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APPLICATION NUMBER:

217186Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Clinical Pharmacology Review

NDA Number	217186
Regulatory Pathway	505(b)(2)
Link to EDR	\\CDSESUB1\evsprod\NDA217186\0017
Submission Date(s)	02/07/2024
Submission Type	505(b)(2) (Standard Review)
Brand Name	CREXONT®
Generic Name	IPX203 (Carbidopa and Levodopa)
Formulation and Strength	Extended-Release Capsules Four strengths of carbidopa/levodopa: 35 mg/140 mg 52.5 mg/210 mg 70 mg/280 mg 87.5 mg/350 mg
Route of Administration	Oral
Proposed Indication	Treatment of: 1. Parkinson's disease 2. Post-encephalitic parkinsonism 3. Parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Applicant	Impax Laboratories, LLC
Associated IND	122793
OCP Review Team	Ramakrishna Samala, Ph.D., Yifei Zhang, Ph.D., Poonam Delvadia, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

Contents

1. Executive Summary

Impax Laboratories, Inc. submitted the original NDA 217186 via 505(b)(2) pathway on August 31, 2022, for Crexont (IPX203), the carbidopa-levodopa extended-release capsule. The Agency issued a Complete Response Letter (CRL) on 06/30/2023, with the following issues:

- An adequate scientific bridge was not established for the carbidopa pharmacokinetic (PK) exposure between IPX203 and Sinemet or Rytary at the highest proposed dosage regimen of Crexont. The exposure of carbidopa from Crexont is substantially higher than that from Sinemet or Rytary; therefore, it is not possible to rely on FDA's finding of safety for Sinemet or cross-reference Rytary for the safety of carbidopa for the approval of Crexont.
- The long-term safety database is insufficient to adequately characterize the long-term safety of Crexont.

In addition, the Agency made the following recommendation to address the issue of QT evaluation:

- Because you are unable to rely on Sinemet or cross-reference Rytary for the safety of carbidopa in Crexont, per ICH E14 section 1.3, you will also need to conduct a thorough QT study to assess potential effects of Crexont on QTc.

In this resubmission, the Applicant is seeking the approval of Crexont. The resubmission included updated long-term safety database and the following study reports for QT evaluation:

- Study IPX203-101-23: An open label, single period, non-randomized, tolerability and safety study of a single oral dose of LODOSYN® (carbidopa) tablets 25 mg when administered at a dose of 400 mg (25 mg x 16 tablets) in healthy adult, human subjects under fasting condition.
- Study IPX203-102-23: A three-way crossover thorough QT/QTc study to evaluate the electrocardiographic effects of a supratherapeutic dose of carbidopa in healthy subjects.

The clinical team reviewed the long-term safety database and determined that the maximum recommended daily dosage of Crexont is 525 mg carbidopa/2100 mg levodopa. Please refer to the clinical review by Dr. Haberfeld and Dr. Getzoff for details.

The focus of this review was to assess QTc prolongation potential of carbidopa from Crexont at high clinical exposure scenario and alcohol dose dumping potential for levodopa from Crexont. Studies IPX203-101-23 and IPX203-102-23 were reviewed by the Interdisciplinary Review Team for Cardiac Safety Studies (QT team) and determined that carbidopa did not prolong the QTcF at the highest evaluated dose of 400 mg which

provided supratherapeutic exposure. Please refer to the QT study review by Liu et al. dated 04/24/2024 for details.

Biopharmaceutics review team determined that Crexont has alcohol-induced dose dumping potential for levodopa with 40% (v/v) ethanol. Please refer to the Biopharmaceutics Review by Dr. Leo and Dr. Eradiri dated 05/01/2023 for details.

Please refer to the Clinical Pharmacology Review for the original NDA submission by Samala et al. dated 06/28/2023 regarding other clinical pharmacology aspects of IPX203.

2. Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under NDA 217186. The review team has determined that the resubmission is approvable from a clinical pharmacology perspective. No post-marketing commitment or post-marketing requirement is needed.

Labeling Recommendations

The Office of Clinical Pharmacology review team accepts the labeling concepts proposed by the Applicant and recommends the following additions into the labeling.

Section 2.4:

- Crexont should not be taken with alcohol.

