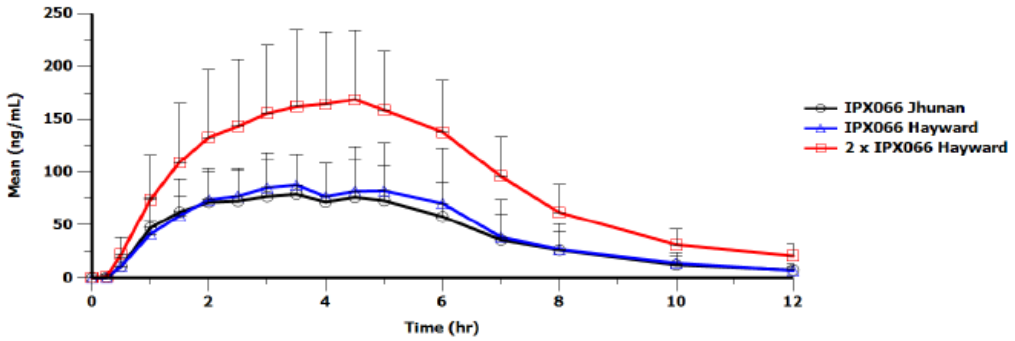
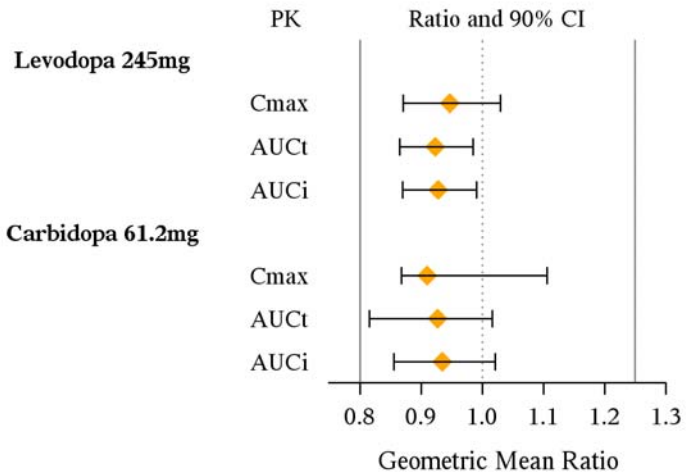


Figure: Mean (SD) Carbidopa Plasma Concentration-Time Profiles (Study IPX066-B10-01)



Statistical analysis for the ratios of LD exposure (Cmax, AUCt, and AUCinf) and the corresponding 90% CIs shows that the highest strength of IPX066 manufactured in Jhunan was bioequivalent to IPX066 of the same strength manufactured in Hayward based on the 80-125% BE acceptance criteria, as illustrated in the figure below.

Figure. Forest Plot: Bioequivalence Analysis of the Log-Transformed Pharmacokinetic Parameters for LD and CD Following a Single Dose of IPX066 245 mg LD Manufactured in Jhunan and Hayward in Study IPX066-B10-01, (N=37)



Analysis using Power Model showed that following administration of one or two capsules of IPX066 245 mg LD, Cmax of LD increased dose-proportionally, whereas the increases in AUC0-t and AUC0-∞ were slightly more than dose-proportional (11~23%). For CD, the increases in AUC0-t and AUC0-∞ were dose-proportional comparing one or two capsules of IPX066 245 mg LD, whereas the increase in Cmax was 16% less than dose-proportional. (See Section 4.1 Individual Study Reviews for details).

Of note, at the request of Division of Neurology Products, the Office of Scientific Investigations (OSI) conducted audit for the clinical and bioanalytical portions of this pivotal bioequivalence study conducted at (b) (4) respectively. The OSI concluded that reliability of source data generated in study IPX066-B10-01 can be accepted for review.

2.6 Analytical

2.6.1 What analytical methods were used to determine LD and CD concentrations and were the analytical assay methods adequately validated?

The quantitation of CD and LD in human plasma was accomplished using a liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. The method was validated for CD over a linear concentration range of 2.00 to 400 ng/mL and for LD over a linear concentration range of 10.0 to 2000 ng/mL. The limits of quantitation (LOQs) were 2.00 ng/mL and 10.0 ng/mL for CD and LD, respectively. The assay validations for CD and LD, including the adequate concentrations of quality controls, are considered acceptable according to the acceptance criteria set by the Agency's Bioanalytical Guidance. The following table provides the summary of bioanalytical method validation used to support the clinical pharmacology studies.

Table: Summary of Bioanalytical Method Validation

Parameters	Carbidopa	Levodopa
Linear Range	2.00 to 400 ng/mL	10.0 to 2000 ng/mL
Linearity	Coefficient of determination ≥ 0.9971	Coefficient of determination ≥ 0.9987
Limit of Quantitation	2 ng/mL	10 ng/mL
	Precision (QCs)	
Interday (%CV)	2.0% to 7.0%	1.5% to 9.2%
Intraday (%CV)	1.5% to 4.3%	1.8% to 6.1%
	Accuracy (QCs)	
Interday (% RE)	-2.3% to 6.5%	0.7% to 2.0%
Intraday (%RE)	0.2% to 7.5%	0.0% to 4.7%
Specificity	No interference from: K2 and K3-EDTA, acetaminophen, acetylsalicylic acid, amoxicillin, caffeine, chlorpheniramine, desipramine, ibuprofen, nicotine, salicylic acid, tetracycline, theobromine, theophylline and xanthine	

Recovery (over calibration range)	42.1% QC A (3.00 ng/mL); %CV: 7.5% 37.3% QC B (30.0 ng/mL); %CV: 3.3% 38.8% QC C (100 ng/mL); %CV: 4.2% 39.1% QC D (150 ng/mL); %CV: 5.6% 41.6% Internal Standard (100 ng/mL); %CV: 1.9%	82.6% QC A (15.0 ng/mL); %CV: 2.2% 74.3% QC B (150 ng/mL); %CV: 3.3% 75.9% QC C (500 ng/mL); %CV: 2.4% 76.6% QC D (750 ng/mL); %CV: 3.4% 79.4% Internal Standard (250 ng/mL); %CV: 3.1%
	Stability (QCs) %RE	
Extract Stability	At least 2.0 hours in an ice-water bath; %RE = -1.2% to 3.5%	At least 2.0 hours in an ice-water bath; %RE = 0.0% to 7.0%
Bench top Stability	At least 8.1 hours in an ice-water bath; %RE = -3.0% to 0.0%	At least 8.1 hours in an ice-water bath; %RE = -5.7% to 1.0%
Freeze-thaw cycles (4 cycles from -80±15 °C to ice	%RE = -14.3% to -2.7%	%RE = -10.3% to -4.3%

3 LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Rytary™ and finds it acceptable pending the following revisions:

(~~Strikethrough text~~ is recommended to be deleted and **underlined text** is recommended to be added.)

2.5 Important Administration Instructions

Swallow Rytary whole with or without food. However, a high-fat, high-calorie meal may delay the absorption of levodopa by about 2 hours. *[See Effect of Food (12.3)]* Do not chew, divide or crush. For patients who have difficulty swallowing intact capsules, Rytary (b) (4) by carefully opening the capsule (b) (4) sprinkling the entire contents on a small amount of applesauce (1 to 2 tablespoons) and (b) (4). Do not store the drug/food mixture for future use.

7 DRUG INTERACTIONS

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

7.3 Dopamine D2-Receptor Antagonists (b) (4) and Isoniazid: Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the (b) (4) of levodopa.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

12.3 Pharmacokinetics

(b) (4)

Absorption:

(b) (4)

Levodopa

The pharmacokinetics of Rytary were evaluated following single doses in healthy subjects and following single and multiple doses in patients with Parkinson's disease. (b) (4) The bioavailability of levodopa from Rytary in patients was approximately 70% relative to immediate-release carbidopa and levodopa (b) (4). Following an initial peak at about one hour, plasma concentrations are maintained for about 4 to 5 hours.

(b) (4)

(b) (4)

(b) (4)

Carbidopa

Following oral dosing of Rytary the (b) (4) occurred at approximately 3 hours. The bioavailability of carbidopa from Rytary relative to immediate-release carbidopa and -levodopa tablets was approximately 50%.

Distribution

(b) (4) Carbidopa is approximately 36% bound to plasma proteins.

Metabolism and Elimination

Levodopa

The terminal phase elimination half-life of levodopa, the active moiety of antiparkinsonian activity, is approximately 2 hours in the presence of carbidopa.

Levodopa is extensively metabolized to various metabolites. The two major metabolic pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-O-methyltransferase (COMT).

Carbidopa

The terminal phase elimination half-life of carbidopa is approximately 2 hours.

Carbidopa is metabolized to two main metabolites: α-(b) (4)-methyl-3-methoxy-4-hydroxyphenylpropionic acid and (alpha)-methyl-3,4-dihydroxy-phenylpropionic acid. These two metabolites are primarily eliminated in the urine unchanged or as glucuronide. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Peripheral dopa decarboxylase may be saturated by carbidopa in other carbidopa-levodopa products at 70 to 100 mg per day, which produces equivalent exposure to 140 to 200 mg of carbidopa provided by Rytary.

Dose Proportionality

Rytary shows approximately dose proportional pharmacokinetics for both levodopa and carbidopa over the levodopa dosage strength range of 95 mg to 245 mg.

Effect of Food

(b) (4)

[redacted] In healthy adults, oral administration of Rytary after a high-fat, high-calorie meal reduced C_{max} approximately 21% and increased AUC_{inf} approximately 13% for levodopa compared to administration in the fasted state. There may be a delay by [redacted] 2 hours in the absorption of levodopa when Rytary is taken with a high-fat, high-calorie meal. In addition, absorption of levodopa is decreased by a high protein meal.

[redacted]

Elderly

In pharmacokinetics studies following a single dose of [TRADE NAME]:

[redacted]

Gender

In pharmacokinetics studies following a single dose of Rytary:

Levodopa

At comparable doses [redacted] are reported to have higher levodopa peak concentrations (approximately 23% to 33%) and systemic exposure (approximately 33% to 37%) compared to males. Median time to peak concentration and terminal half-life are comparable between males and females.

Carbidopa

At comparable doses [redacted] are reported to have higher carbidopa peak concentrations and systemic exposure (approximately 33%) compared to males.

Median time to peak concentration and terminal half-life are comparable between males and females.

Drug (b) (4) Interactions

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4 APPENDICES

4.1 Individual Study Reviews

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

Objective:
To assess the bioavailability of two capsules of IPX066 49.75-195 mg (total dose 97.5-390 mg) carbidopa-levodopa (CD-LD) relative to Sinemet® 25-100 mg CD-LD, Sinemet® CR 25-100 mg CD-LD, and Stalevo® 25-100-200 mg CD-LD-entacapone under fasted conditions.

Study Design	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.
Study Population	Healthy males and females Age: 18 -45 years BMI: 18 to 29.5 kg/m2 24 subjects were enrolled, and 22 completed the study
Treatment Groups	Each subject received a single, oral administration of IPX066, Sinemet, Sinemet CR, or Stalevo on each of four occasions with at least a 6-day washout period between treatments.
Test and Reference Products	The investigational product was IPX066, an extended-release oral capsule formulation of CD-LD. Each subject received a single oral dose of IPX066. The IPX066 dose assessed was two capsules of 48.75-195 mg (total dose 97.5-390 mg) CD-LD. Three commercial reference products were used in this study: Sinemet, Sinemet CR, and Stalevo. Each subject received a single oral dose of 1 tablet of Sinemet 25-100 mg CD-LD or 1 tablet of Sinemet CR 25-100 mg CD-LD or 1 tablet of Stalevo 25 mg-100 mg-200 mg CD-LD entacapone at the start of each treatment period.
PK Sampling	A total of 17 plasma samples were collected during each of the four treatment periods (IPX066, Sinemet, Sinemet CR, Stalevo) at predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours postdose.
Analysis	Carbiodopa and levodopa concentrations were determined in plasma samples using a validated method for high performance liquid chromatography with tandem mass spectrometric detection with a lower limit of quantification of 2 ng/mL and 10 ng/mL respectively. Carbidopa:

<table>
<tr><td></td><td>
<table>
<tr><td>Parameter</td><td>Quality Control Samples</td><td>Standard Curve Samples</td></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>6, 60, 200 and 300</td><td>2, 4, 10, 40, 80, 160, 240, 280, 360 and 400</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>1.3 to 5.1</td><td>2.1 to 3.6</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-3.5 to 1.9</td><td>-0.2 to 1.0</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X2), mean r^2= 0.996</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">2 to 400</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">2</td></tr>
</table>

Levodopa:
<table>
<tr><td>Parameter</td><td>Quality Control Samples</td><td>Standard Curve Samples</td></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>30, 300, 1000, and 1500</td><td>10, 20, 50, 200, 400, 800, 1200, 1400, 1800 and 2000</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.5 to 4.2</td><td>1.3 to 4.6</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-0.7 to 1.7</td><td>-5.5 to 2.3</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation (1/X2), mean r^2= 0.995</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">10 to 2000</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">10</td></tr>
</table>
</td></tr>
<tr><td>Urine</td><td>None</td></tr>
<tr><td>Feces</td><td>None</td></tr>
<tr><td>PK Assessments</td><td>The following PK parameters were estimated for CD and LD maximum plasma concentration (Cmax), time to maximum concentration (Tmax), area under the plasma concentration-time curve (AUC) from time zero up to time t (AUC0-t), and AUC from time zero to infinity (AUC0-∞), elimination constant (k), and terminal half-life (t1/2).</td></tr>
<tr><td>PD Assessments</td><td>None</td></tr>
<tr><td>Statistical Methods</td><td>Descriptive statistics were calculated for the following PK parameters: Cmax, Tmax, AUC0-t, AUC0-∞, t1/2, and k. A</td></tr>
</table>

	mixed effect analysis of variance (ANOVA) model which included treatment, period, sequence as fixed effects, and subject-within-sequence as a random effect was used for the analysis of log-transformed CD and LD PK parameters (AUC and Cmax).

RESULTS:

Levodopa:

Figure: Mean Levodopa Plasma Concentration-Time Profiles

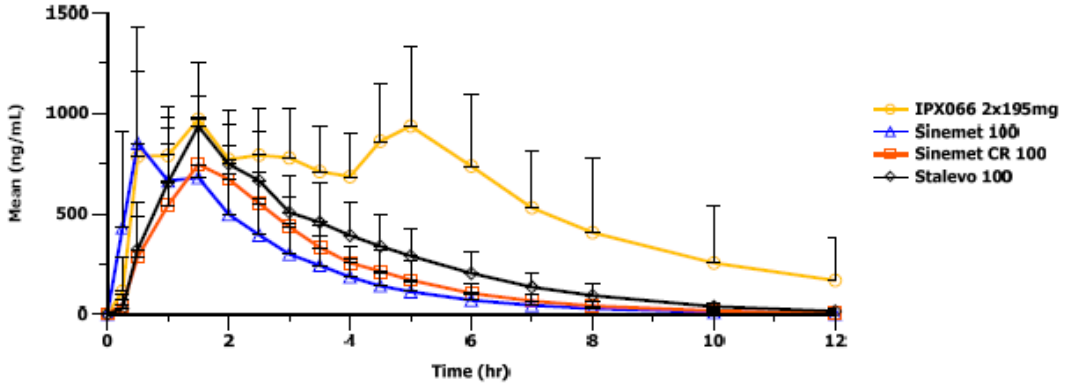


Table: Summary of Levodopa Pharmacokinetics Following a Single Dose of IPX066 97.5-390 mg CD-LD, Sinemet® 25-100 mg CD-LD, Sinemet® CR 25-100 mg CD-LD or Stalevo® 25-100-200 mg CD-LD-entacapone in Study IPX066-B08-10, Mean ± SD, (N = 22).

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**
Tmax (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)
Cmax (ng/mL)	1325.64 ± 267.88	1094.36 ± 401.14	854.96 ± 299.28	1026.77 ± 284.29
AUC0-t (ng.hr/mL)	6752.81 ± 2086.16	2215.35 ± 665.20	2372.43 ± 682.29	3250.82 ± 1135.40
AUC0-∞ (ng.hr/mL)	7243.98 ± 2553.23	2250.63 ± 664.36	2403.06 ± 679.99	3290.75 ± 1149.47
t1/2 (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

Bioavailability of LD from IPX066 Relative to Reference Products	NA	80.4% (74.30, 86.89)	75.1% (69.45, 81.22)	56.1% (51.90, 60.69)
Bioavailability of LD Relative to Sinemet	80.4% (74.30, 86.89)	Reference	107.0% (98.93, 115.69)	143.2% (132.39, 154.83)

[a] Median (range).
[b] Data reported are the ratio of the geometric means expressed as a percentage and 90% confidence interval.
Abbreviations: CD = carbidopa, LD = levodopa, Tmax = time to maximum concentration, Cmax = maximum observed plasma concentration, AUC0-t = area under the concentration time curve from time zero up to the last measureable timepoint, AUC0-∞ = area under the concentration time curve from time zero up to infinity, t1/2 = elimination half-life, NA = not applicable.

Carbidopa:

Figure: Mean Carbidopa Plasma Concentration-Time Profiles

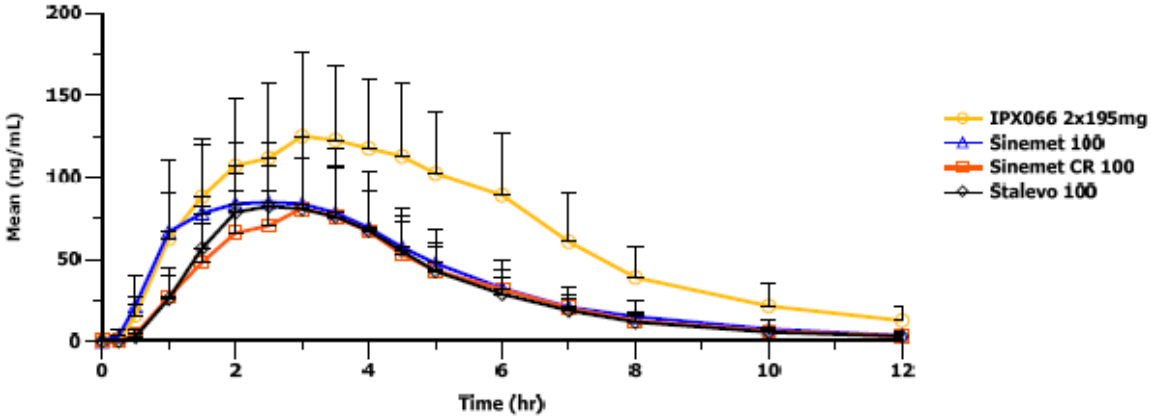


Table: Summary of Carbidopa Pharmacokinetics Following a Single Dose of IPX066 97.5-390 mg CD-LD, Sinemet® 25-100 mg CD-LD, Sinemet® CR 25-100 mg CD-LD or Stalevo® 25-100-200 mg CD-LD-entacapone in Study IPX066-B08-10, Mean ± SD, (N = 22)

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**
Tmax[a](h)	3.50 (1.50 - 6.00)	2.50 (1.00 - 5.00)	3.00 (2.00 - 4.50)	2.50 (2.00 - 4.00)
Cmax (ng/mL)	147.89 ± 49.45	106.39 ± 42.90	85.87 ± 31.96	92.47 ± 29.50
AUC0-t (ng.hr/mL)	769.12	437.11	361.50	371.62

	± 250.98	± 155.33	± 114.54	± 109.97
AUC0-∞	822.40 ± 275.67	447.86 ± 157.38	372.76 ± 117.05	380.74 ± 11.52
t1/2 (h)	2.54 ± 1.10	1.84 ± 0.24	2.04 ± 0.42	1.82 ± 0.31
Bioavailability of CD from IPX066 Relative to Reference Products	NA	47.5% (42.25, 53.46)	57.0% (50.69, 64.15)	54.9% (48.85, 61.82)
Relative Bioavailability to Sinemet	47.5% (42.25, 53.46)	Reference	83.3% (74.08, 93.75)	86.5% (76.88, 97.29)

a. Median (range)

Discussion:

For IPX066, the duration of LD concentrations above 50% of Cmax was longer (4.88 hours) when compared to Sinemet, Sinemet CR, and Stalevo treatments (1.45 hours, 2.11 hours, 2.13 hours, respectively).