Section 12.2:

- At exposures corresponding to the maximum recommended dose of carbidopa in Crexont, clinically significant QTc interval prolongation was not observed.

Section 12.3:

- In healthy adults, oral administration of Crexont after a high-fat, high-calorie meal decreased both C_{max} and AUC by approximately 64% for carbidopa compared to administration in the fasted state. The peak plasma concentrations of carbidopa were observed approximately one hour later when Crexont is taken with a high-fat high-calorie meal.
- Effect of Ethanol: Ethanol-induced dose dumping of CREXONT was observed in the presence of 40% ethanol (80 proof) solution in a dissolution study; however, dose dumping was not observed in the presence of lower ethanol concentrations. The clinical significance of this dose dumping was not fully characterized in humans.

3. Background and Regulatory History

Crexont is an extended-release combination capsule of carbidopa and levodopa in 1:4 ratio. In the original NDA submission, the Applicant conducted relative bioavailability studies of IPX203 with Sinemet (NDA 017555), Sinemet CR (NDA 019856), and Rytary (NDA 203312) as reference drugs. Sinemet is an immediate release combination tablets of carbidopa and levodopa indicated for the treatment of Parkinson's disease and syndrome. Sinemet CR (CR CD-LD) is a sustained-release combination tablets of carbidopa and levodopa in 1:4 ratio. The Applicant has previously developed Rytary which is an extended-release combination capsule of carbidopa and levodopa in 1:4 ratio.

The original NDA was submitted on August 31, 2022, and received a CRL on June 30, 2023, with the following issues and recommendations to address the issues.

Issues:

- An adequate scientific bridge was not established between Crexont and Sinemet or Rytary. The exposure of carbidopa from Crexont is substantially higher than that from Sinemet or Rytary; therefore, it is not possible to rely on FDA's finding of safety for Sinemet or cross-reference Rytary for the safety of carbidopa for the approval of Crexont.
- The long-term safety database is insufficient to adequately characterize the long-term safety of Crexont.

Recommendation to address QT issue:

- Because you are unable to rely on Sinemet or cross-reference Rytary for the safety of carbidopa in Crexont, per ICH E14 section 1.3, you will also need to conduct a thorough QT (TQT) study to assess potential effects of Crexont on QTc.

The Applicant had a Type A End of Review meeting with the Agency on October 4, 2023, and proposed to (b) (4) . The Agency did not agree with the plan because of potential safety risks associated with higher carbidopa exposure (i.e., C_{max} and AUC) compared to the reference drugs. In response, the Applicant proposed that (b) (4) . However, the Agency did not agree with this proposal for two reasons: (1) this is not an unmet medical need since several carbidopa-levodopa products have already been approved for the same indication; and (2) it is not practical (b) (4) . The Applicant acknowledged the Agency's comments and proposed to conduct a pilot study IPX203-101-23 followed by a

TQT study IPX203-102-23 with carbidopa alone, which was agreed by the Agency. Please refer to the Type A End of Review Meeting Minutes dated 11/03/2023.

The objective of Study IPX203-101-23 was to evaluate the tolerability and safety of a single oral dose of Carbidopa 400 mg. The results of this study were used to inform the selection of supratherapeutic dose in the TQT study, IPX203-102-23, which is a three-way crossover study to assess the electrocardiographic effects of a supratherapeutic dose of Carbidopa (400 mg single dose) in healthy adults under fasted condition. The study reports are included in the current NDA resubmission.

4. Summary of Clinical Pharmacology Assessment

Evaluation of QT Prolongation

The Applicant conducted studies IPX203-101-23 and IPX203-102-23 in response to the Agency's recommendations to resolve the issues listed in the CRL dated 06/30/2023. Interdisciplinary Review Team for Cardiac Safety Studies (QT team) reviewed these studies and determined that carbidopa did not prolong the QTcF at the highest evaluated dose of 400 mg. Please refer to the QT study review by Liu et al. dated 04/24//2024 for further details.

The calculated high clinical exposure scenario results in carbidopa $C_{max,ss}$ of 1236 ng/mL at 245 mg dose in fasted state which is based on (b) (4) carbidopa daily dosage divided into 3 doses (b) (4)[1] Carbidopa 400 mg dose evaluated in the TQT study, IPX203-102-23, provided 1.1-fold therapeutic exposures (observed geometric mean $C_{max,ss}$ = 1333.8 ng/mL).

The clinical team reviewed the long-term safety database and determined that the maximum recommended daily dosage of Crexont is 525 mg carbidopa/2100 mg levodopa, instead of the Applicant's proposed maximum daily dosage (b) (4) levodopa. Please refer to the clinical review by Dr. Haberfeld and Dr. Getzoff for details. The reduction in the maximum recommended daily dosage does not affect the conclusion that "At exposures corresponding to the maximum recommended dose of carbidopa in Crexont, clinically significant QTc interval prolongation was not observed".

Alcohol Dose Dumping

The Applicant conducted an *in vitro* alcohol dose dumping study in the presence of 0.1 N HCl up to 2 hours with 0%, 5%, 20%, and 40% ethanol for the lowest (CD/LD 35 mg/140 mg) and the highest (CD/LD 87.5 mg/350 mg) strengths of Crexont. This study

[1] QT Study Review by Liu et al. dates 04/24/2024. Page 5, Table 2

was reviewed by Dr. Leo and Dr. Eradiri from Biopharmaceutics and concluded that Crexont has alcohol-induced dose dumping potential for levodopa in the presence of 40% alcohol, but dose dumping was not observed in the presence of lower alcohol concentrations. Please refer to the Biopharmaceutics review dated 05/01/2023 for further details. However, clinical significance of this dose dumping is not fully characterized in humans. Therefore, the review team recommends including this information in the labeling and state that Crexont should not be taken with alcohol.

5. Summary of Bioanalytical Method Validation and Performance

Carbidopa and moxifloxacin were extracted from human plasma using a Liquid-Liquid extraction procedure and quantified using a LC-MS/MS. The procedure includes 0.1 mL of plasma spiked with internal standard (Carbidopa-d3 and Moxiflaxacind-d4). Samples were chromatographically separated on a Thermo Aquasil C18 analytical column (100 mm x 2.1 mm) and a Restek Bi-Ph analytical column (50 mm x 2.1 mm) by a gradient method using water and methanol/acetonitrile with formic acid. The API 4500 mass spectrometric instrument is operated in positive ion mode using a Turbo ion-spray source and MRM detection. The total run time for a 10 µL injection is 5.00 minutes per sample for Carbidopa and total run time for a 10 µL injection is 2.00 minutes per sample for Moxifloxacin.

Incurred sample reanalysis (ISR) for carbidopa and moxifloxacin was performed on 81 (about 10% of total samples) samples. ISR for carbidopa met overall acceptance criteria (within 20%) and there was no impact on the data. Seventy-nine samples, 97.5% of samples met ISR for moxifloxacin. The total storage time of samples from dosing dates to the last date of sample injections for any sample was not more than 25 days. A summary of the method validation for carbidopa and moxifloxacin is provided in Table 1. Based on the method validation and bioanalytical performance reports, the LC-MS/MS methods for carbidopa and moxifloxacin are considered validated adequately.

Table 1. LC-MS/MS Method Summary for Carbidopa and Moxifloxacin in Human Plasma

Validation Parameters	Carbidopa	Moxifloxacin
Standard Curve Range	15 ng/mL – 3000 ng/mL	45 ng/mL to 9000 ng/mL
Linearity (r2 Range of STD Curves)	0.9936 to 0.9995	0.9973 to 0.9998
Range of Between Run Precision (% CV)	2.3 to 5.3	1.7 to 3.8

Range of Between Run Accuracy (% Bias)	-1.6 to 2.3	-1.3 to 1.6
Selectivity	No significant baseline interference was detected at the retention times of Carbidopa or IS.	No significant baseline interference was detected at the retention times of Moxifloxacin or IS.
% Recovery of the Analyte	45.5	74.4
% Recovery of the Internal Standard	51	37.4
Freeze-Thaw Stability	Stable over 4 freeze/thaw (-70°C ± 20°C/ 5°C ± 3°C) cycles.	Stable over 4 freeze/thaw (-70°C ± 20°C/ 5°C ± 3°C) cycles.
Long-Term Stability	27 days at -70°C ± 20°C	27 days at -70°C ± 20°C

Source: Bioanalytical Method AP 096_00 Samples Analysis Report.