According to the sponsor the flatter LD plasma profile from IPX066 treatment may allow a prolonged duration of effect without an increased incidence of peak concentration-related dyskinesia in PD patients with motor complications.

Reviewer's Comment: The LD plasma concentrations directly correlate to wearing off effect related to dyskinesias. However, these results will be further evaluated in a pharmacodynamic study IPX066-08-11.

CONCLUSIONS:

- The bioavailability of LD from IPX066 relative to Sinemet, Sinemet CR, and Stalevo was 80.4%, 75.1%, and 56.1%, respectively
- The relative bioavailability for CD to Sinemet, Sinemet CR, and Stalevo was 47.5%, 57.0%, and 55.0%, respectively.
- IPX066 produced extended LD plasma concentration-time profile than Sinemet, Sinemet CR, and Stalevo.

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

Objectives:
To compare the single- and multiple-dose pharmacokinetics (PK) of IPX066 (carbidpa-levodopa extended-release [ER] capsules) capsule formulation with immediate release (IR) carbidopa-levodopa (CD-LD) (Sinemet®) tablet formulation and explore pharmacodynamic measures.

Study Design	This study was a randomized, multicenter, open-label, single and multiple oral dose, two-treatment, two-period, crossover study in LD-experienced subjects with Parkinson's disease (PD).
Study Population	PD patients (21 males and 6 females) Age: 30 years or older 27 subjects were enrolled and 27 completed the study
Methodology	Subjects received 7 days of one treatment (IPX066 or IR CD-LD) followed by an approximate 7-day washout period followed by another 7 days of the other treatment (IR CD-LD or IPX066). During the approximate 7- day washout period, subjects took their pre-study CD-LD regimen. Pharmacokinetic and efficacy/ pharmacodynamic measurements were done on Days 1 and 8. Subjects completed PD diaries for 3 days prior to study entry and prior to the end of each treatment period.
Treatment Groups	Treatments A and B were administered Q6H. Treatment A (Reference) - IR CD-LD 25 - 100 mg CD-LD (Sinemet: Lots X5339, X3836). Treatment B (Test) - IPX066, two dosage strengths: 48.75 - 195 mg, 61.25 - 245 mg CD-LD
Efficacy/ PD	Subjects completed PD diaries for 3 days prior to study entry and prior to the end of each treatment period. On Day 1 of each treatment period, assessments for Tapping and Walk Time and Investigator Assessments of Dyskinesia were conducted every 30 minutes, UPDRS Part III score was conducted every hour for 8 hours. On Day 8 of each treatment period, assessments for Tapping, Walk Time, UPDRS Part III score, and Investigator Assessments of Dyskinesia were conducted every hour for 12 hours.
PK Sampling	Blood samples (6 mL) were collected for measurement of CD and LD from each subject predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, and 8 hours on Day 1 and predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours on Day 8 of both treatment periods.

<table>
<tr><td>Analysis</td><td>Carbiodopa and levodopa concentrations were determined in plasma samples using a validated method for high performance liquid chromatography with tandem mass spectrometric detection with a lower limit of quantification of 2 ng/mL and 10 ng/mL respectively.

Carbidopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>6, 60, 200 and 300</td><td>2, 4, 10, 40, 80, 160, 240, 280, 360 and 400</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>3.1 to 4.9</td><td>1.8 to 5.6</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>0.5 to 0.7</td><td>-2.0 to 1.1</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.994</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">2 to 400</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">2</td></tr>
</table>
Levodopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>30, 300, 1000, and 1500</td><td>10, 20, 50, 200, 400, 800, 1200, 1400, 1800 and 2000</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.9 to 4.9</td><td>1.9 to 7.6</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>0.7 to 2.3</td><td>-6.0 to 3.0</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.996</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">10 to 2000</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">10</td></tr>
</table></td></tr>
<tr><td>Statistical Methods for PK Assessments</td><td>Descriptive statistics were calculated for PK parameters (maximum concentration [Cmax], time to maximum drug concentration [Tmax], area under the concentration-time curve [AUC]) following single- and multiple-dosing of IPX066 and IR CD-LD. In addition, the bioavailability of IPX066 relative to IR CD-LD based on PK data on Day 1, and accumulation and fluctuation following multiple dosing (Day 8) were also estimated. Fluctuation index is calculated as (Cmax - Cmin)/Cave (average concentration of plasma concentration over 12 hours).</td></tr>
<tr><td>PD Assessments</td><td>Descriptive statistics were calculated for the efficacy/ PD parameters. Efficacy was examined during three separate intervals: Day 1 of each treatment period (efficacy across 8</td></tr>
</table>

	hours associated with a single dose); Day 8 of each treatment period (efficacy across 12 hours associated with multiple doses); and subjects' 3-day PD diaries prior to entry into the study and at the end of each treatment period. Standard analyses for a crossover design were conducted with Analysis of Variance used for the Patient Diaries and Investigator Dyskinesia assessments, and Analysis of Covariance with Day 1 predose values as the covariate employed for the motor effects (Tapping, Walking Time, and UPDRS Part III score).

RESULTS:

Levodopa:

Figure: Day 1, Single-Dose, Mean (SD) Levodopa Concentration-Time Profile following administration of Sinemet (IR, LD-CD).

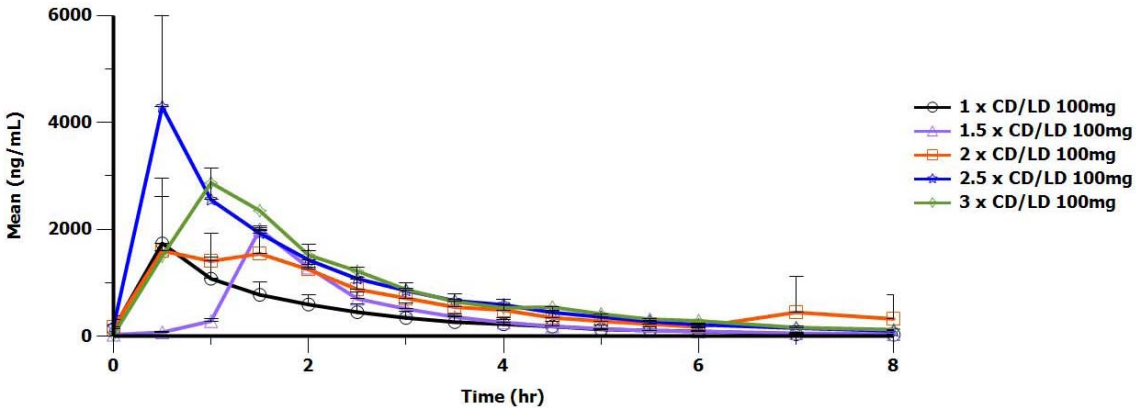


Table: Summary of levodopa PK parameters

Descriptive Statistics for Plasma Levodopa Pharmacokinetic Parameters Following IR CD-LD - Single Dose (All Treated Subjects)

	All Treated Subjects							
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC8 (h*ng/mL)	AUCinf (h*ng/mL)	t 1/2 (h)	k (1/h)
N	27	27	27	27	27	27	27	27
Mean	2356.444	0.870	3881.298	5.074	4575.543	4881.133	1.52	0.4652
Median	2160.000	0.500	3920.000	4.500	4407.700	4508.570	1.55	0.4500
Std Dev	1080.541	0.4921	1586.9059	2.8223	1890.7940	2211.665	0.276	0.08903
%CV	45.9	56.5	40.9	55.6	41.3	45.3	18.1	19.1
Minimum	884.00	0.50	1221.53	2.00	1815.83	1902.50	0.9	0.320
Maximum	6220.00	2.00	7065.38	12.00	8496.85	9530.30	2.2	0.770

Carbidopa:

Figure: Day 1, Single-Dose, Mean (SD) Carbidopa Concentration-Time Profile following administration of Sinemet (IR, LD-CD).

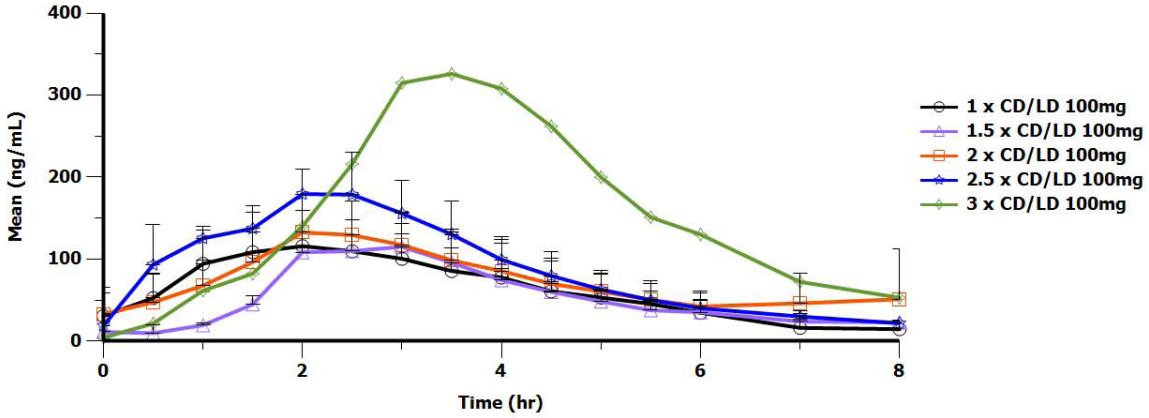


Table: Summary of carbidopa PK parameters

Descriptive Statistics for Plasma Carbidopa Pharmacokinetic Parameters Following IR CD-LD - Single Dose (All Treated Subjects)

	All Treated Subjects							
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC8 (h*ng/mL)	AUCinf (h*ng/mL)	t 1/2 (h)	k (1/h)
N	27	27	27	27	27	27	27	27
Mean	146.848	2.296	401.694	5.074	589.040	679.531	1.97	0.3622
Median	140.000	2.000	356.700	4.500	594.850	678.340	1.91	0.3500
Std Dev	58.787	0.6086	177.8239	2.8223	240.8952	311.326	0.434	0.07202
%CV	40.0	26.5	44.3	55.6	40.9	45.8	22.1	19.9
Minimum	45.20	1.50	86.35	2.00	155.99	173.59	1.4	0.240
Maximum	326.00	3.50	720.53	12.00	1238.67	1498.72	3.0	0.510

Levodopa:

Figure: Day 1, Single-Dose, Mean (SD) Levodopa Concentration-Time Profile following administration of IPX066 (ER, LD-CD).

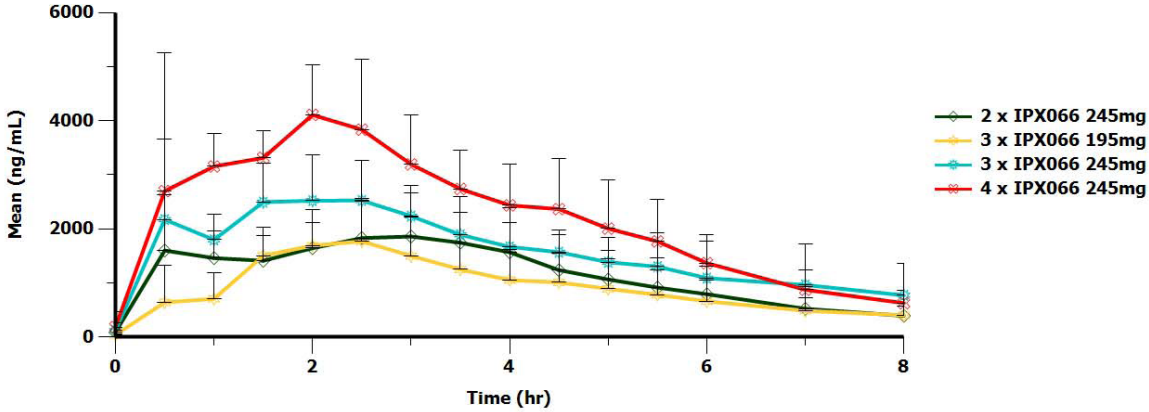


Table: Summary of levodopa PK parameters

Descriptive Statistics for Plasma Levodopa Pharmacokinetic Parameters Following IPX066 - Single Dose (All Treated Subjects)

	All Treated Subjects								
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC8 (h*ng/mL)	AUCinf (h*ng/mL)	t 1/2 (h)	k (1/h)	REL BA (%)
N	27	27	27	27	27	27	27	27	27
Mean	3000.000	2.037	10902.194	6.417	11834.505	13124.322	1.57	0.4526	68.909
Median	2900.000	2.000	9796.580	6.000	11165.050	12405.010	1.52	0.4500	67.840
Std Dev	1301.608	1.0735	4619.2284	1.7348	4465.6266	4949.069	0.324	0.08990	22.8001
%CV	43.4	52.7	42.4	27.0	37.7	37.7	20.7	19.9	33.1
Minimum	1210.00	0.50	4218.90	3.00	4218.90	5296.92	1.0	0.260	31.15
Maximum	6130.00	4.50	21694.20	12.00	20847.50	22681.26	2.5	0.700	114.16

Carbidopa:

Figure: Day 1, Single-Dose, Mean (SD) Carbidopa Concentration-Time Profile following administration of IPX066 (ER, LD-CD).

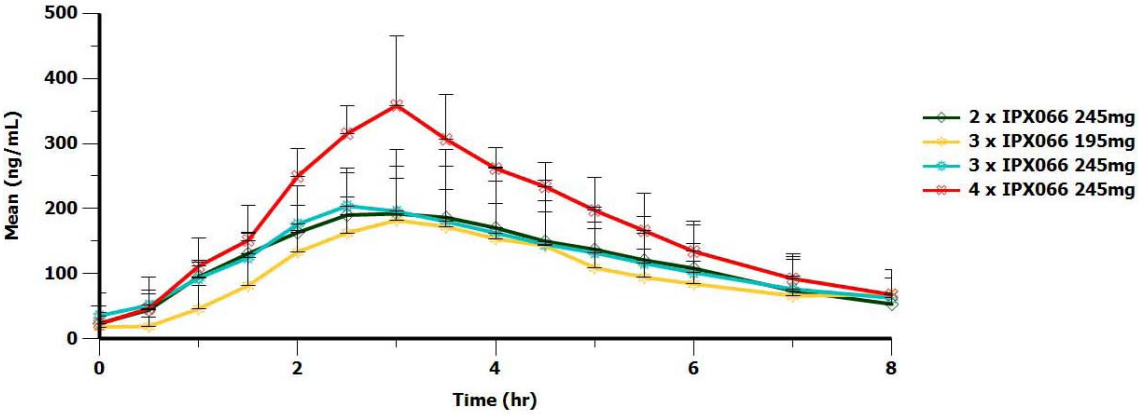


Table: Summary of carbidopa PK parameters

Descriptive Statistics for Plasma Carbidopa Pharmacokinetic Parameters Following IPX066 - Single Dose (All Treated Subjects)

	All Treated Subjects								
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC8 (h*ng/mL)	AUCinf (h*ng/mL)	t 1/2 (h)	k (1/h)	REL BA (%)
N	27	27	27	27	27	27	27	27	27
Mean	238.852	2.944	917.067	6.417	1037.264	1216.584	2.15	0.3359	49.889
Median	220.000	3.000	992.090	6.000	1168.630	1328.310	2.03	0.3400	40.540
Std Dev	91.004	0.5604	373.9147	1.7348	346.1070	419.428	0.521	0.07592	28.8305
%CV	38.1	19.0	40.8	27.0	33.4	34.5	24.2	22.6	57.8
Minimum	106.00	2.00	395.29	3.00	402.30	505.19	1.4	0.190	19.01
Maximum	522.00	4.00	1726.55	12.00	1647.28	1880.69	3.6	0.510	153.33

Levodopa:

Figure: Day 8, Multiple-Dose, Mean (SD) Levodopa Concentration-Time Profile following administration of Sinemet (IR, LD-CD).

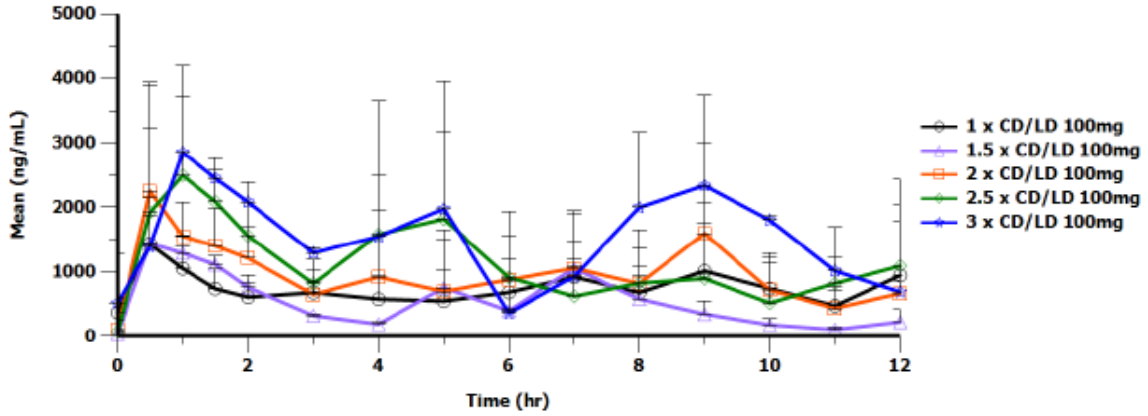


Table: Summary of levodopa PK parameters

Descriptive Statistics for Plasma Levodopa Pharmacokinetic Parameters Following IR CD-LD - Multiple Dose (All Treated Subjects)

	All Treated Subjects							
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC12 (h*ng/mL)	Accumulation	Time Invariance	Fluctuation
N	27	27	27	27	27	27	27	27
Mean	2761.852	3.611	4167.151	5.074	10896.522	1.105	0.899	3.226
Median	2700.000	1.000	3867.830	4.500	10411.930	1.030	0.810	2.940
Std Dev	1002.984	4.2161	1799.2567	2.8223	4724.9178	0.3421	0.3119	1.2646
%CV	36.3	116.8	43.2	55.6	43.4	31.0	34.7	39.2
Minimum	1360.00	0.00	1469.70	2.00	4347.90	0.66	0.51	1.80
Maximum	5360.00	12.00	7560.75	12.00	23369.75	2.10	1.87	7.18

Carbidopa:

Figure: Day 8, Multiple-Dose, Mean (SD) Carbidopa Concentration-Time Profile following administration of Sinemet (IR, LD-CD).