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/s/

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Office of Clinical Pharmacology

Clinical Pharmacology review

NDA Number	217186
Regulatory Pathway	505(b)(2)
Link to EDR	\\CDSESUB1\evsprod\NDA217186\0001
Submission Date(s)	08/31/2022
Submission Type	505(b)(2) (Standard Review)
Brand Name	CREXONT®
Generic Name	IPX203 (Carbidopa and Levodopa)
Formulation and Strength	Extended-Release Capsules Four strengths of carbidopa/levodopa: 35 mg/140 mg 52.5 mg/210 mg 70 mg/280 mg 87.5 mg/350 mg
Route of Administration	Oral
Proposed Indication	Treatment of: 1. Parkinson's disease 2. Post-encephalitic parkinsonism 3. Parkinsonism that may follow carbon monoxide intoxication or manganese intoxication
Applicant	Impax Laboratories, LLC
Associated IND	122793
Primary Reviewer	Ramakrishna Samala, Ph.D.
Secondary Reviewer	Yifei Zhang, Ph.D.
Team Leader	Bilal AbuAsal, Ph.D.
Final Signatory	Mehul Mehta, Ph.D.

Contents

1. Executive Summary

Impax Laboratories, Inc. is seeking approval for Crexont (IPX203) under 505(b)(2) pathway for the treatment of Parkinson's disease (PD), post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. IPX203 is an extended-release capsule formulation of carbidopa (CD) and levodopa (LD) in 1:4 ratio. IPX203 is designed to provide therapeutic LD plasma concentrations rapidly and maintain constant LD plasma concentrations for an extended duration with minimal peak-to trough fluctuations. The proposed dose of IPX203 is determined for each patient based on the most frequent single dose of LD in immediate-release carbidopa-levodopa product, Sinemet® (IR CD-LD), with a 100 mg unit dose of IR CD-LD converted to a 280 mg unit dose of IPX203. The proposed strengths of IPX203 (CD/LD) are 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, and 87.5 mg/350 mg.

The clinical efficacy and safety of IPX203 in patients with PD was evaluated in a randomized, double-blind, Phase 3 study IPX203-B16-02. IPX203-B16-03 is an open-label study to assess the long-term safety. The application package also included the following clinical pharmacology studies:

- Study IPX203-B16-05 evaluated the relative bioavailability of IPX203 compared with Sinemet® (IR CD-LD) and Sinemet® CR (CR CD-LD).
- Study IPX203-B16-01 assessed the PK, pharmacodynamics/efficacy, and safety of IPX203 in subjects with PD after multiple doses.
- Study IPX203-B14-02 assessed the PK, pharmacodynamics/efficacy, and safety of single dose of IPX203 in subjects with PD.
- Study IPX203-B16-04 evaluated the effect of food on the pharmacokinetics of CD and LD following IPX203 administration.
- Study IPX203-B16-06 evaluated dose proportionality of IPX203 capsules over the CD/LD dosage strength range of 35 mg/140 mg to 87.5mg/350 mg, and assessed bioequivalence between the IPX203 capsules manufactured in New York site (for the commercial product) and (b) (4) (for the Phase 3 clinical trial).

The primary focus of this review was to evaluate adequacy of the bridging and clinical pharmacology information to support the approval of IPX203. The Office of Clinical Pharmacology (OCP) review team concluded that no adequate pharmacokinetic bridging was established between IPX203 and FDA approved products (IR CD-LD, CR CD-LD or Rytary). At the maximum proposed total daily dose of IPX203, carbidopa AUC was 2-folds and 3.1-3.7-folds greater than those following the administration of the maximum recommended total daily doses of Rytary and IR CD-LD, respectively, while the AUCs of levodopa were similar and support a scientific bridge of safety information for the levodopa PK exposures. Therefore, exposure comparison with Rytary cannot support the safety of IPX203 at more than half of the proposed maximum total daily

dose, given that the CD exposure of IPX203 is dose proportional. Hence, the approvability of IPX203 at the proposed dosing regimen will depend on the evaluation of safety based on nonclinical data and clinical evidence from Phase 3 clinical studies. Please refer to clinical review by Drs. Elizabeth Haberfeld and Natalie Getzoff for additional details.