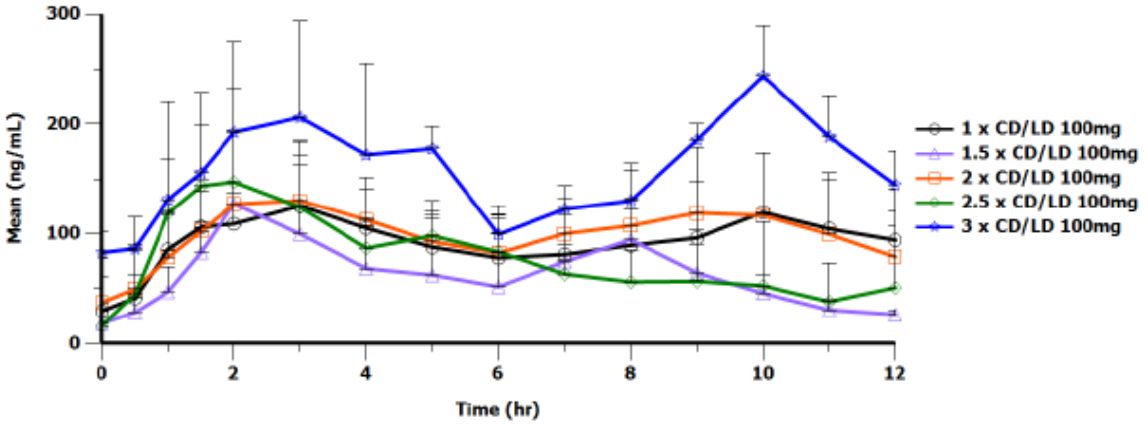


Table: Summary of carbidopa PK parameters

Descriptive Statistics for Plasma Carbidopa Pharmacokinetic Parameters Following IR CD-LD - Multiple Dose (All Treated Subjects)

	All Treated Subjects							
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC12 (h*ng/mL)	Accumulation	Time Invariance	Fluctuation
N	27	27	27	27	27	27	27	27
Mean	167.515	5.685	449.584	5.074	1178.152	1.222	0.796	1.542
Median	171.000	4.000	393.750	4.500	1139.950	0.990	0.540	1.480
Std Dev	51.204	3.5711	273.8498	2.8223	422.2177	0.7445	0.6309	0.4495
%CV	30.6	62.8	60.9	55.6	35.8	60.9	79.2	29.2
Minimum	97.90	1.50	108.57	2.00	456.00	0.34	0.15	0.78
Maximum	276.00	12.00	1158.23	12.00	2127.73	3.48	2.54	2.86
GeoMean	160.170	4.614	377.658	4.492	1104.941	1.054	0.618	1.484
Mean(ln)	5.076	1.529	5.934	1.502	7.008	0.052	-0.481	0.395
SD(ln)	0.306	0.6723	0.6128	0.4862	0.3729	0.5429	0.7137	0.2814

Levodopa:

Day 8, Multiple-Dose, Mean (SD) Levodopa Concentration-Time Profile following administration of IPX066 (ER, LD-CD).

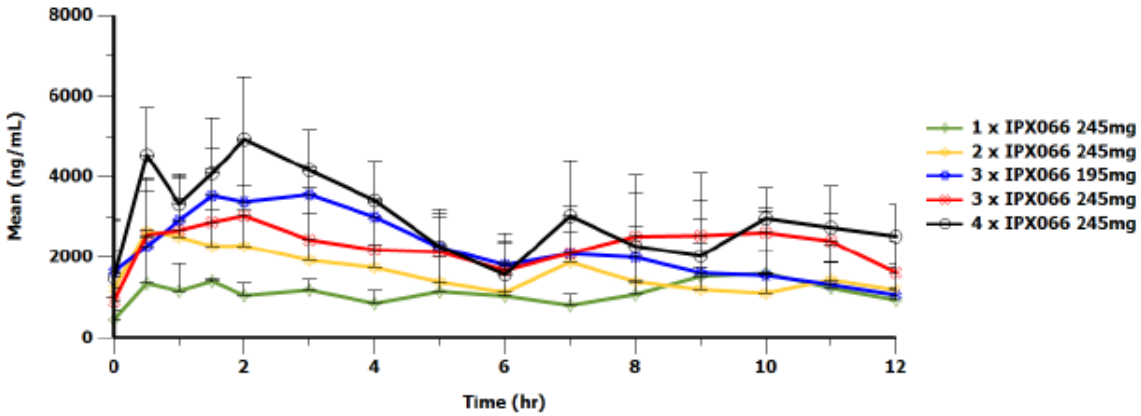


Table: Summary of levodopa PK parameters

Descriptive Statistics for Plasma Levodopa Pharmacokinetic Parameters Following IPX066 - Multiple Dose (All Treated Subjects)

	All Treated Subjects							
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC12 (h*ng/mL)	Accumulation	Time Invariance	Fluctuation
N	27	27	27	27	27	27	27	27
Mean	3807.037	4.407	13903.380	6.417	24828.271	1.415	1.149	1.509
Median	3580.000	3.000	13147.310	6.000	24469.500	1.270	1.070	1.570
Std Dev	1547.120	3.7597	6990.0405	1.7348	9732.7417	0.8487	0.6562	0.4100
%CV	40.6	85.3	50.3	27.0	39.2	60.0	57.1	27.2
Minimum	1450.00	0.50	4247.50	3.00	8909.25	0.47	0.38	0.26
Maximum	7750.00	11.00	28654.63	12.00	48387.50	4.36	3.47	2.11

Table: Summary of Levodopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate-Release CD-LD

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 $AUC_{0-\tau}$ on Day 8/$AUC_{0-\tau}$ 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.

Carbidopa:

Day 8, Multiple-Dose, Mean (SD) Carbidopa Concentration-Time Profile following administration of IPX066 (ER, LD-CD).

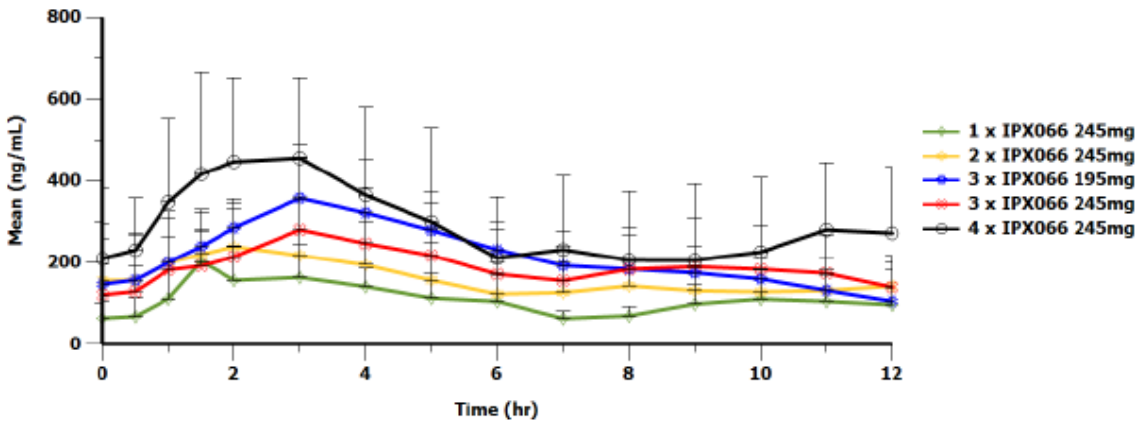


Table: Summary of carbidopa PK parameters

Descriptive Statistics for Plasma Carbidopa Pharmacokinetic Parameters Following IPX066 - Multiple Dose (All Treated Subjects)

	All Treated Subjects							
	Cmax (ng/mL)	Tmax (h)	AUCTau (h*ng/mL)	Tau (h)	AUC12 (h*ng/mL)	Accumulation	Time Invariance	Fluctuation
N	27	27	27	27	27	27	27	27
Mean	313.222	3.815	1344.436	6.417	2265.063	1.629	1.204	1.186
Median	258.000	3.000	1072.750	6.000	1954.500	1.290	0.980	1.220
Std Dev	167.924	2.6390	818.1622	1.7348	1222.9615	1.1173	0.8432	0.4906
%CV	53.6	69.2	60.9	27.0	54.0	68.6	70.0	41.4
Minimum	141.00	1.50	424.75	3.00	794.03	0.44	0.35	0.19
Maximum	799.00	12.00	3216.50	12.00	5583.25	4.96	3.95	2.12

Table: Summary of Carbidopa Pharmacokinetics Following Multiple-Dose Oral Administration of IPX066 and Immediate-Release CD-LD

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 $AUC_{0-\tau}$ on Day 8/$AUC_{0-\tau}$ 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.

Note: PD assessment from this study will be reviewed as part of the population PD analysis in a separate study report.

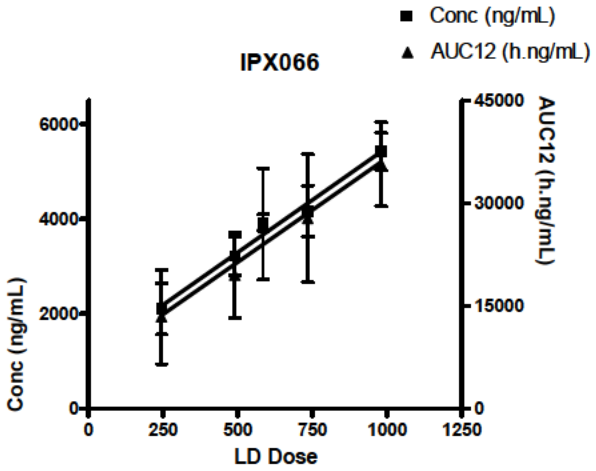
Discussion

The current multiple dose study is not designed to evaluate dose proportionality. The numbers of PD patients in each dose group were not similar (see table below).

LD Dose (mg)	Conc (ng/mL)	AUC12 (ng·h/mL)

	Mean	SD	n	Mean	SD	n
100	2209	744	11	8889	2441	11
150	2195	714	2	6533	315	2
200	3056	1107	9	11633	4602	9
250	3963	185	3	13783	6091	3
300	3240	806	2	18648	6676	2

Given that, the linearity analysis shows that exposure in different LD dose groups were approximately dose-proportional for IPX066 (see figure below).



CONCLUSIONS:

Pharmacokinetics

- The bioavailability of LD from IPX066 was approximately 70% relative to IR CD-LD in PD patients.
- Following multiple-dose administration of IPX066, accumulation of LD when dosed approximately Q6H was comparable to IR CD-LD.
- Following multiple dosing, LD from IPX066 had a lower fluctuation compared to IR CD-LD (fluctuation of 1.51 ± 0.41 and 3.23 ± 1.26 for IPX066 and IR CDLD, respectively), while accumulation of LD was slightly higher for IPX066 (1.42 ± 0.85 and 1.11 ± 0.34 for IPX066 and IR CD-LD, respectively).

IPX066-B08-09: ASSESSMENT OF DOSE PROPORTIONALITY OF IPX066

Objective: To assess the dose proportionality of four strengths of IPX066 in healthy subjects.

<table>
<tr><td>Study Design</td><td>Open-label, randomized, single-dose, 4-sequence, 4-treatment cross-over study with at least a 6-day washout between treatment periods.</td></tr>
<tr><td>Study Population</td><td>Healthy males and females
Age: 18 -45 years
31 subjects were enrolled, and 28 completed the study</td></tr>
<tr><td>Treatment Groups</td><td>IPX066 is an extended release (ER) oral capsule formulation of carbidopa-levodopa (CD-LD) supplied by Impax (Hayward, CA). Four dosage strengths of IPX066 capsules were administered orally to each subject, one capsule per treatment period, in a randomized fashion</td></tr>
<tr><td>Duration of Treatment</td><td>Four administrations of a single dose of IPX066 separated by a 6-day washout between treatment periods.</td></tr>
<tr><td>PK Sampling</td><td>A total of 17 plasma samples for measurement of CD and LD were collected at the following intervals: predose, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours postdose.</td></tr>
<tr><td>Analysis</td><td>Carbiodopa and levodopa concentrations were determined in plasma samples using a validated method for high performance liquid chromatography with tandem mass spectrometric detection with a lower limit of quantification of 2 ng/mL and 10 ng/mL respectively.

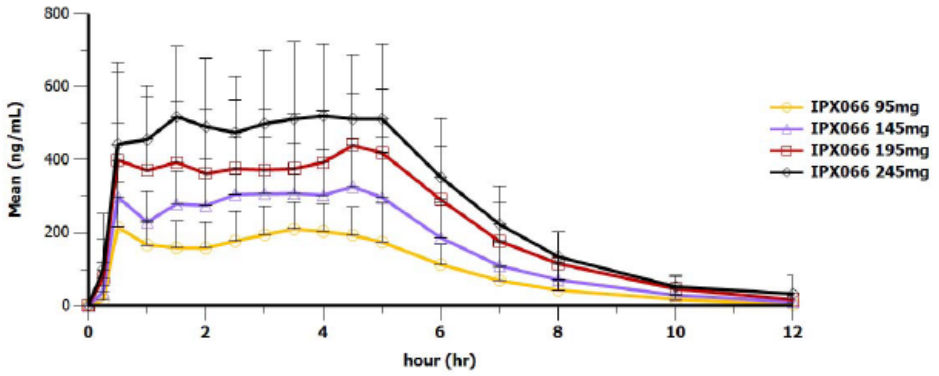
Carbidopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>6, 60, 200 and 300</td><td>2, 4, 10, 40, 80, 160, 240, 280, 360 and 400</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.5 to 3.9</td><td>1.6 to 4.8</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-2.5 to -1.0</td><td>-2.0 to 1.7</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.994</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">2 to 400</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">2</td></tr>
</table>
Levodopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>30, 300, 1000, and 1500</td><td>10, 20, 50, 200, 400, 800, 1200, 1400, 1800 and</td></tr>
</table>
</td></tr>
</table>

				2000
		Between Batch Precision (%CV)	2.7 to 4.1	1.9 to 5.3
		Between Batch Accuracy (%RE)	–1.1 to 1.0	–2.5 to 1.7
		Linearity	Weighted linear equation ($1/X^2$), mean r^2= 0.995	
		Linear Range (ng/mL)	10 to 2000	
		Sensitivity (LLOQ, ng/mL)	10	
PK Assessments	A total of 17 plasma samples for measurement of CD and LD were collected at the following intervals: predose, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours postdose. Observed maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time zero up to time t (AUC_{0-t}), and AUC from time zero to infinity ($AUC_{0-\infty}$), elimination constant (k), and terminal half-life ($t_{1/2}$) were estimated for CD and LD.			
PD Assessments	None			
Statistical Methods	Subjects who completed all four PK assessments were included in the statistical analysis. Descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) were used to summarize the PK parameters for each treatment group. Dose proportionality was assessed using a power model ($Y = \alpha*(Dose)^{\beta}$) and by using a bioequivalence approach following dose normalization.			

RESULTS:

Levodopa:
The mean plasma concentration profiles for levodopa for all the treatments are represented in the figure below:

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



Dose proportionality of levodopa PK parameters following administration of IPX066 was assessed by dose normalized to IPX066 245 mg LD. The 90% CI for the Ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were within the 80 to 125% range.

Table: Summary of Levodopa Pharmacokinetic Parameters for Study IPX066-B08-09, Mean ± SD, (N=28)

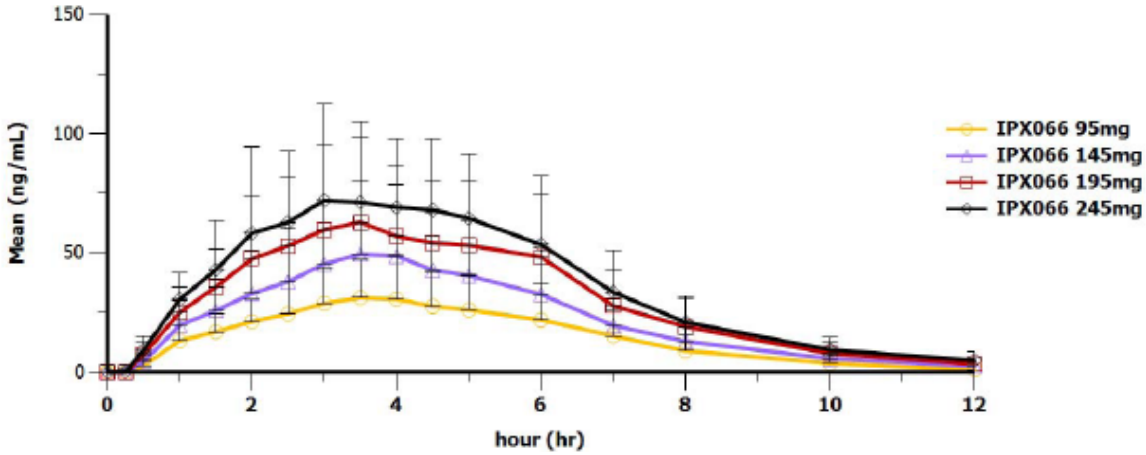
	IPX066 CD-LD Dose (mg)			
PK Parameters	**23.75-95**	**36.25-145**	**48.75-195**	**61.25-245**
T_{max} (h)[a]	2.75 (0.50 - 5.00)	2.75 (0.50 - 5.00)	4.00 (0.50 - 5.00)	3.5 (0.50 - 5.00)
C_{max} (ng/mL)	317.14 ± 90.28	490.57 ± 125.33	630.46 ± 186.77	763.00 ± 155.59
AUC_{0-t} (ng·h/mL)	1214.43 ± 262.66	1968.14 ± 520.98	2765.60 ± 699.49	3474.92 ± 636.82
$AUC_{0-\infty}$ (ng·h/mL)	1247.48 ± 264.71	2008.18 ± 515.97	2810.40 ± 701.21	3553.09 ± 633.56
$t_{1/2}$ (h)	1.50 ± 0.29	1.44 ± 0.20	1.53 ± 0.59	1.52 ± 0.29

a. Median (range)

The Cmax and AUC of LD from IPX066 increased in a dose-proportional manner over the LD dose strengths of 95 mg to 245 mg.

Carbidopa:

Figure: Mean (± SD) Carbidopa Plasma Concentration-Time Profiles



Dose proportionality of carbidopa PK parameters following administration of IPX066 was assessed by dose normalized to IPX066 61.25 mg CD. The 90% CIs for

the ln-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were within the 80% to 125% range.

Table: Summary for Carbidopa Pharmacokinetic Parameters for Study IPX066-B08-09, Mean ± (SD), (N=28)

	IPX066 CD-LD Dose mg			
PK Parameters	**23.75-95**	**36.25-145**	**48.75-195**	**61.25-245**
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 ± 140.52
$AUC_{0-\infty}$ (ng·h/mL)	182.73 ± 81.52	277.87 ± 128.10	374.49 ± 149.72	447.16 ± 146.09
$t_{1/2}$ (h)	1.66 ± 0.32	1.79 ± 0.32	1.69 ± 0.27	1.88 ± 0.47

a. Median (range)

The Cmax and AUC of CD from IPX066 increased in a dose-proportional manner over the CD dose strengths of 23.75 mg to 61.25 mg.

CONCLUSIONS:

Dose-proportional increases in systemic exposure for LD over the dose strengths of 95 mg to 245 mg and for CD over the dose strengths of 23.75 mg to 61.25 mg were demonstrated for single doses of IPX066.

IPX066-B09-01: EFFECT OF FOOD ON THE PHARMACOKINETICS OF IPX066

Objective:
To assess the effect of a high-fat, high-calorie meal on the pharmacokinetics of IPX066 (Carbidopa-Levodopa extended-release [ER]) capsules and to evaluate the effect of sprinkling the IPX066 capsule contents on applesauce on the PK of IPX066.

Study Design	Single-center, single-dose, open-label, randomized, three-sequence, three-treatment crossover study in healthy subjects with a 6-day washout period between the 3 treatment periods.
Study Population	Healthy males and females Age: 18 -55 years BMI: 18 to 29.5 kg/m^2 21 subjects were enrolled, and 19 completed the study

<table>
<tr><td>Treatment Groups</td><td>
<table>
<tr><th></th><th>Fed Treatment</th><th>Sprinkled</th><th>Fasted</th></tr>
<tr><td>IPX066 Dose (CD-LD) mg</td><td>2 x 61.25 - 245</td><td>2 x 61.25 - 245</td><td>2 x 61.25 - 245</td></tr>
<tr><td>Mode of administration</td><td>Oral, two capsules taken 30 minutes after the start of ingestion</td><td>Oral, contents of two capsules sprinkled on applesauce and swallowed</td><td>Oral, two capsules taken in a fasted state.</td></tr>
<tr><td>Lot number(s)</td><td>RB0910-80A</td><td>RB0910-80A</td><td>RB0910-80A</td></tr>
</table>
</td></tr>
<tr><td>PK Sampling</td><td>A total of 17 PK plasma samples were collected during each of the 3 treatment periods (Fed, Sprinkled, Fasted) at predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours postdose.</td></tr>
<tr><td>Analysis</td><td>Carbiodopa and levodopa concentrations were determined in plasma samples using a validated method for high performance liquid chromatography with tandem mass spectrometric detection with a lower limit of quantification of 2 ng/mL and 10 ng/mL respectively.

Carbidopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>6, 60, 200 and 300</td><td>2, 4, 10, 40, 80, 160, 240, 280, 360 and 400</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.4 to 6.9</td><td>1.4 to 8.2</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-0.3 to 1.0</td><td>-4.0 to 1.3</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.9953</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">2 to 400</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">2</td></tr>
</table>

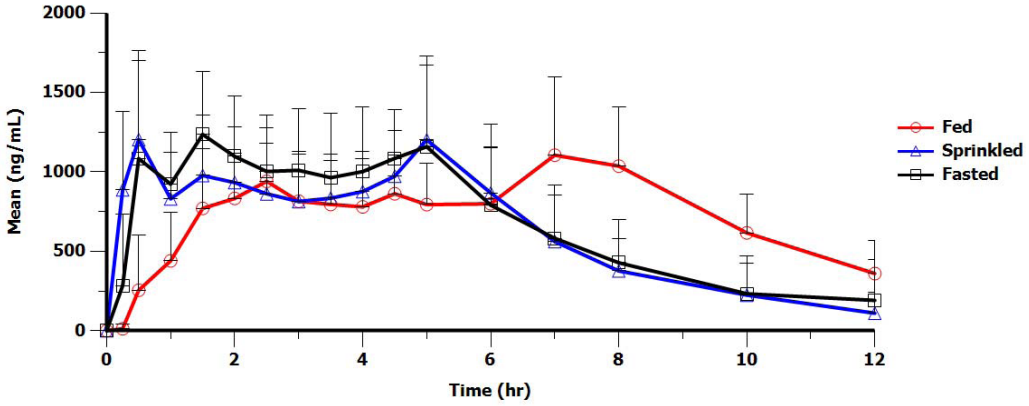
Levodopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>30, 300, 1000, and 1500</td><td>10, 20, 50, 200, 400, 800, 1200, 1400, 1800 and 2000</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.3 to 2.9</td><td>1.9 to 6.9</td></tr>
</table>
</td></tr>
</table>

		Between Batch Accuracy (%RE)	-0.3 to 1.0	-4.4 to 2.0
		Linearity	Weighted linear equation ($1/X^2$), mean r^2= 0.995	
		Linear Range (ng/mL)	10 to 2000	
		Sensitivity (LLOQ, ng/mL)	10	
PK Assessments	The following PK parameters were estimated for CD and LD maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time zero up to time t (AUC_{0-t}), and AUC from time zero to infinity ($AUC_{0-\infty}$), elimination constant (k), and terminal half-life ($t_{1/2}$).			
PD Assessments	None			
Statistical Methods	PK parameters for CD and LD were estimated and descriptive statistics were summarized. A mixed-effect Analysis of Variance (ANOVA) was used to analyze CD and LD PK parameters (natural log transformed AUC and Cmax). Subjects who dropped out prior to the end of the study were not replaced.			

RESULTS:

Levodopa:
The mean plasma concentration profiles for levodopa for all the treatments are presented below:

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



Following table provides summary of levodopa PK parameters:

Table: Summary of Levodopa Pharmacokinetic Parameters for IPX066 in Study IPX066-B09-01, Mean ± SD, (N = 19)

PK Parameters	Fed	Sprinkled	Fasted
T_{max} (h)[a]	7.0 (1.5 - 12.0)	4.0 (0.25 - 6.0)	1.5 (0.5 - 7.0)
C_{max} (ng/mL)	1341.42 ± 388.96	1567.42 ± 443.57	1658.95 ± 428.54
AUC_{0-t} (ng.h/mL)	8861.87 ± 2304.13	7675.78 ± 1785.78	8176.37 ± 1675.63

$AUC_{0-\infty}$ (ng.h/mL)	9902.41 ± 2244.02	8048.33 ± 2028.80	8683.60 ± 1786.11
$t_{1/2}$ (h)	1.97 ± 0.43	1.89 ± 1.20	1.67 ± 0.34

a. Median (range)

Food-Effect Assessment:

Table: Statistical comparison of different treatments with the reference

PK Parameters	Fed	Sprinkled	Fasted
C_{max}, (ng/mL)	79.41 (71.90 - 87.70)	92.37 (83.63 - 102.01)	Reference
AUC_{0-t}, (ng.h/mL)	106.08 (98.52 - 114.22)	92.28 (85.70 -99.36)	Reference
$AUC_{0-\infty}$, (ng.h/mL)	112.75 (104.74 -121.37)	90.70 (84.26 - 97.63)	Reference

* Values expressed as geometric mean ratio (90% CI)

Carbidopa:

Figure: Mean (± SD) Carbidopa Plasma Concentration-Time Profiles

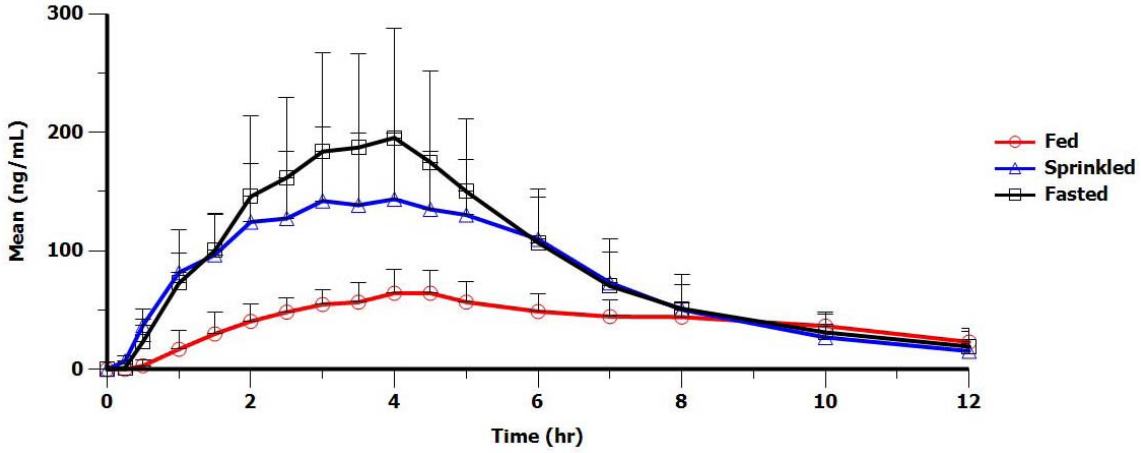


Table: Summary of Carbidopa Pharmacokinetic Parameters for IPX066 in Study IPX066-B09-01, Mean ± SD, (N = 19)

PK Parameters	Fed	Sprinkled	Fasted
T_{max} (h)[a]	4.5 (1.5 - 10.0)	3.0 (1.5 - 7.0)	3.5 (1.5 -6.0)
C_{max} (ng/mL)	72.16 ± 16.15	167.43 ± 51.56	206.18 ± 88.77
AUC_{0-t} (ng·h/mL)	487.11 ± 81.59	935.53 ± 283.94	1068.16 ± 366.61
$AUC_{0-\infty}$ (ng·h/mL)	574.38 ± 104.20	985.11 ± 284.76	1140.13± 387.10
$t_{1/2}$ (h)	2.60 ± 0.33	2.22 ± 0.50	2.31 ± 0.56

a. Median (range)

Food-Effect Assessment:

Table: Statistical comparison of different treatments with the reference

PK Parameters	Fed	Sprinkled	Fasted
C_{max} (ng/mL)	38.09 (33.14 – 43.79)	85.41 (74.30 – 98.18)	Reference
AUC_{0-t}, (ng·h/mL)	48.33 (43.06 – 54.24)	88.28 (78.66 – 99.08)	Reference
$AUC_{0-\infty}$, (ng·h/mL)	53.31 (47.67 – 59.61)	87.34 (78.11 – 97.67)	Reference

* Values expressed as geometric mean ratio (90% CI)

Discussion:

Following administration of IPX066 capsules to healthy subjects in a fed state (high-fat, high-calorie food) there was a 13% increase in the extent of absorption of LD (AUCinf). There was a delay in LD absorption by 5.5 hours and a decrease in LD Cmax by approximately 21%. Sprinkling the IPX066 capsule contents on applesauce did not affect LD PK compared to the intact capsule. However, there was a delay in LD absorption by 2.5 hours.

Carbidopa AUC and Cmax values were decreased by 40% and 50%, respectively, in the presence of high fat and high calorie food when compared to the fasted state.

In the Phase 2 and Phase 3 studies with IPX066, subjects were instructed to continue their normal practices in taking LD with regards to meal. Foods rich in proteins or amino acids may interfere with the oral absorption and pharmacological effects of LD, similar to other CD-LD products.

IPX066 may be taken with or without food. However, the patients should be informed about the delay in absorption of LD when taken with food.

CONCLUSIONS:

When IPX066 was administered under fed conditions:

- The Levodopa AUC was 113% of that in the fasted state.
- Levodopa Cmax values were decreased by approximately 20% and there was a delay in LD Tmax by approximately 5.5 hour compared to the fasted state.
- Carbidopa AUC and Cmax values were reduced to 40% to 50%, respectively, and there was a delay in CD Tmax by approximately 1 hour compared to the fasted state.

When IPX066 was administered after sprinkling on apple sauce compared to swallowing the intact capsule under fasted conditions:

- Sprinkling the contents of the IPX066 capsule on applesauce did not affect the LD PK (AUC and C_{max}) and there was a delay in LD Tmax by approximately 2.5 hours compared to the fasted state
- There was an approximately 15% reduction in CD $AUC_{0-\infty}$ and C_{max}.

IPX066-B09-04: THE EFFECT OF ALCOHOL ON IPX066

Objective: To assess the effect of alcohol on the pharmacokinetics (PK) of IPX066.

<table>
<tr><td>Study Design</td><td>Single dose, open-label, randomized, three-sequence, three-treatment (0%, 5%, 20% alcohol) crossover study followed by a fixed treatment (40% alcohol) in Period 4 with a 6- day washout between treatment periods.</td></tr>
<tr><td>Study Population</td><td>Healthy males and females
Age: 21 to 45 years
BMI: 18 to 35 kg/m^2
27 subjects were enrolled, and 18 completed the study</td></tr>
<tr><td>Treatment Groups</td><td>
<table>
<tr><th>Treatment</th><th>0%</th><th>5% Alcohol</th><th>20% alcohol</th><th>40% Alcohol</th></tr>
<tr><td>IPX066 Total Dose (CD-LD) mg</td><td>97.5 - 390</td><td>97.5 - 390</td><td>97.5 - 390</td><td>97.5 - 390</td></tr>
<tr><td>% of Alcohol</td><td>0%</td><td>5%</td><td>20%</td><td>40%</td></tr>
<tr><td>Lot number(s)</td><td>RB09028A-120A</td><td>RB09028A-120A</td><td>RB09028A-120A</td><td>RB09028A-120A</td></tr>
<tr><td>Duration of treatment</td><td>1 dose</td><td>1 dose</td><td>1 dose</td><td>1 dose</td></tr>
</table>
</td></tr>
<tr><td>PK Sampling</td><td>A total of 18 PK samples were collected during each of the 4 treatment periods at predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, and 24 hours postdose following each treatment.</td></tr>
<tr><td>Analysis</td><td>Carbiodopa and levodopa concentrations were determined in plasma samples using a validated method for high performance liquid chromatography with tandem mass spectrometric detection with a lower limit of quantification of 2 ng/mL and 10 ng/mL respectively.

Carbidopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>6, 60, 200 and 300</td><td>2, 4, 10, 40, 80, 160, 240, 280, 360 and 400</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.2 to 3.3</td><td>1.6 to 6.0</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-1.2 to 0.0</td><td>-1.5 to 0.8</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.993</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Linear Range (ng/mL)</td><td>2 to 400</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td>2</td></tr>
</table>

Levodopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>30, 300, 1000, and 1500</td><td>10, 20, 50, 200, 400, 800, 1200, 1400, 1800 and 2000</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>-0.7 to 1.7</td><td>2.1 to 6.0</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>2.9 to 3.8</td><td>-5.9 to 2.5</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.9934</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">10 to 2000</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">10</td></tr>
</table>
</td></tr>
<tr><td>PK Assessments</td><td>The following PK parameters were estimated for CD and LD maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time zero up to time t (AUC_{0-t}), and AUC from time zero to infinity ($AUC_{0-\infty}$), elimination constant (k), and terminal half-life ($t_{1/2}$).</td></tr>
<tr><td>PD Assessments</td><td>None</td></tr>
<tr><td>Statistical Methods</td><td>Pharmacokinetic parameters for CD and LD were estimated and descriptive statistics were summarized. For the first three periods, a mixed-effect Analysis of Variance (ANOVA) was used to analyze CD and LD PK parameters (natural log transformed AUC and Cmax). For the 40% alcohol treatment, a comparison to the 0% alcohol treatment was made using an ANOVA model with treatment as an effect.</td></tr>
</table>

RESULTS:

Levodopa:
The mean plasma concentration-time profiles for levodopa for all the treatments are presented below:

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

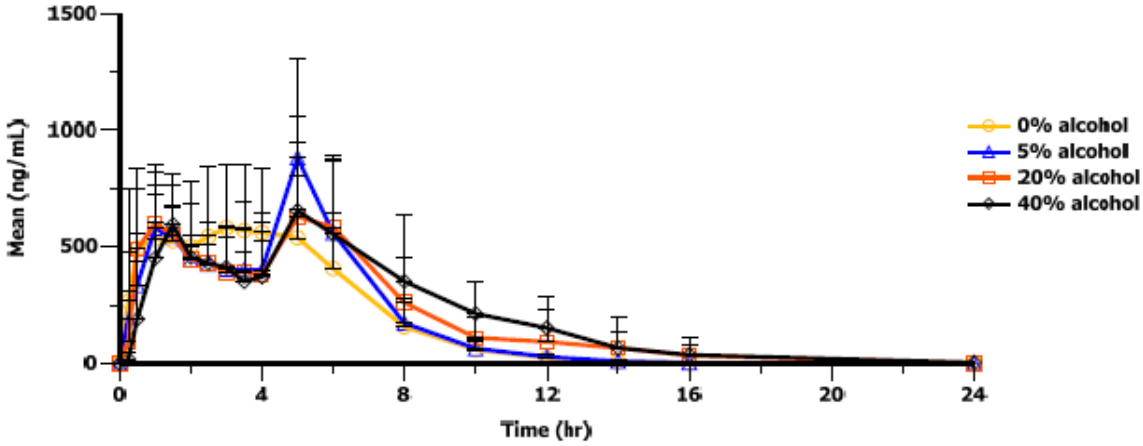


Table: Summary of Levodopa Pharmacokinetics for Completed Subjects for IPX066 in Study IPX066-B09-04, Mean ± SD, (N = 15)

PK Parameters	0% Alcohol	5% Alcohol	20% Alcohol	40% Alcohol
T_{max} (h)[a]	3.00 (0.25 - 6.00)	5.00 (0.25 - 5.00)	2.50 (0.50 - 6.00)	5.00 (1.00 - 6.00)
C_{max} (ng/mL)	898.80 ± 288.16	1017.80 ± 270.92	874.53 ± 254.29	851.60 ± 310.44
AUC_{0-3} (ng.h/mL)	1449.73 ± 596.71	1272.30 ± 252.63	1320.83 ± 327.64	1144.45 ± 410.40
AUC_{0-t} (ng.h/mL)	3923.72 ± 1139.97	4127.08 ± 1104.43	4574.78 ± 1470.57	4830.81 ± 1548.96
$AUC_{0-\infty}$ (ng.h/mL)	3962.98 ± 1137.92	4169.11 ± 1095.15	4650.18 ± 1478.08	4930.89 ± 1523.23
$t_{1/2}$ (h)	1.62 ± 0.51	1.59 ± 0.24	1.87 ± 0.81	1.99 ± 1.29

a. Median (range)

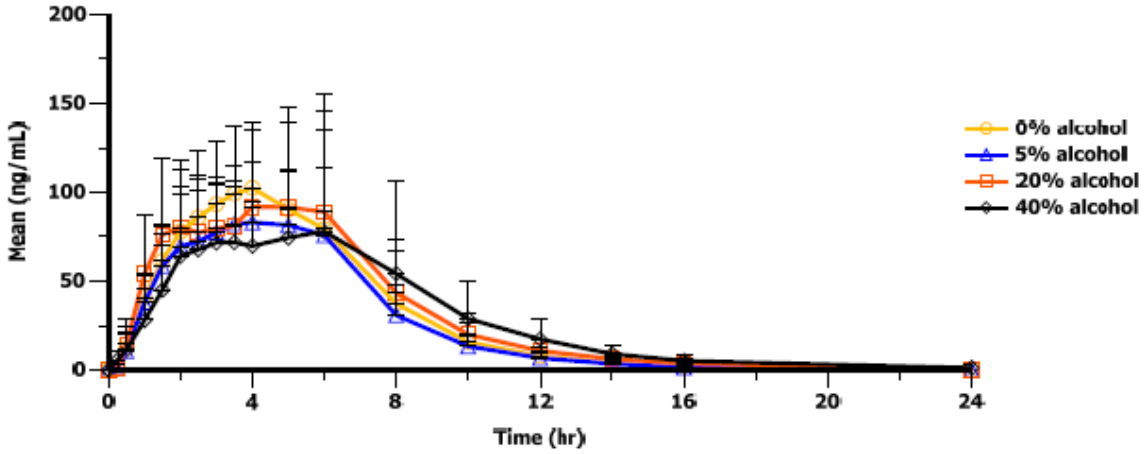
Following table provides statistical comparison of different treatments with the reference.

Table: Summary of 90% CI Assessment for Levodopa in Study IPX066-B09-04, (N = 15).