The Office of Study Integrity and Surveillance (OSIS) was consulted for analytical site inspection for study IPX203-B16-06 regarding the bioequivalence between clinical trial formulation and to-be-marketed formulation. On 02/22/2023, OSIS concluded that the data from study IPX203-B16-06 are reliable.

1.1 Recommendation

The Division of Neuropsychiatric Pharmacology has reviewed the submitted application and has found that the carbidopa exposures from the proposed product IPX203 are higher than the listed drugs, Sinemet (IR CD-LD), Sinemet CR (CD-LD sustained-release tablet) or Rytary (CD-LD extended-release capsules), resulting in inadequate scientific bridging to support the safety for IPX203. The OCP team defers to nonclinical and clinical review teams regarding the evaluation of safety of IPX203.

1.2 Post Marketing Requirement

None

2. Summary of Clinical Pharmacology assessment

2.1 The Pharmacology and Clinical pharmacokinetics

CD and LD pharmacokinetic parameters are dose proportional between 35 mg/140 mg and 87.5 mg/350 mg of IPX203. On average, 2.8 times higher dose of CD and LD are proposed to be administered as the starting dose of IPX203 relative to the most frequent IR CD-LD dose of a patient. Using IR CD-LD as the reference product, the relative bioavailabilities of carbidopa and levodopa are 103%-123% and 88%-99% for IPX203, 78% and 90% for CR CD-LD, and 53% and 78% for Rytary. However, the highest recommended daily dose for the proposed and listed drugs are different. Please refer to Section 3.3.2 for further details.

Compared to fasted state, high-fat, high-calorie meal decreased CD exposures, both Cmax and AUC, from IPX203 by 64%, whereas LD Cmax and AUC were increased by 19% and 18%, respectively. CD Cmax and AUC are decreased by 14% and 9% when the contents of IPX203 were sprinkled on applesauce relative to fasted state, however, LD exposures were not affected by IPX203 contents sprinkling on applesauce.

At the maximum proposed daily dose of IPX203, carbidopa AUCs are 2-folds and 3.1 to 3.7-folds greater than those after the maximum recommended daily doses of Rytary and

IR CD-LD, respectively, while the AUCs of LD are similar. The higher CD exposures from IPX203 are attributable to the increased bioavailability compared to Rytary and 2.8 times higher total daily dose of CD from IPX203 than IR CD-LD.

2.2 Dosing and Therapeutic Individualization

Available data from the Phase 2 study IPX203-B16-01 and the pivotal efficacy study IPX203-B16-02 support IPX203 administration in patients who are already on the stable IR CD-LD treatment. The (b) (4) steps to convert patients from IR CD-LD to IPX203:

1. Determine the patient's most frequent single dose of IR CD-LD.
2. Convert to IPX203 by multiplying the most frequent single dose of IR CD-LD dose by 2.8 and administer three times a day as recommended in Table 8.
3. For patients whose most frequent single dose of IR CD-LD is >200 mg, the recommended starting dosing regimen of IPX203 is 700 mg levodopa TID.
4. For patients who are on a total daily IR CD-LD dose of <500 mg, the recommended starting IPX203 dosing frequency is BID.
5. Dosing frequency is 2 to 4 times per day. Adjust the dose or frequency as needed based on the individual patient's response. The maximum recommended total daily dose of Crexont is (b) (4).

The rationale for the dose conversion ratio of 2.8 from IR CD-LD to IPX203 is to achieve similar LD exposures between IR CD-LD and IPX203, although this dose conversion does not result in similar exposures for CD. This dose conversion and regimen was followed in the pivotal efficacy study, IPX203-B16-02 and long-term safety study, IPX203-B16-03. However, the long-term safety of this dosing regimen is not established yet. Please refer to Section 3.3.2 and the clinical review by Drs. Elizabeth Haberfeld and Natalie Getzoff for additional details.