PK Parameters	5% Alcohol vs. 0% Alcohol	20% Alcohol vs. 0% Alcohol	40% Alcohol vs. 0% Alcohol
C_{max},%	114.59 (101.52 - 129.35)	97.96 (86.79 - 110.58)	91.54 (71.70 - 116.86)
AUC_{0-3},%	91.91 (80.34 - 105.15)	94.62 (82.71 - 108.25)	78.00 (59.85 - 101.66)
AUC_{0-t},%	105.72 (94.43 - 118.36)	115.34 (103.02 - 129.13)	121.46 (101.46 - 145.40)
$AUC_{0-\infty}$,%	105.79 (94.68 - 118.20)	116.05 (103.86 - 129.67)	122.97 (102.80 - 147.09)

* Values expressed as geometric mean ratio (90% CI)

Figure: Mean (± SD) Carbidopa Plasma Concentration-Time Profiles



Following table provides summary of carbidopa PK parameters:

Table: 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
AUC0-4 (ng.h/mL)	259.95 ± 90.23	223.91 ± 81.56	252.75 ± 103.25	197.00 ± 88.33
AUC0-t (ng.h/mL)	650.69 ± 303.22	568.72 ± 210.01	689.20 ± 342.65	658.56 ± 318.82
AUC0-∞ (ng.h/mL)	660.58 ± 305.49	577.34 ± 211.14	705.90 ± 341.09	684.72 ± 319.39
t1/2 (h)	2.14 ± 0.42	2.15 ± 0.27	2.75 ± 1.02	3.35 ± 2.37

a. Median (range)

Following table provides statistical comparison of different treatments with the reference.

Table: Summary of 90% CI Assessment for Carbidopa for IPX066 in Study IPX066-B09-04, (N = 15)

PK Parameters	5% Alcohol vs. 0% Alcohol	20% Alcohol vs. 0% Alcohol	40% Alcohol vs. 0% Alcohol
C_{max} (ng/mL)	83.09 (73.22 - 94.29)	89.45 (78.82 - 101.50)	84.29 (66.05 - 107.58)
AUC_{0-4} (ng.h/mL)	85.84 (75.32 - 97.82)	94.17 (82.63 - 107.33)	71.34 (56.36 - 90.29)

AUC_{0-t} (ng.h/mL)	89.69 (79.83 - 100.78)	106.19 (94.51 - 119.31)	99.97 (79.90 - 125.10)
$AUC_{0-\infty}$ (ng.h/mL)	89.66 (80.01 - 100.46)	107.54 (95.98 - 120.51)	102.65 (81.92 - 128.64)

* Values expressed as geometric mean ratio (90% CI)

CONCLUSIONS:

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

IPX066-B10-01: ASSESSMENT OF THE BIOEQUIVALENCE OF IPX066 MANUFACTURED AT TWO SITES

Objective:
To assess bioequivalence (BE) of IPX066 manufactured in Hayward, California (IPX066 245 mg LD Hayward) and in Jhunan, Taiwan (IPX066 245 mg LD Jhunan); and to assess the dose proportionality of one and two capsules of IPX066 245 mg LD.

Study Design	A randomized, single-center, single-dose, open-label, two-sequence, two-treatment crossover study with at least a 6-day washout period in healthy subjects under fasted conditions.
Study Population	Healthy males and females Age: 18 years and above BMI: 18 to 29.5 kg/m^2 39 subjects were enrolled, and 37 completed the study
Treatment Groups	Subjects received a single dose of IPX066 245 mg LD from two different manufacturing sites, Hayward (CA) and Jhunan (Taiwan), in a randomized fashion during Period 1 and Period 2. For subjects that completed Periods 1 and 2, subjects received an additional treatment of a single dose of two capsules of IPX066 245 mg LD.
PK Sampling	A total of 17 plasma samples for measurement of CD and LD were collected at the following intervals: predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 hours postdose in each treatment period.

<table>
<tr><td>Analysis</td><td>Carbiodopa and levodopa concentrations were determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with a lower limit of quantification of 2 ng/mL and 10 ng/mL respectively.

Carbidopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>6, 60, 200 and 300</td><td>2, 4, 10, 40, 80, 160, 240, 280, 360 and 400</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.1 to 3.6</td><td>1.3 to 5.1</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>–0.2 to 1.0</td><td>–3.5 to 1.9</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.996</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">2 to 400</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">2</td></tr>
</table>
Levodopa:
<table>
<tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr>
<tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>30, 300, 1000, and 1500</td><td>10, 20, 50, 200, 400, 800, 1200, 1400, 1800 and 2000</td></tr>
<tr><td>Between Batch Precision (%CV)</td><td>2.5 to 4.2</td><td>1.3 to 4.6</td></tr>
<tr><td>Between Batch Accuracy (%RE)</td><td>-0.7 to 1.7</td><td>-5.5 to 2.3</td></tr>
<tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r^2= 0.995</td></tr>
<tr><td>Linear Range (ng/mL)</td><td colspan="2">10 to 2000</td></tr>
<tr><td>Sensitivity (LLOQ, ng/mL)</td><td colspan="2">10</td></tr>
</table></td></tr>
<tr><td>PK Assessments</td><td>The following PK parameters were estimated for CD and LD maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time zero up to time t (AUC0-t), and AUC from time zero to infinity ($AUC_{0-\infty}$), elimination constant (k), and terminal half-life ($t_{1/2}$).</td></tr>
<tr><td>PD Assessments</td><td>None</td></tr>
<tr><td>Statistical Methods</td><td>Subjects who completed Periods 1 and 2 were included in the BE analysis; subjects who completed Periods 1, 2 and 3 were included in the dose proportionality analysis. Descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) were used to summarize the PK parameters. Dose proportionality was assessed using a power model ($Y = \alpha*(Dose)^{\beta}$). In addition, a BE approach following</td></tr>
</table>

	dose normalization was used to assess dose proportionality.

RESULTS:

Following figure indicates PK profile of levodopa and cabidopa upon administration of IPX066 manufactured at Hayward, CA or Jhunan, Taiwan.

Figure: Mean (± SD) Levodopa Plasma Concentration−Time Profiles

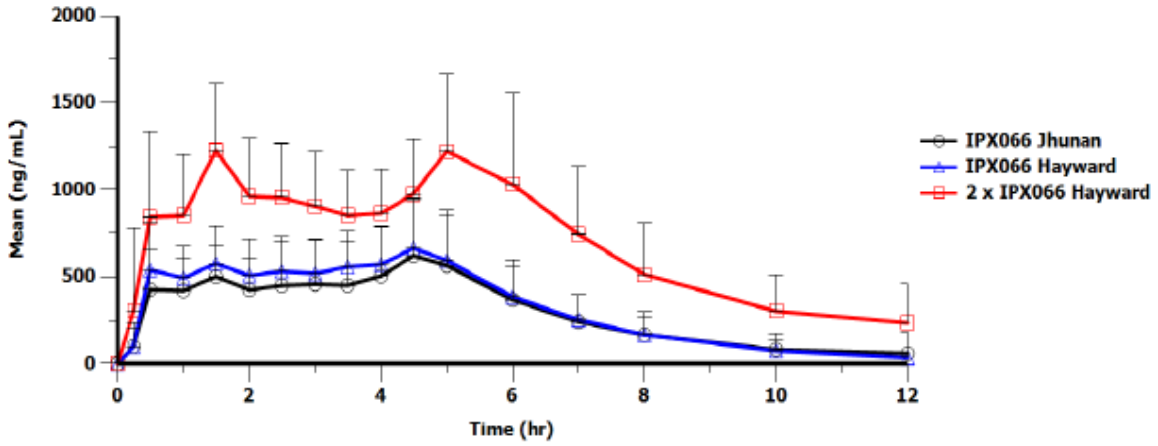


Figure: Mean (± SD) Carbidopa Plasma Concentration - Time Profiles

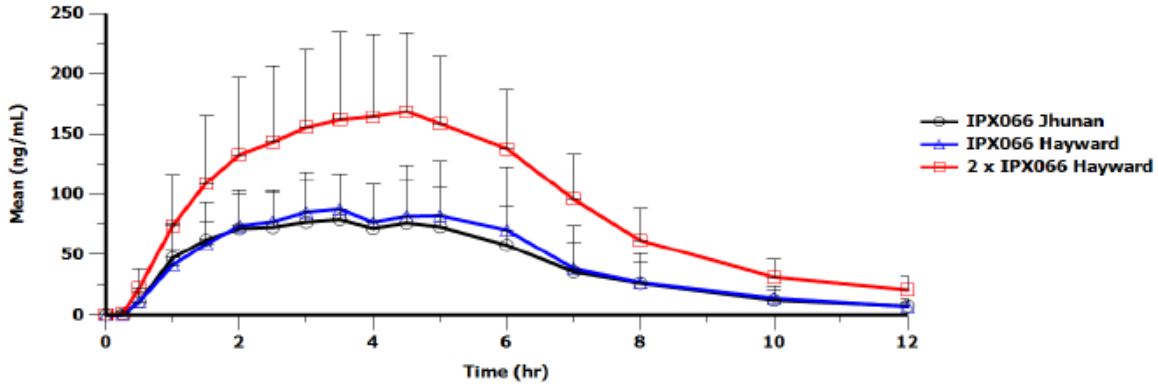


Table: Pharmacokinetic Summary for Levodopa and Carbidopa for IPX066 Manufactured in Jhunan, Taiwan and Hayward, CA in Study IPX066-B10-01, Mean ± SD

PK Parameters	**1 Capsule IPX066 245 mg Jhunan (N=37)**	**1 Capsule IPX066 245 mg Hayward (N=37)**	**1 Capsule IPX066 245 mg Hayward (N=34)**	**2 Capsules IPX066 245 mg Hayward (N=34)**
Levodopa				
Tmax (h)	4.5 (0.5-8.0)	4.5 (0.5-6.0)	4.25 (0.5-6.0)	2.5 (0.25-6.0)
Cmax (ng/mL)	837.6 ± 262.5	880.0 ± 252.5	881.27 ± 259.49	1629.24 ± 392.18

AUC0-t (ng.h/mL)	3581.2 ± 960.3	3905.5 ± 1058	3951.2 ± 1050	8485.4 ± 2251.9
AUC0-∞ (ng.h/mL)	3722.5 ± 1063.5	4023.9 ± 1109.9	4069.8 ± 1101.2	9460.6 ± 2792.2
t1/2 (h)	1.6 ± 0.3	1.8 ± 0.8	1.8 ± 0.8	2.4 ± 1.4
Carbidopa (1 to 4 ratio CD-LD)				
Tmax (h)	4.0 (1.5-6.0)	3.5 (1.5-6.0)	3.5 (1.5-6.0)	4.25 (1.0-6.0)
Cmax (ng/mL)	96.03 ± 37.69	105.34 ± 47.50	109.35 ± 47.17	193.14 ± 71.60
AUC0-t (ng.h/mL)	488.31 ± 200.09	521.51 ± 219.60	539.73 ± 217.11	1090.82 ± 348.49
AUC0-∞ (ng.h/mL)	510.49 ± 206.96	541.71 ± 225.09	560.70 ± 222.14	1171.39 ± 364.26
t1/2 (h)	2.1 ± 0.6	2.0 ± 0.5	2.0 ± 0.5	2.4 ± 1.0

Table: Bioequivalence Analysis of the Log-Transformed Pharmacokinetic Parameters for Levodopa and Carbidopa Following a Single Dose of IPX066 245 mg LD Manufactured in Jhunan and Hayward in Study IPX066-B10-01, (N=37)

PK Parameters	**Geometric Mean Ratio (%;** Jhunan/Hayward**) (90% CIs)**
Levodopa 245 mg LD	
Cmax (ng/mL)	94.69 (87.06, 102.98)
AUC0-t (ng.h/mL)	92.31 (86.51, 98.50)
AUC0-∞ (ng.h/mL)	92.81 (86.96, 99.06)
Carbidopa (1 to 4 ratio CD-LD)	
Cmax (ng/mL)	91.05 (81.61, 101.59)
AUC0-t (ng.h/mL)	92.66 (84.49, 101.63)
AUC0-∞ (ng.h/mL)	93.49 (85.62, 102.08)

Table: Dose Proportionality Assessment for Levodopa and Carbidopa Using Power Model Analysis in Study IPX066-B10-01, (N=34)

PK Parameters	**Acceptance Criteria**	**β**	**90% CIs**
Levodopa 245 mg LD			
C_{max} (ng/mL)	(0.6781, 1.3219)	0.9117	(0.8313, 0.9999)
AUC_{0-t} (ng.h/mL)	(0.6781, 1.3219)	1.1109	(1.0232, 1.2060)

$AUC_{0-\infty}$ (ng.h/mL)	(0.6781, 1.3219)	1.2322	(1.1239, 1.3509)
Carbidopa (1 to 4 ratio CD-LD)			
C_{max} (ng/mL)	(0.6781, 1.3219)	0.8418	(0.7383, 0.9597)
AUC_{0-t} (ng.h/mL)	(0.6781, 1.3219)	1.0351	(0.9247, 1.1587)
$AUC_{0-\infty}$ (ng.h/mL)	(0.6781, 1.3219)	1.0884	(0.9637, 1.2292)

CONCLUSIONS:

- The IPX066 manufactured in Jhunan was bioequivalent to IPX066 manufactured in Hayward based on the BE acceptance criteria (80-125%).
- The increase in levodopa Cmax was dose linear. However, the increases in AUC0-t and AUC0-∞ were slightly more than dose-proportional comparing one to two capsules of IPX066 245 mg LD.
- The AUC0-t and AUC0-∞ of carbidopa were dose-proportional comparing one to two capsules of IPX066 245 mg LD. However, the increase in Cmax was 16% less comparing one to two capsules of IPX066 245 mg LD.

Comment:
At the request of Division of Neurology Products, the Office of Scientific Investigations conducted audit of this pivotal bioequivalence study:

The clinical and analytical portions of the studies were conducted at (b) (4) (b) (4), respectively. Following the inspection at (b) (4) no Form 483 was issued. However, following inspection of (b) (4), Form 483 (Inspectional Observations) was issued. The clinical and analytical audit was based on 100% audit of source data.

OSI evaluated the Establishment Inspection Report (EIR), (b) (4) response to the Form 483 and associated exhibits related to objectionable observation and concluded that reliability of source data generated in study IPX066-B10-01 can be accepted for review.

4.2 PHARMACOMETRICS REVIEW

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

What is the Dose/Dosing Regimen for Initial Conversion from Immediate-Release Levodopa (IR LD) Product to IPX066 in Parkinson's disease Patients?

The rationale for dose/dosing regimen for initial conversion from immediate-release Levodopa Product (IR LD) to IPX066 in Parkinson's disease patients is discussed below.

Sponsor evaluated a guideline for initial conversion from IR LD to IPX066 in clinical trials as shown in Table 1.

Table 1: Guidelines for Initial Conversion from IR Levodopa Product to IPX066 in Parkinson's disease Patients.

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	[TRADE NAME] 95	4 capsules
750 to	[TRADE NAME] 145	3 capsules
950 to	[TRADE NAME] 195	3 capsules
(b) (4)	[TRADE NAME] 195	4 capsules
	or	
	[TRADE NAME] 245	3 capsules
		(b) (4)

Source: Table 1 on page 4, from Label

The systemic exposure using dosing regimen (Table 1) was estimated as displayed in Table 2. The daily IPX066 LD dose (second column) was calculated using Table 1 for each daily dose of IR LD in 50 mg dose increments (first column). The third column of Table 2 displays the daily dose of IPX066 corrected for the reduced bioavailability (70%) of levodopa (LD) from IPX066. The right column displays the ratio of daily LD from IPX066 corrected for bioavailability to the daily IR LD dose.

Table 1: Estimation of IPX066 LD Systemic Exposure Compared to IR LD

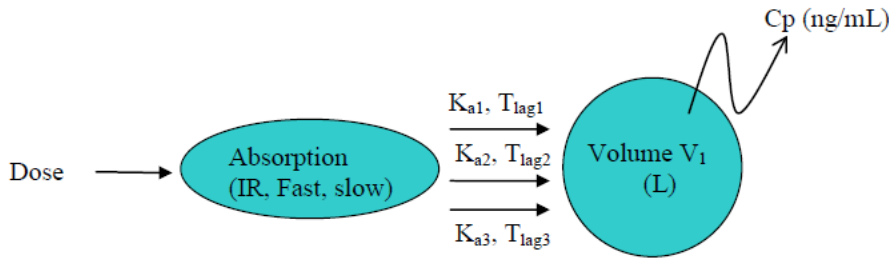
IR LD Daily Dose (mg)	IPX066 Daily Dose (mg LD)	bioavailability-Corrected IPX066 Daily Dose (mg LD)	IPX066/IR bioavailability -Corrected AUC Ratio
400	855	599	1.50
450	855	599	1.33
500	855	599	1.20
550	855	599	1.09
600	1140	798	1.33
650	1140	798	1.23

IR LD Daily Dose (mg)	IPX066 Daily Dose (mg LD)	bioavailability-Corrected IPX066 Daily Dose (mg LD)	IPX066/IR bioavailability-Corrected AUC Ratio
700	1140	798	1.14
750	1140	798	1.06
800	1305	914	1.14
850	1305	914	1.07
900	1305	914	1.02
950	1305	914	0.96
1000	1755	1229	1.23
1050	1755	1229	1.17
1100	1755	1229	1.12
1150	1755	1229	1.07
1200	1755	1229	1.02
1250	1755	1229	0.98
1300	2205	1544	1.19
1350	2205	1544	1.14
1400	2205	1544	1.10
1450	2205	1544	1.06
1500	2205	1544	1.03
1550	2205	1544	1.00
1600	2205	1544	0.96
1650	2205	1544	0.94
1700	2940	2058	1.21
1750	2940	2058	1.18
1800	2940	2058	1.14
1850	2940	2058	1.11
1900	2940	2058	1.08
1950	2940	2058	1.06
2000	2940	2058	1.03
Mean			1.12
Median			1.10
SD			0.12

Source: Sponsor’s analysis

The FDA reviewer simulated mean LD concentration time profile when patients are initially treated with IR LD for one week and switched to IPX066 for another week. The simulation was to characterize the mean PK of IPX066 in healthy volunteers and in patients with PD when they were treated with IR and IPX066.
The simulation model was based on sponsor’s pharmacokinetic (PK) model with 85% bioavailability. The PK model that described the data for IR LD was a one-compartment model with first-order absorption, first-order elimination, and an absorption lag time. The PK model that described the data for IPX066 included three-phase absorption corresponding to the IR component and the two ER components (Figure 1) in addition to first-order elimination.

Figure 1 One Compartment Pharmacokinetic Disposition Model with First-order Absorption, First-order Elimination, and a Lag Time



$$\frac{dA_1}{dt} = D_{IR}k_{a1} + D_{ER1}k_{a2} + D_{ER2}k_{a3} - A_1k_{10}$$

$$\hat{y}_{ij} = \frac{A_{1ij}}{V_{1i}}$$

$$k_i = \frac{Cl_i}{V_i}$$

$i = subject, j = time$

k_{a1}, k_{a2}, k_{a3} – IR, ER1 and ER2 absorption rate constant (1/hr)
T_{lag1}, T_{lag2}, T_{lag3} – Lag time for IR, ER1 and ER2 absorption (hr)
V_1 - Volume of distribution (L)
CL - Clearance for central compartment (L/hr)
$\hat{y}_{ij}$ - Model predicted Cp of subject i at time j (ng/mL)

For IPX066, three absorption phases, each with a corresponding lag time were used.

Source: Figure 4 on page 17, from PPK study report

The 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.

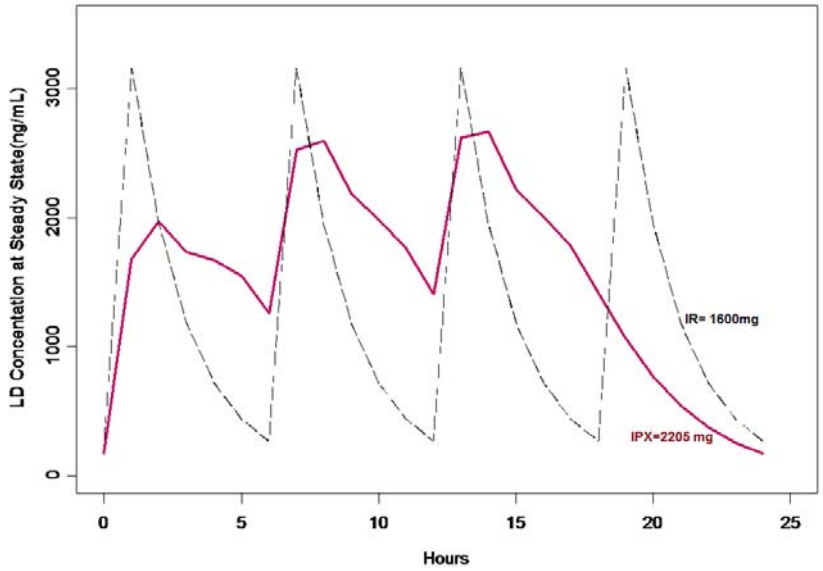
Table 3 shows the comparison of Cmax, AUC of LD at steady state under scenario 1.

IR LD Daily Dose (mg)	Cmax	AUC(Daily)	IPX066 LD Daily Dose (mg)	Cmax	↑%Cmax	AUC(Daily)	↑%AUC
400	790	7779			30.63		91.25
475	938	9238	855	1032	10.02	14877	61.04
550	1086	10696			-4.97		39.09
550	1086	10696			26.7		85.45
650	1283	12641	1140	1376	7.25	19836	56.92
750	1481	14586			-7.09		35.99
750	1481	14586			6.35		55.68
850	1678	16531			-6.14		37.36
950	1875	18475	1305	1575	-16	22707	22.90

950	1875	18475			13.01		65.29
1100	2172	21393	1755	2119	-2.44	30537	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

Figure 2 shows LD exposure comparison at steady state between IR (2205mg) & IPX066 (1600mg)



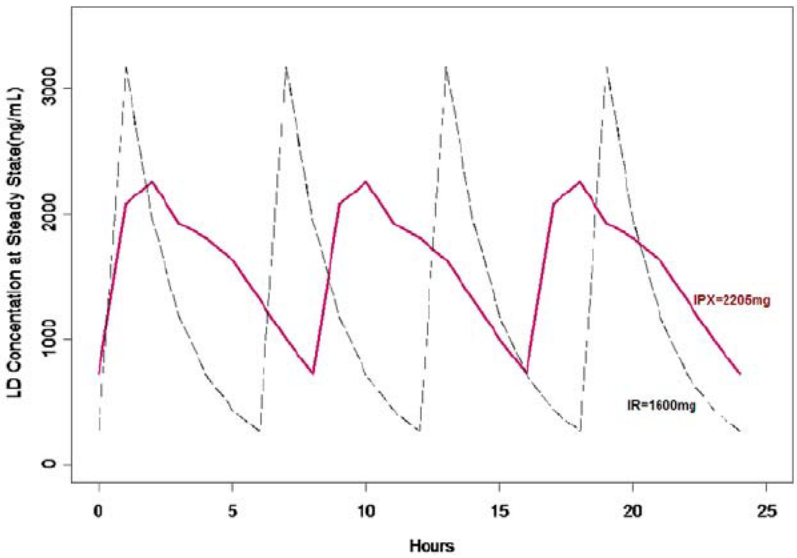
Source: FDA Reviewer's analysis

Table 4 shows the 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			10.63		94.00
475	938	9238	855	874	-6.82	15091	63.36
550	1086	10696			-19.52		41.09
550	1086	10696			7.27		88.13
650	1283	12641	1140	1165	-9.2	20122	59.18
750	1481	14586			-21.34		37.95
750	1481	14586			-9.93		57.92
850	1678	16531	1305	1334	-20.5	23034	39.34
950	1875	18475			-28.85		24.68
950	1875	18475			-4.37		67.67
1100	2172	21393	1755	1793	-17.45	30977	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 Reviewer's analysis

Figure 3 shows LD exposure comparison at steady state between IR (2205mg) & IPX066 (1600mg)



Source: FDA Reviewer's analysis

Due to the proposed conversion strategy to a IPX066 dose for a range of starting IR LD doses, it is expected that similar Cmax of LD, at all doses, will not be achieved. To overcome this issue, sponsor proposes that patients can take an additional IPX 066 dose during bed time if symptoms are not controlled. The proposed dosing guidelines are reasonable for initial conversion, although in clinical trials the dose of IPX 066 was adjusted further to maximize benefit-risk in each individual patient (Refer to review by Medical Officer Dr. Podskalny, Gerald).

Recommendations

N/A

Label Statements

N/A

Pertinent regulatory background

This is a 505(b) (2) NDA to support the marketing approval of IPX066. IPX066 is an extended-release (ER) capsule formulation of CD (carbidopa) and LD (levodopa) in 1:4 ratio intended for treatment of (b) (4) Parkinson's disease, post-encephalitic Parkinsonism, and (b) (4) Parkinsonism (b) (4) may follow injury to the nervous system by carbon monoxide (b) (4) or manganese intoxication. IPX066 will be available in 4 dosage strengths: 23.75–95 mg, 36.25–145 mg, 48.75–195 mg, and 61.25–245 mg CD-LD.

Results of Sponsor's Analysis

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 PK model utilized was a one-compartment model with first-order absorption and elimination. For IPX066, three first-order absorption rates, each with a lag time, were incorporated corresponding to the IR and two ER components of the IPX066 formulation. Age, body weight, gender and population status (healthy volunteer versus PD patient) were tested as covariates in the PK model. Total number of observations is 1756 and total number of individuals is 71.

The typical value of the apparent clearance (CL/F) and volume of distribution (V/F) for LD from IPX066 were 56.8 L/hr and 114.4 L, respectively. Bioavailability of LD from IPX066 relative to IR CD-LD was 85%. None of the covariates tested had a significant effect on the PK.

Based on the population PK analyses from healthy volunteers and patients with PD, the following conclusions are made:

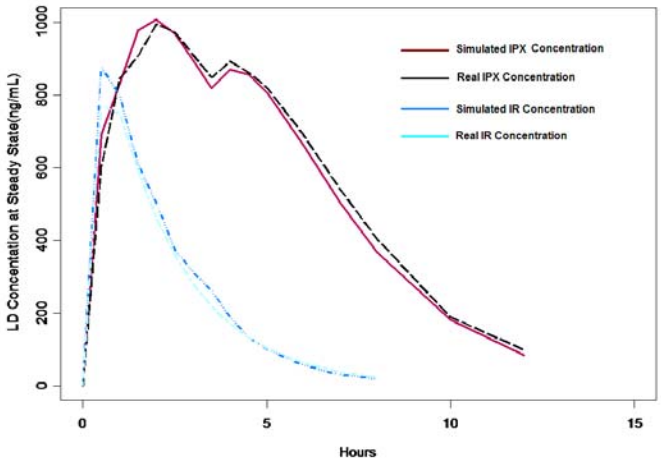
1) IPX066 PK can be adequately described by a one-compartment model with first-order absorption and elimination, and a lag time for the IR and two ER components of the IPX066 formulation.
2) Relative bioavailability for LD from IPX066 compared to IR LD was 85%. Of the LD absorbed from IPX066, the IR phase contributes 27%, with 48% and 25% contribution from the second and third ER phases, respectively.
3) Apparent CL/F was 56.8 L/hr and apparent V/F was 114.4 L.
4) Age, body weight, gender, and subjects' status (healthy volunteer versus PD patient) had no significant effect on the model parameters.

Population pharmacodynamic modeling was conducted using LD plasma concentration data and pharmacodynamic assessments (tapping, UPDRS Part III scores, and Investigator-rated dyskinesia) from the open-label Phase 2 study in patients with advanced PD (Study IPX066-B08-11).
Pharmacodynamic modeling indicated the following:
1) The concentration-effect relationship for IPX066 is comparable to IR CD-LD for tapping and UPDRS Part III.
2) The estimated onset of effect for IPX066 as measured by tapping rate and UPDRS Part III occurs within 45 minutes of oral administration. The onset of effect for IPX066 is comparable to that noted with IR CD-LD.
3) The duration of effect is approximately 2 hours longer for IPX066 than for IR CD-LD for both tapping and UPDRS Part III. The longer duration of effect is consistent with the sustained LD plasma concentration profile from an extended-release formulation. The longer pharmacodynamic effect translates into the sustained effect noted predose on Day 8.
4) The Investigator-rated dyskinesia scores support the observations noted with tapping and UPDRS Part III.

Reviewer's Analysis

The reviewer's analyses are mainly discussed in Section 1.
Simulations were conducted to compare LD concentrations after administration of IR LD or IPX 066 formulation. The simulation code was checked for any errors by comparing LD concentrations in a typical subject versus observed mean (study 08-10) as shown in Figure 4.

Figure 4 Comparison of LD concentrations in a simulated (typical subject) and observed mean after single dose (IPX390mg or IR 100mg) in study 08-10



Source: FDA Reviewer's analysis

Introduction

N/A

Objectives

N/A

Methods

Data Sets

Data sets used are summarized in Table 2.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
ipx066pk.xpt	PPK input	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Carbidopalevodopa _NDA203312_LZ\Sponsor Data and Reports\

Software

NONMEM Ver 7.2.0, SPLUS

Models

N/A

Results

N/A

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
run1.ctl	NONMEM simulation control file	Reviews\Ongoing PM Reviews\Carbidopalevodopa _NDA203312_LZ\ER Analyses\Final Model\Model10
CDLD_ET.ssc	S-plus Plotting program	Reviews\Ongoing PM Reviews\Carbidopalevodopa _NDA203312_LZ\ER Analyses\Final Model\Model10
Conv1.csv	NONMEM simulation input	Reviews\Ongoing PM Reviews\Carbidopalevodopa _NDA203312_LZ\ER Analyses\Final Model\Model10
pk21.csv	NONMEM simulation output	Reviews\Ongoing PM Reviews\Carbidopalevodopa _NDA203312_LZ\ER Analyses\Final Model\Model10

4.3 OCP Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	203312	Brand Name	IPX066
OCPB Division (I, II, III)	DCP-1	Generic Name	Levodopa-Carbidopa
Medical Division	HFD-120	Drug Class	Dopamine
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Parkinson'sdisease
OCPB Team Leader	Angela Men	Dosage Form	Extended Release Capsule
Date of Submission	12/21/2011	Dosing Regimen	(b) (4)
Estimated Due Date of OCP Review	9/13/2012	Route of Administration	Oral
Division Due Date	9/29/2012	Sponsor	Impax Labs Inc.
PDUFA Due Date	10/21/2012	Priority Classification	S

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of IPX066. IPX066 is an extended-release (ER) capsule formulation of CD (carbidopa) and LD (levodopa) in 1:4 ratio intended for treatment of (b) (4) Parkinson's disease, post-encephalitic parkinsonism, and (b) (4) parkinsonism (b) (4) may follow (b) (4) carbon monoxide (b) (4) or manganese intoxication. IPX066 will be available in 4 dosage strengths: 23.75–95 mg, 36.25–145 mg, 48.75–195 mg, and 61.25–245 mg CD-LD. The proposed ER oral capsule can be swallowed whole or opened and sprinkled on apple sauce.

According to the sponsor, the rationale for development of IPX066 is to

Provide reliable and faster initial absorption of LD compared to Sinemet CR to assure an early "on" state that is comparable to IR CD-LD
Provide stable LD concentrations with reduced maximum observed plasma concentration/minimum observed plasma concentration (Cmax/Cmin) excursions in order to reduce motor fluctuations associated with pulsatile stimulation of dopamine receptors and to minimize end-of-dose dyskinesia
Reduce the dosing frequency, targeting a (b) (4), for all stages of the disease

The clinical pharmacology evaluation included the following:
Dose proportionality of IPX066 over an LD dose range of 95 to 245 mg (IPX066-B08-09)
Pharmacokinetics and pharmacodynamics of IPX066 in patients with advanced PD compared to immediate-release CD-LD (IPX066-B08-11) and to CD-LD-entacapone (Stalevo®) (IPX066-B09-06)
Single and multiple dose pharmacokinetics in subjects with PD (IPX066-B08-11)
Effect of food on IPX066 pharmacokinetics (IPX066-B09-01)
Comparison of IPX066 pharmacokinetics to the marketed CD-LD products (IPX066-B08-10)

Intrinsic and Extrinsic Factors
The effect of demographic factors (age, weight, body mass index [BMI], race, gender, and estimated creatinine clearance [CrCL]) on the pharmacokinetics of LD and CD was assessed using pooled data from the Phase 1 studies and, separately, data from subjects with PD. Since CD-LD products have been available since 1975, results from the published literature and the package inserts for reference listed drugs are provided as appropriate.

Bioanalytical
The quantitation of CD and LD in human plasma was accomplished using a liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. The method was validated for CD over a linear concentration range of 2.00 to 400 ng/mL and for LD over a linear concentration range of 10.0 to 2000 ng/mL. The limits of quantitation (LOQs) were 2.00 ng/mL and 10.0 ng/mL for CD and LD, respectively.

Population PK Analysis
Levodopa plasma concentration-time data following IPX066 and IR CD-LD were modeled using a population approach. 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) were used.

Title: Population pharmacokinetics of IPX066 in healthy volunteers and patients with Parkinson's Disease.

List of Clinical Studies

IPX066-B08-04: To compare the bioavailability of one 2 x 47.5-190 test formulation of carbidopa-levodopa capsules with that of one 50-200 mg SINEMET® CR tablet and that of one 25-100 mg SINEMET® tablet in healthy adult subjects administered under fasting conditions.

IPX066-B08-09: To assess the dose proportionality of four strengths of IPX066 under fasted conditions in healthy subjects.

IPX066-B08-11: • To compare the single- and multiple-dose pharmacokinetics (PK) of IPX066 capsule formulation with IR CD-LD tablet formulation. • To assess the accumulation of IPX066 at steady state when dosed approximately Q6H. • To examine the efficacy and pharmacodynamics.

IPX066-B08-10: To assess the bioavailability of two capsules of IPX066 49.75-195 mg (total dose 97.5-390 mg) CD-LD relative to Sinemet 25-100 mg CD-LD, Sinemet CR 25-100 mg CD-LD, and Stalevo 25-100-200 mg CD-LD-entacapone (CLE) under fasting conditions.

IPX066-B09-01: To assess the effect of a high-fat, high-calorie meal on the PK of IPX066 and to assess the effect of sprinkling the IPX066 capsule contents on applesauce on the PK of IPX066.

IPX066-B09-04: To investigate the effect of 240 mL of 0%, 5%, 20%, and 40% v/v alcohol on the IPX066 capsule formulation in healthy volunteers.

IPX066-B10-01: • To assess the bioequivalence of IPX066 manufactured in Hayward, CA, USA and in Jhunan, Taiwan. • To assess the dose proportionality between one and two capsules of IPX066.

61.25-245 mg CD-LD formulation manufactured in Hayward, CA, USA.

Efficacy and Safety Studies

IPX066-B09-06 (ASCEND-PD): Part 1: • 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. Part 2: • 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.

IPX066-B08-05 (APEX-PD): • 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.

IPX066-B09-02 (ADVANCE-PD): To evaluate the safety and efficacy of IPX066 in the treatment of advanced PD subjects in comparison to IR CD LD.

IPX066-B09-03: To evaluate the long-term safety and clinical utility of IPX066 in subjects with Parkinson's disease (PD).

Pilot Studies

IPX066-B05-07: To compare the bioavailability of three test formulations of carbidopa-levodopa 50-200 mg with that of the marketed Reference Product, SINEMET® CR 50-200 mg tablets when administered under fasting conditions.
IPX066-B06-02: To compare the rate and extent of absorption of two Test Formulations of carbidopa-levodopa 50-200 mg tablets and two Test Formulations of carbidopa-levodopa 50-200 mg capsules with that of the marketed Reference Product, SINEMET® CR 50-200 mg tablets when administered under fasting conditions.
IPX066-B07-02: To compare the bioavailability of two test formulations of 25-100 mg carbidopa-levodopa (CD-LD) tablets and one test formulation of 50-200 mg CD-LD tablet with that of 50-200 mg SINEMET® CR tablet in healthy adult subjects administered under fasting conditions.
IPX066-B07-03: To compare the bioavailability of four test formulations of 25-100 mg carbidopa-levodopa (CD-LD) capsules (2 capsules per dose) with that of 50-200 mg SINEMET® CR tablet in healthy adult subjects administered under fasting conditions.
IPX066-B08-01: To compare the bioavailability of one test formulation of 37.5-150 mg carbidopa-levodopa (CD-LD) capsule (2 capsules per dosing) and three test formulations of 25-100 mg carbidopa-levodopa (CD-LD) capsule (2 capsules per dosing) with that of 50-200 mg Sinemet® CR in healthy adult subjects administered under fasting conditions.
IPX066-B08-03: To compare the bioavailability of 2 x 37.5-150 mg, 3 x 30-120 mg, and two 2 x 45-180 mg test formulations of Carbidopa-Levodopa (CD-LD) capsules with that of 50-200 mg SINEMET® CR tablet in healthy adult subjects administered under fasting conditions.
IPX066-B08-08: To assess the effect of high fat meal on the PK of IPX066 • To assess the PK of IPX066 after sprinkling of the capsule contents on applesauce

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	2	2	
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:				
Patients-				
single dose:	X	-	-	
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:				
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 1:	X	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	X	1	1	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -	X	2	2	Comparative bioavailability studies IPX06-B09-01, IPX06-B08-10, IPX06-B08-04 Pilot Studies IPX06-B05-07, IPX06-B06-02, IPX06-B07-02, IPX06-B07-03, IPX06-B08-01, IPX06-B08-03, IPX06-B08-08
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	1) Bridging study for the products manufactured at different sites IPX066-B10-01
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	-	-	-	
(IVIVC):				
In vivo alcohol dose dumping	X	1	1	Study IPX066-B09-04

BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	-	-	
Total Number of Studies		11	11	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		
QBR questions (key issues to be considered)	How does PK of IPX066 compare with approved formulations of Sinemet® and Stalevo® (reference)? Is final commercial product manufactured at two different sites bioequivalent? Does the application support dosing frequency of (b) (4) dosing interval, for all stages of the disease?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Electronic data sets available
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	

14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CC: NDA 203312 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Ta-Chen Wu, Angela Men, Ramana Uppoor, Mehul Mehta)

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

/s/

JAGAN MOHAN R PAREPALLY
11/19/2012

LI ZHANG
11/19/2012

VENKATESH A BHATTARAM
11/19/2012

TA-CHEN WU
11/19/2012

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 203-312	**Reviewer:** Sandra Suarez Sharp, PhD	
Division:	DNP		
Applicant:	Impax Laboratories	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	----------	**Biopharmaceutics Supervisory Lead (acting)**: Richard Lostritto, Ph.D.	
Generic Name:	Carbidopa+Levodopa fixed dose combination (FDC) extended release (ER) capsules	**Date Assigned:**	Feb 10, 2012
Indication	Treatment of [redacted] (b) (4) Parkinson's disease	**Date of Review:**	Aug 16, 2012
Formulation/ Strength	Capsule;23.75/95mg, 36.25/145mg, 48.75/195mg, and 61.25/245 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	Primary Review due in DARRTS
Dec 21, 2011 (original submission) March 30, 2012 (Response to 74-day letter) Jul 24, 2012 (response to IR letter) Aug 10, 2012 (response to communication request) Aug 24, 2012 (updated sheet of specifications)	Feb 10, 2012	Aug 27, 2012

Type of Submission:	Original 505 (b)(2) Application
Type of Consult:	Dissolution method and specifications/IVIVC/in vitro alcohol dose-dumping

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Impax Laboratories seeks approval to market IPX066 (Carbidopa-Levodopa Extended Release Capsules), a fixed combination product of carbidopa-levodopa (CD-LD) for the treatment of patients with idiopathic Parkinson's disease [redacted] (b) (4) IPX066 will be available in four dosage strengths in a 1:4 ratio of CD:LD: 23.75/95 mg, 36.25/145 mg, 48.75/195 mg, and 61.25/245 mg.

IPX066 capsules consist of [redacted] (b) (4) components [redacted] (b) (4) The [redacted] (b) (4) active components of the IPX066 formulation exhibit a combination of immediate release, [redacted] (b) (4) and extended release (ER) [redacted] (b) (4) .

This NDA for IPX066 relies, in part, on previous findings of the safety and efficacy of CD-LD in

the treatment of the motor symptoms of PD as described in the product labels of currently marketed CD-LD products. Sinemet (CD-LD), Sinemet CR (CD-LD sustained release), Stalevo (CD-LD-entacapone), and Lodosyn (CD) are used to supplement the Biopharmaceutics and clinical pharmacology studies with IPX066.

The development program supporting this submission consisted of several pivotal Clinical Pharmacology and Biopharmaceutics studies and three efficacy/safety trials. All the PK studies are being reviewed by OCP. In addition, a (b) (4) in vitro-in vivo correlation (IVIVC) was developed using in vitro and in vivo data from specific studies conducted as part of the Biopharmaceutics program.

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method and acceptance criteria, the in vitro alcohol-dose dumping study, and the IVIVC model. Note that the approval of the lower strengths is based on the results of a PK dose-proportionally study being reviewed by OCP.

1. Dissolution Method and Acceptance Criteria

a. Drug Product (Capsule)

The following dissolution method and acceptance criteria for all the strengths of IPX066 have been agreed upon with the Applicant (refer to submission dated Aug 24, 2012).

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
1 (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 for240 min.	900 mL for all Strengths 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) 180 min: (b) (4) % 360 min: ≥ (b) (4) %

The proposed dissolution method is deemed acceptable. The discriminating power of the method was demonstrated based on its ability to discern for aberrant batches. The recommended dissolution acceptance criteria for LD and CD were based on the performance of pivotal clinical and stability batches. The acceptance criteria for TA is based on the results of a PK study which evaluated the BA/BE of formulations with a wide range of release rates and on the in vitro performance of batches tested in phase 3 pivotal trials.

b. Dissolution Acceptance criteria for the individual components

The evaluation of the individual component used the same dissolution method as listed in the table below. The dissolution acceptance criteria for components (b) (4) have been agreed upon with the Applicant (refer to submission dated Jul 24, 2012). Note that the acceptance criteria for the individual components are not part of the drug product specifications, but they are in process specifications.

2) Assessment of the In Vitro Alcohol Dose-Dumping

Although alcohol concentrations above 25% v/v had a concentration-dependent effect on increasing the in vitro dissolution, these effects were not observed in vivo (refer to in vivo alcohol-interaction study being reviewed by OCP). Therefore, from the overall in vivo perspective, the product does not have the potential for dumping its content in the presence of alcohol.

3) Evaluation of the Acceptability of the IVIVC Model

A (b) (4) IVIVC model was developed to predict the LD and CD plasma levels from data for six lots of IPX066 formulations. These lots were manufactured with the same release rates as demonstrated by in vitro release tests using the QC dissolution method proposed for IPX066. The (b) (4) IVIVC was developed as a (b) (4) stage approach. (b) (4) . The model was found not acceptable, despite it meeting the 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). On a teleconference with the Applicant dated Aug 7, 2012, this Reviewer discussed the IVIVC model deficiencies and gave several recommendations in terms of study design and model development.

RECOMMENDATION:

The ONDQA-Biopharmaceutics team has reviewed NDA 203-312 and its amendments submitted on Dec 19, 2011, Dec 21, 2011, March 30, 2012, Jul 24, 2012, Aug 10, 2012 and Aug 24, 2012.

The following dissolution method and dissolution acceptance criteria have bee agreed upon with the Applicant 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):

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) %

From the Biopharmaceutics perspective 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 is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: R Lostritto;

BIOPHARMACEUTICS ASSESSMENT

SUBMISSION

In this application Impax Laboratories is seeking approval to market IPX066 (Carbidopa-Levodopa Extended Release Capsules), a fixed combination product of carbidopa-levodopa (CD-LD) for the treatment of (b) (4) Parkinson's disease (b) (4). IPX066 will be available in four dosage strengths in a 1:4 ratio of CD:LD: 23.75/95 mg, 36.25/145 mg, 48.75/195 mg, and 61.25/245 mg.

This NDA for IPX066 relies, in part, on previous findings of the safety and efficacy of CD-LD in the treatment of the motor symptoms of PD as described in the product labels of currently marketed CD-LD products. Sinemet (CD-LD), Sinemet CR (CD-LD sustained release), Stalevo (CD-LD-entacapone), and Lodosyn (CD) are used to supplement the biopharmaceutics and clinical pharmacology studies with IPX066.

The development program supporting this submission consisted of several pivotal Clinical Pharmacology and Biopharmaceutic studies (such as relative BA study to Sinemet and Stalevo, dose proportionality, food effect, in vivo alcohol dose-dumping, a PK study comparing the BA of the drug product in USA vs. Taiwan) and three efficacy/safety trials. All the PK studies are being reviewed by OCP. In addition, a (b) (4) (b) (4) in vitro-in vivo correlation (IVIVC) was developed using in vitro and in vivo data from specific studies conducted as part of the biopharmaceutics program.

The Biopharmaceutics review is focused on the evaluation and acceptability of the; 1) dissolution method and acceptance criteria, 2) the in vitro alcohol-dose dumping study, and 3) the proposed IVIVC model.

Drug Substance

Levodopa

Levodopa, an aromatic amino acid, is slightly soluble in water, freely soluble in 3N HCl, and insoluble in alcohol. Levodopa has an acceptable solubility profile throughout the gastrointestinal tract (> 3 mg/mL). The Applicant reports that, based on published literature, Levodopa is considered a BCS Class I compound based on its high solubility and high permeability of the highest strength. Levodopa absorption is limited to the upper gastrointestinal tract and mediated by active transport. Orally administered LD is almost completely absorbed, with less than 2% of the drug appearing in the feces. However, only about 30% to 50% of the dose reaches the systemic circulation as LD when not administered with CD. The bioavailability of LD is increased 2 to 3 times in the presence of decarboxylase inhibitors such as carbidopa and benserazide.

Carbidopa

Carbidopa is an inhibitor of aromatic amino acid decarboxylation that is slightly soluble in water and in methanol, freely soluble in 3N HCl, very slightly soluble in ethanol, and practically insoluble in acetone, ether and chloroform. The Applicant reports that based on published literature, Carbidopa is considered a BCS Class 3/1 compound. Approximately 40%-70% of an oral dose of CD is absorbed in humans. Carbidopa is

absorbed more slowly than LD, with Tmax occurring ~2 hours after oral dosing of Sinemet.

Drug Product

Table 1 summarizes the composition of the final capsule formulations.

Table 1. Qualitative and Quantitative Composition of IPX066 Capsule Final Formulation

Ingredients	Composition (w/w%)	23.7-95 mg (mg/capsule)	36.25-145 mg (mg/capsule)	48.7-195 mg (mg/capsule)	61.25-245 mg (mg/capsule)
Carbidopa	(b) (4)				(b) (4)
Levodopa		95.00	145.00	195.00	245.00
(b) (4) tartaric Acid					(b) (4)
Microcrystalline Cellulose					
Mannitol					
Ethylcellulose					
Hypromellose, (b) (4)					
Sodium Starch Glycolate					
Sodium Lauryl Sulfate					
Povidone					
Talc					
Methacrylic acid copolymer, (b) (4)					
Triethyl Citrate					
Croscarmellose Sodium					
Magnesium Stearate					
(b) (4)	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA
Total	**100.00**	**261.79**	**399.59**	**537.38**	**675.18**
Hard Gelatin Capsules	NA	Standard Blue (b) (4) Body with Light blue (b) (4) Cap, Size	Green (b) (4) Body with Light Green (b) (4) Cap,	Yellow (b) (4) Body with Yellow (b) (4) Cap, Size	White (b) (4) Body with White (b) (4) Cap, Size

IPX066 capsules consist of (b) (4) components (b) (4)

active components of the IPX066 formulation exhibit a combination of immediate release (LD, CD) and (b) (4) extended release for LD and CD as follows:

(b) (4)

The IPX066 formulation components and their in-vitro dissolution characteristics are summarized in Table 2.

Table 2. In-vitro Dissolution Characteristics of IPX066 Formulation Components

IPX066 Formulation Component	Component Content		In-vitro Dissolution Characteristics		
	CD and LD	TA	Acid Phase Dissolution Medium (Simulated Gastric Fluid)	Buffer Phase Dissolution Medium (pH 7)	Duration of Release
(b) (4)					
(b) (4)					

The drug product is manufactured by filling Components (b) (4) into capsules. The formulation is shown in Table 3.

Table 3. Quantitative Composition of Capsule

Ingredient	%w/w	Function
(b) (4)		
Hard Gelatin Capsule Shells	N/A	Capsule
Total - Capsule	**100.00**	

The manufacturing process was scaled up to (b) (4) kg in Taiwan for the commercial manufacture. (b) (4) These process studies were conducted at the Taiwan facility to establish the commercial process. Note that a BE study was conducted to bridge between the current (US site) and the new site (Taiwan). This study was evaluated by OCP.

DISSOLUTION METHOD

Dissolution testing is performed at release and on stability. The dissolution method being proposed for all the strengths and all components of IPX066 is summarized below:

USP Apparatus/RPM	Medium	Volume
App 1 (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 Strengths except 500 mL for the Lower strength

Dissolution Method Development

Evaluation of Dissolution Media

(b) (4) the Applicant chose a two-phase procedure described in the USP for (b) (4)-release dosage forms, where testing is performed in an acidic media followed by a buffered media. To simulate the *in-vivo* absorption of the drugs, simulated gastric fluid without enzyme was selected for the first (b) (4) of the dissolution. After that, a buffer at pH 7.0 was used to simulate the intestinal environment.

According to the Applicant, the enteric coating on both of the (b) (4)-release components is a (b) (4) of the (b) (4) NF, where dissolution begins at pH 6

and pH 7, respectively. Because of this pH dependency, a buffered media at pH 7 was used to assure full dissolution of the coating during dissolution testing instead of the simulated intestinal fluid (SIF), pH 6.8, which could retard the coating dissolution and thereby slow drug dissolution and possibly induce higher test-based variability as shown in Figure 1.

The solubility of CD and LD at various pH values is summarized in the Table 4 below. The media provide sink conditions for both drugs at their highest concentrations in the media. The buffer capacity of the pH 7 medium after dissolution was verified by confirming that the pH of the medium after the test remained in the range of 6.95 – 7.05.

Table 4. Solubility of CD and LD at pH 1 ad 7

Parameter	CD	LD
Highest strength (mg)	(b) (4)	
Solubility (mg/mL) pH 1		
Solubility (mg/mL) pH 7		
Maximum concentration[1] (mg/mL), pH 1		
Maximum concentration[2] (mg/mL), pH 7		

[1] Calculated as (b) (4) % of the total capsule dosage strength assuming only immediate release portion of the formulation.
[2] Calculated as (b) (4) % of the total capsule dosage strength assuming only (b) (4) -extended release portion of the formulation.

Medium Volume

According to the Applicant, a 900 mL vessel volume was used for all the strengths except for the smallest strength capsule, 23.75/95 mg of CD and LD for which 500 mL was

used to increase the concentration of analytes and thereby improve method quantitation and accuracy.

Dissolution Apparatus and Agitation

According to the Applicant, the basket was selected (b) (4)

The Applicant stated that a rotation speed of 75 rpm was initially chosen as being within a typical basket range and that this speed has proven to be reliable and able to function as part of the overall discriminatory power of the method.

Data Supporting the Discriminating Ability of the Selected Dissolution Method

The discriminating ability of the method was demonstrated by the result of a component weight variation study that supported (b) (4) process development and component (b) (4) control specification development. In the study, the composition of the capsule contents was varied by changing the individual component fill weights. Figure 2 shows the dissolution profiles obtained from the component weight DOE studies.

Figure 2. Component Weight Fill DOE Overall Dissolution Profiles

Another study evaluated the effect of coated particle size from component (b) (4) on dissolution profile. Figure 3 shows that the method is able to discern coated particles with different particle sizes.

Figure 3. Component (b) (4) Dissolution by Particle Size.

(b) (4)

Figure 4 shows that the changes in (b) (4) container would not meet the (b) (4) min specification limits at the (b) (4) week time point, while the (b) (4) container samples would remain within the limits but a time-trend is readily detectable.

Figure 4. Degradation in (b) (4); Accelerated Stability.

Reviewer's Conclusions/Dissolution Method

The proposed dissolution method is acceptable. A comparative in vitro dissolution study was performed, demonstrating that IPX066 capsules manufactured in Hayward, CA had a similar in vitro dissolution and demonstrated in vivo BE to IPX066 capsules manufactured in Jhunan, Taiwan. However, the method may be over-discriminating for

(b) (4) *as shown by the results on the in vitro alcohol-dose dumping finding (refer to section below on alcohol-dose dumping).*

ACCEPTANCE CRITERIA

This section describes the dissolution acceptance criteria communications that took place with the Applicant during the review cycle and the agreements reached for the following items:

- The dissolution acceptance criteria for the active ingredients (LD, CD) as part of the product specification (IPX066)
- The dissolution acceptance criteria for LD, CD and TA as part of the capsule's individual components (Components (b) (4))
- The dissolution acceptance criteria for the functional ingredient (TA) as part of the product specification (IPX066)

Applicant's Originally Proposed Dissolution Acceptance Criteria for IPX066 (Product Specification)

(b) (4)

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(b) (4)

Final Dissolution Acceptance Criteria for IPX066 (Product Specification) (Active Ingredients Only)

On a submission dated July 24, 2012, the Applicant responded to the IR letter comments with the following proposal for the active ingredients dissolution acceptance criteria:

Table 7. Proposed Adjustments to LD and CD Dissolution Acceptance Criteria

Dissolution Time Point	LD % Dissolved		CD % Dissolved	
	FDA Recommendation	Impax Proposed	FDA Recommendation	Impax Proposed
30 min	(b) (4)			
120 min				
180 min				
360 min				

As noted in Table 7, the range for the 30 minute specification limits was adjusted which according to the Applicant, will provide a more accurate match to the data.

Reviewer's Comments

The revised dissolution acceptance criteria at 30 min for LD and CD (Capsule formulation) are acceptable. All batches under stability testing (long Term Storage (25°C/60% RH) meet the agreed upon acceptance criteria summarized in Table 7 (refer to Figure 12, report 1.11.4 submitted on Jul 24, 2012).

Dissolution Acceptance Criteria for the Individual Components (b) (4) of IPX066

As recommended in the IR letter, The Applicant revised the acceptance criteria for the individual components as shown in Table 8. *The revised specifications are acceptable.*

Table 8. IPX066 Component Dissolution Specification Limits

Component	Dissolution Method (Medium)	Dissolution Time Point (min)	Acceptance Criteria					
			Mean % CD Dissolved		Mean % LD Dissolved		Mean % TA Dissolved	
			Submitted in NDA	Revised	Submitted in NDA	Revised	Submitted in NDA	Revised
(b) (4)								

Dissolution Acceptance Criteria for TA

This section describes the dissolution acceptance criteria for TA as part of the product specification and as an individual component (component (b) (4)).

The evaluation of the TA's dissolution as part of the product specification (capsule) and as an individual component (component (b) (4)) utilizes the (b) (4) dissolution method as described above for LD and CD. In submission dated Jul 24, 2012 the Applicant agreed to implement dissolution testing for TA as recommended in the IR letter. Data provided in the June 24, 2012, submission included the dissolution method report for TA and data demonstrating that the method is also discriminating for manufacturing changes affecting the release of TA(refer to Figure 3 and Table 3 in report (b) (4) of submission dated Jun 24, 2012).

TA's dissolution profile (Figure 8) was developed to be (b) (4) to the LD Component (b) (4) profile (minimal acid release and controlled release in buffer). Therefore, the Applicant proposes to use the (b) (4) sampling time points as implemented for LD and CD dissolution, because all three analytes are quantified in same analytical run.

Figure 8. Overall Tartaric Acid Dissolution Profile – Individual Capsule Data at Lot Release for Pivotal Clinical Lots and Primary Stability Lots

Table 9 summarizes the Applicant's proposed dissolution acceptance criteria for TA as part of product specifications and individual component (Component (b) (4)).

Table 9. TA Dissolution Specification Limits as Product and Individual Component

Component	Dissolution Method (Medium)	Dissolution Time Point (min)	Mean % TA Dissolved Acceptance Criteria	
			Submitted in NDA	Revised
(b) (4)	T066DS (SGF for (b) (4)	120		(b) (4)
		180		
		360		

Reviewer's Comments

It was noted that a wider than (b) (4) variation in the acceptance criterion at (b) (4) min is being proposed for TA (Table 9). Therefore, in a teleconference dated Aug 7, 2012, the Applicant was requested to justify this proposed range given the following observations raised by the reviewer:

1. *The Agency acknowledges the studies conducted to evaluate the effect of different amounts of TA in the formulation on the BA of levodopa. However, these studies were conducted using (b) (4) TA formulations which varied not only the (b) (4), but also the (b) (4) (Figure 3, Table 22 Module 3.2.P.2.2, same as Figure 9 and Table 10 below). In addition, these studies (b) (4) evaluate the interaction between these two variables. Therefore, the results of BA studies*

IPX066-B08-03 in terms of no effect of TA release in the range proposed (e.g. (b) (4) % at (b) (4) min) on the BA of levodopa was questionable.

Figure 9. In-vitro Dissolution Profiles of IPX066 Componen (b) (4) Prototype Formulations.

Table 10. Test Formulations of IPX066 Prototype Capsules in Single Dose Relative BA Studies IPX066-B08-03

Test Formulation	Batch	CD:LD (mg:mg)	TA (mg)	TA:LD mg Ratio
IPX066-C0011	PB02608-30	(b) (4)		(b) (4)
IPX066-C0012	PB02708-30			
IPX066-C0013	PB02408-30			

2. *The reviewer added that to support their proposal for wider specifications than those allowed by the guidance, dissolution profiles of the products (not components, as shown in Figure 8) listed in table 8 would be needed. The Applicant mentioned that the data, although available, was not submitted as part of the NDA, but that would be submitted by Aug 10, 2012 for the Agency's review.*

On an Email communication dated Aug 10, 2012, the Applicant submitted data supporting their proposed dissolution acceptance criteria range for (b) (4) min. This information relies on data from three sources as follows:

1. Dissolution profile comparisons (Figure 10) from drug product (capsule) batches (Table 10 above) tested in BA Study IPX066-B08-03.
    a. Data from this in vitro studies showed that the batches tested in this BA study have mean dissolution profiles ranging from (b) (4)% to about (b) (4)% (Table 11), indicating that all batches between these ranges will be BE. However, these data alone does not support the proposed range of (b) (4)% to (b) (4)%.

2. Data from BE Study IPX066-B10-01 comparing the Hayward site vs. the Taiwan site.

a. These data indicated that a batch with a lower bound release of (b)(4)% (Table 11) was (b) (4) a formulation with a much faster release. Thus, these findings allows for the setting of a (b) (4) specification (e.g. lower bound of (b)(4)%). However, these data alone does not support the proposed range of (b)(4)% to (b)(4)%.

3. Data for batches tested in Phase 3 pivotal trials.
   a. Batches tested in clinical trials had release rates ranging from (b)(4)% to (b)(4)% (Table 11).

Figure 10. TA Dissolution Profiles (Shown as %TA Mean and Individual Range) of IPX066 Test Formulations of BA Study IPX066-B08-03.

Table 11. TA Dissolution Profiles of IPX066 Capsules

Time (min)	TA Dissolution (%)						
	IPX066-B08-03 BA Study Lots (Development Report (b) (4)			Site BE Study Lots		Pivotal Clinical and Primary Stability Lots[1]	Proposed Specification Limits
	Test formulation (b) (4)	Test formulation (b) (4)	Test formulation (b) (4)	Hayward 245 mg (Lot Naïve)	Taiwan 245 mg (Lot SQ1)		
120	(b) (4)						
180							
360							

Reviewer's conclusion-Dissolution acceptance criteria for TA

Data provided by the Applicant on Aug 10, 2012, (e.g. dissolution profiles for batches tested in pivotal phase 3 clinical trials) support the proposed acceptance criteria of (b) (4) % at t= (b) (4) min for TA as an individual component (Componen (b) (4) and as part of product specification (capsule).

It should be noted that the updated information send on Jul 24, 2012 with reference to the fill weight limits for (b) (4) and PARs for all relevant process parameters is being qualified by the CMC reviewer.

IVIVC DEVELOPMENT

A (b) (4) IVIVC was developed to predict the LD and CD plasma levels from data for six lots of IPX066 formulations. These lots were manufactured with the (b) (4) release rates as demonstrated by in vitro release tests using the QC dissolution method proposed for IPX066. The (b) (4) IVIVC was developed as a two stage approach using the WinNonlin Software version 5.2.1 with IVIVC Toolkit from (b) (4). The first stage consisted of (b) (4)n. Data from the immediate-release Sinemet® 25-100 mg CD-LD treatment from Study IPX066-B08-10 were used to define/estimate the (b) (4) (b) (4) .

(b) (4)

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On submission dated Jul 24, 2012 the Applicant acknowledged the model deficiencies, and withdrew the model from the NDA submission.

IN VITRO EVALUATION OF THE POTENTIAL FOR ALCOHOL DOSE-DUMPING

The dissolution profiles of IPX066 were evaluated using dissolution apparatus 1 (USP) using a rotation speed of 75 rpm in SGF for 2 hrs then pH 7.0 phosphate buffer/37°C, containing 0%, 20%, 25%, 30%, 35%, and 40% alcohol. The dissolution profiles of IPX066 in the presence of several concentration of alcohol using the acid media are shown in Figure 16. Alcohol concentrations up to 25% v/v had a negligible effect of the *in vitro* release of LD. Although alcohol concentrations above 25% v/v had a concentration-dependent effect on increasing the in vitro dissolution, these effects were not observed in vivo.

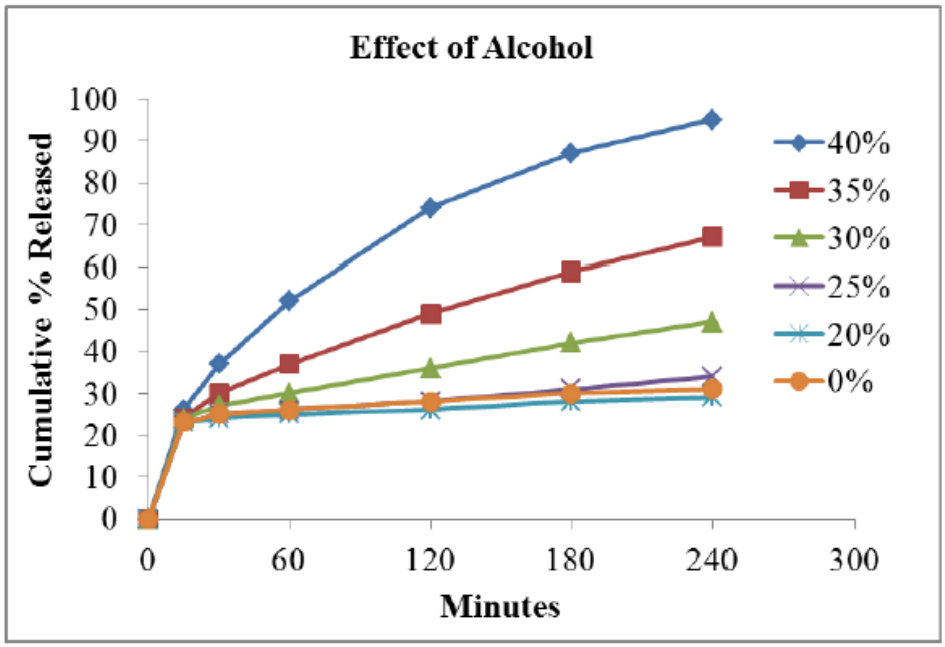

Figure 16. Dissolution Profiles of IPX-066 using a rotation speed of 75 rpm in SGF for 2 hrs then pH 7.0 phosphate buffer/37°C, containing 0%, 20%, 25%, 30%, 35%, and 40% alcohol

Reviewer's Conclusion/ In Vitro Alcohol Dose-Dumping

Alcohol concentrations above 25% v/v had a concentration-dependent effect on increasing the in vitro dissolution; however, these effects were not observed (b) (4) (refer to (b) (4) alcohol-interaction study being reviewed by OCP).

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

/s/

SANDRA SUAREZ
08/26/2012

ANGELICA DORANTES
08/26/2012

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**203312**	**Brand Name**	**IPX066**
OCPB Division (I, II, III)	**DCP-1**	**Generic Name**	**Levodopa-Carbidopa**
Medical Division	**HFD-120**	**Drug Class**	**Dopamine**
OCPB Reviewer	**Jagan Mohan Parepally**	**Indication(s)**	**Treatment of Parkinson'sdisease**
OCPB Team Leader	**Angela Men**	**Dosage Form**	**Extended Release Capsule**
Date of Submission	**12/21/2011**	**Dosing Regimen**	(b) (4)
Estimated Due Date of OCP Review	**8/21/2012**	**Route of Administration**	**Oral**
Division Due Date	**8/29/2012**	**Sponsor**	**Impax Labs Inc.**
PDUFA Due Date	**10/21/2012**	**Priority Classification**	**S**

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of IPX066. IPX066 is an extended-release (ER) capsule formulation of CD (carbidopa) and LD (levodopa) in 1:4 ratio intended for treatment of (b) (4) Parkinson's disease, post-encephalitic parkinsonism, and (b) (4) parkinsonism which may follow injury to the nervous system by carbon monoxide (b) (4) or manganese intoxication. IPX066 will be available in 4 dosage strengths: 23.75–95 mg, 36.25–145 mg, 48.75–195 mg, and 61.25–245 mg CD-LD. The proposed ER oral capsule can be swallowed whole or opened and sprinkled on apple sauce.

According to the sponsor, the rationale for development of IPX066 is to

- Provide reliable and faster initial absorption of LD compared to Sinemet CR to assure an early "on" state that is comparable to IR CD-LD
- Provide stable LD concentrations with reduced maximum observed plasma concentration/minimum observed plasma concentration (Cmax/Cmin) excursions in order to reduce motor fluctuations associated with pulsatile stimulation of dopamine receptors and to minimize end-of-dose dyskinesia
- Reduce the dosing frequency, targeting a (b) (4), for all stages of the disease

The clinical pharmacology evaluation included the following:

- Dose proportionality of IPX066 over an LD dose range of 95 to 245 mg (IPX066-B08-09)
- Pharmacokinetics and pharmacodynamics of IPX066 in patients with advanced PD compared to immediate-release CD-LD (IPX066-B08-11) and to CD-LD-entacapone (Stalevo®) (IPX066-B09-06)
- Single and multiple dose pharmacokinetics in subjects with PD (IPX066-B08-11)
- Effect of food on IPX066 pharmacokinetics (IPX066-B09-01)
- Comparison of IPX066 pharmacokinetics to the marketed CD-LD products (IPX066-B08-10)

Intrinsic and Extrinsic Factors

The effect of demographic factors (age, weight, body mass index [BMI], race, gender, and estimated creatinine clearance [CrCL]) on the pharmacokinetics of LD and CD was assessed using pooled data from the Phase 1 studies and, separately, data from subjects with PD. Since CD-LD products have been available since 1975, results from the published literature and the package inserts for reference listed drugs are provided as appropriate.

Bioanalytical

The quantitation of CD and LD in human plasma was accomplished using a liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. The method was validated for CD over a linear concentration range of 2.00 to 400 ng/mL and for LD over a linear concentration range of 10.0 to 2000 ng/mL. The limits of quantitation (LOQs) were 2.00 ng/mL and 10.0 ng/mL for CD and LD, respectively.

Population PK Analysis

Levodopa plasma concentration-time data following IPX066 and IR CD-LD were modeled using a population approach. 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) were used.

Title: Population pharmacokinetics of IPX066 in healthy volunteers and patients with Parkinson's Disease.

List of Clinical Studies

IPX066-B08-04: To compare the bioavailability of one 2 x 47.5-190 test formulation of carbidopa-levodopa capsules with that of one 50-200 mg SINEMET® CR tablet and that of one 25-100 mg SINEMET® tablet in healthy adult subjects administered under fasting conditions.

IPX066-B08-09: To assess the dose proportionality of four strengths of IPX066 under fasted conditions in healthy subjects.

IPX066-B08-11: • To compare the single- and multiple-dose pharmacokinetics (PK) of IPX066 capsule formulation with IR CD-LD tablet formulation. • To assess the accumulation of IPX066 at steady state when dosed approximately Q6H. • To examine the efficacy and pharmacodynamics.

IPX066-B08-10: To assess the bioavailability (BA) of two capsules of IPX066 49.75-195 mg (total dose 97.5-390 mg) CD-LD relative to Sinemet 25-100 mg CD-LD, Sinemet CR 25-100 mg CD-LD, and Stalevo 25-100-200 mg CD-LD-entacapone (CLE) under fasting conditions.

IPX066-B09-01: To assess the effect of a high-fat, high-calorie meal on the PK of IPX066 and to assess the effect of sprinkling the IPX066 capsule contents on applesauce on the PK of IPX066.

IPX066-B09-04: To investigate the effect of 240 mL of 0%, 5%, 20%, and 40% v/v alcohol on the IPX066 capsule formulation in healthy volunteers.

IPX066-B10-01: • To assess the bioequivalence of IPX066 manufactured in Hayward, CA, USA and in Jhunan, Taiwan. • To assess the dose proportionality between one and two capsules of IPX066.

61.25-245 mg CD-LD formulation manufactured in Hayward, CA, USA.

Efficacy and Safety Studies

IPX066-B09-06 (ASCEND-PD): Part 1: • 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. Part 2: • 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.

IPX066-B08-05 (APEX-PD): • 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.

IPX066-B09-02 (ADVANCE-PD): To evaluate the safety and efficacy of IPX066 in the treatment of advanced PD subjects in comparison to IR CD LD.

IPX066-B09-03: To evaluate the long-term safety and clinical utility of IPX066 in subjects with Parkinson's disease (PD).

Pilot Studies

IPX066-B05-07: To compare the bioavailability of three test formulations of carbidopa-levodopa 50-200 mg with that of the marketed Reference Product, SINEMET® CR 50-200 mg tablets when administered under fasting conditions.

IPX066-B06-02: To compare the rate and extent of absorption of two Test Formulations of carbidopa-levodopa 50-200 mg tablets and two Test Formulations of carbidopa-levodopa 50-200 mg capsules with that of the marketed Reference Product, SINEMET® CR 50-200 mg tablets when administered under fasting conditions.

IPX066-B07-02: To compare the bioavailability of two test formulations of 25-100 mg carbidopa-levodopa (CD-LD) tablets and one test formulation of 50-200 mg CD-LD tablet with that of 50-200 mg SINEMET® CR tablet in healthy adult subjects administered under fasting conditions.

IPX066-B07-03: To compare the bioavailability of four test formulations of 25-100 mg carbidopa-levodopa (CD-LD) capsules (2 capsules per dose) with that of 50-200 mg SINEMET® CR tablet in healthy adult subjects administered under fasting conditions.

IPX066-B08-01: To compare the bioavailability of one test formulation of 37.5-150 mg carbidopa-levodopa (CD-LD) capsule (2 capsules per dosing) and three test formulations of 25-100 mg carbidopa-levodopa (CD-LD) capsule (2 capsules per dosing) with that of 50-200 mg Sinemet® CR in healthy adult subjects administered under fasting conditions.

IPX066-B08-03: To compare the bioavailability of 2 x 37.5-150 mg, 3 x 30-120 mg, and two 2 x 45-180 mg test formulations of Carbidopa-Levodopa (CD-LD) capsules with that of 50-200 mg SINEMET® CR tablet in healthy adult subjects administered under fasting conditions.

IPX066-B08-08: To assess the effect of high fat meal on the PK of IPX066 • To assess the PK of IPX066 after sprinkling of the capsule contents on applesauce

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**		
I. Clinical Pharmacology				
Mass balance:	**-**	**-**	**-**	
Isozyme characterization:				
Blood/plasma ratio:	**-**	**-**	**-**	
Plasma protein binding:	**-**	**-**	**-**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**-**	
multiple dose:				
Patients-				
single dose:	**X**	**1**	**-**	
multiple dose:	**X**	**2**	**-**	
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**-**	
fasting / non-fasting multiple dose:	**-**	**-**	**-**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**-**	**-**	**-**	
In-vivo effects of primary drug:	**-**	**-**	**-**	
In-vitro:				
Subpopulation studies -				
ethnicity:	**-**	**-**	**-**	
gender:	**-**	**-**	**-**	
pediatrics:	**-**	**-**	**-**	
geriatrics:				
renal impairment:	**-**	**-**	**-**	
hepatic impairment:	**-**	**-**	**-**	
PD:				
Phase 1:	**X**	**-**	**-**	
Phase 3:	**-**	**-**	**-**	
PK/PD:				
Phase 1 and/or 2, proof of concept:	**-**	**-**	**-**	
Phase 3 clinical trial:	**-**	**-**	**-**	
Population Analyses -				
Data rich:	**X**	**1**	**-**	
Data sparse:	**-**	**-**	**-**	
II. Biopharmaceutics				
Absolute bioavailability:	**-**	**-**	**-**	
Relative bioavailability -	**X**	**3**		Comparative BA studies IPX06-B09-01, IPX06-B08-10, IPX06-B08-04 Pilot Studies IPX06-B05-07, IPX06-B06-02, IPX06-B07-02, IPX06-B07-03, IPX06-B08-01, IPX06-B08-03, IPX06-B08-08
solution as reference:				
alternate formulation as reference:				

Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		1) Bridging study for the products manufactured at different sites IPX066-B10-01
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		
Dissolution:	**-**	**-**	**-**	
(IVIVC):				
In vivo alcohol dose dumping	**X**	**1**	**-**	Study IPX066-B09-04
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	**-**	**-**	**-**	
Chronopharmacokinetics	**-**	**-**	**-**	
Pediatric development plan	**-**	**-**	**-**	
Literature References	**X**	**-**	**-**	
Total Number of Studies		**12**		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		
QBR questions (key issues to be considered)	How does PK of IPX066 compare with approved formulations of Sinemet® and Stalevo® (reference)? Is final commercial product manufactured at two different sites bioequivalent? Does the application support dosing frequency of (b) (4) r dosing interval, for all stages of the disease?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Electronic data sets available
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA	X			

	organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CC: NDA 203312 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Angela Men, Ramana Uppoor, Mehul Mehta)

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

/s/

JAGAN MOHAN R PAREPALLY
04/18/2012

YUXIN MEN
04/25/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	203-312
Product name, generic name of the active, and dosage form and strength	IPX066, Carbidopa+Levodopa fixed dose combination (FDC) extended release (ER) capsules; 23.75/95 mg, 36.25/145 mg, 48.75/195 mg, and 61.25/245 mg (4 strengths)
Submission date	Dec. 20, 2011
Applicant	Impax Labs, Inc.
Medical Division	DNP
Type of Submission	Original NDA under 505(b)(2)
Biopharmaceutics Reviewer	Tien-Mien, Chen, Ph.D. & Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Lead	Angelica Dorantes. Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		The following dissolution method is proposed for routine testing: Medium A (Acid phase): SGF (without enzyme) for 120 min then switch to Medium B (Buffer phase): Phosphate buffer pH 7.0 for 240 min Apparatus: USP 1 (basket) Speed: 75 rpm Temperature: 37°C ± 0.5°C.
2.	Is the dissolution test part of the DP specifications?	X		Carbidopa / Levodopa 0.5 hr: (b) (4) % / (b) (4) % 2 hrs: (b) (4) % / (b) (4) % 3 hrs: (b) (4) % / (b) (4) % 6 hrs: ≥ (b) (4) % / ≥ (b) (4) % The acceptability of the proposed acceptance criteria will be a review issue.
3.	Does the application contain the dissolution method development report?	X		The Applicant submitted the report ((b) (4)), however, incomplete to support the proposed method. Additional information is needed.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		The analytical method ((b) (4) ; HPLC/UV) used for analysis of samples collected during dissolution testing is included in 3.2.P.5.3.

5.	Does the application include a biowaiver request?		X	All the strengths were tested clinically and had PK data available.
6.	Does the application include an IVIVC model?	X		A report including the development and validation of a [redacted] (b) (4) IVIV C was included. The results are to be used to support [redacted] (b) (4) the dissolution acceptance criteria.
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?	X		The *in vitro* alcohol dose-dumping study did show interaction potential. Therefore, an *in vivo* alcohol interaction PK study was conducted.
8.	Is there any in *vivo* BA or BE information in the submission?	X		
B. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
9.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		➢ The NDA is filable from Biopharmaceutics Perspective ➢ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue.
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
12.	Are there any potential review issues identified?	X		The proposed in vitro in vivo correlation (IVIVC) does not meet the criteria for development stated in the IVIVC guidance for industry.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

13.	Are there any comments to be sent to the Applicant as part of the 74-Day letter? (b) (4)

{See appended electronic signature page}

Tien-Mien Chen, Ph.D. and Sandra Suarez Sharp, Ph.D. — 02/09/12
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D. — 02/09/12
Acting Biopharmaceutics Lead — Date
Office of New Drug Quality Assessment

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

/s/

TIEN MIEN CHEN
02/10/2012

SANDRA SUAREZ
02/10/2012

ANGELICA DORANTES
02/10/2012