2.3 Outstanding Issues

1. As discussed in Section 2.2, IPX203 dose conversion is based on multiplying the most frequent single dose of IR CD-LD by 2.8 (Table 8). No adequate pharmacokinetic bridging was established between IPX203 and FDA approved products (Sinemet®, Sinemet® CR or Rytary) (Section 3.3.2). At the maximum proposed total daily dose of IPX203, carbidopa AUC was 2-folds and 3.1-3.7-folds greater than those following the administration of the maximum recommended total daily doses of Rytary and IR CD-LD, respectively, while the AUCs of levodopa were similar (Tables 5-7). Therefore, exposure comparison with IR CD-LD or Rytary cannot support the safety of IPX203 at the proposed maximum total daily dose.
2. With the proposed maximum total daily dose of IPX203, carbidopa AUC was found to be higher compared to the maximum recommended daily dose of IR CD-LD or

Rytary (Section 3.3.2). It is not clear whether these higher levels of carbidopa will lead to drug interactions and/or QTc prolongation. Therefore, the Applicant need to conduct a thorough QT study to assess potential effects of Crexont on QTc. In addition, the review team encourages the Applicant to evaluate the drug interaction potential of carbidopa as perpetrator of major CYP enzymes and drug transporters at the therapeutic exposure. Please refer to QT memo by Dr. Eliford Kitabi and Dr. Christine Garnett for further information.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Crexont (IPX203) is an extended-release combination capsule of carbidopa and levodopa in 1:4 ratio. IPX203 is designed to provide therapeutic LD plasma concentrations rapidly and maintain constant LD plasma concentrations for an extended duration with minimal peak-to-trough fluctuations. Maximum proposed total daily dose of carbidopa and levodopa are (b) (4) respectively. In this NDA, the applicant plans to rely on Agency's previous findings of safety and efficacy of carbidopa and levodopa from Sinemet (NDA 017555), Sinemet CR (NDA 019856) and Rytary (NDA 203312).

Sinemet® (IR CD-LD) is an immediate release combination tablets of carbidopa and levodopa. IR CD-LD is indicated for the treatment of Parkinson's disease and syndrome under NDA 017555. Maximum recommended total daily dose of levodopa is (b) (4) (eight tablets), while experience with total daily dosages of carbidopa greater than 200 mg is limited.

Sinemet® CR (CR CD-LD) is a sustained-release combination tablets of carbidopa and levodopa in 1:4 ratio. CR CD-LD is indicated for the treatment of Parkinson's disease and syndrome under NDA 019856. CR CD-LD that provide 400 to 1600 mg of levodopa per day is effective in most of the patients. Higher doses of CR CD-LD (2400 mg or more of levodopa per day) have been used but are not usually recommended.

The applicant has previously developed Rytary which was approved on 01/07/2015. Rytary is an extended-release combination capsule of carbidopa and levodopa in 1:4 ratio. Rytary is indicated for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. Maximum recommended total daily dose of carbidopa and levodopa are 612.5 mg and 2450 mg, respectively.

As described in the Pre-NDA meeting minutes dated 04/08/2022, the Agency has communicated following major concerns to the applicant, which have not been fully addressed with the current NDA submission for Crexont:

- An internal analysis of the exposure of carbidopa (Cmax and AUC) at the highest dose of (b) (4) of the proposed drug product is higher than the exposure of

carbidopa at the highest approved regimen of listed drugs. It is not clear to us how are you going to justify the higher exposures of carbidopa of your product compared to reference product at the highest proposed regimen.

- If a PK bridge is not possible, exposure for chronic use in patients with Parkinson's disease should include a minimum number of 100 patients treated for one year with at least 50% of patients using the highest dose intended for labeling.

3.2 General Pharmacological and Pharmacokinetic Characteristics

The pharmacokinetic properties of carbidopa and levodopa are summarized in Table 1.

Table 1. Summary of pharmacological and pharmacokinetic characteristics

Mechanism of Action	*Carbidopa* Inhibits the decarboxylation of peripheral levodopa. *Levodopa* Expected to convert to dopamine in the brain and help relieves symptoms of Parkinson's disease.
Absorption	*Carbidopa* • Bioavailability: 103%-123% relative to IR CD-LD. • Dose proportional over IPX203 dosage strength range of 35 mg/140 mg to 87.5mg/350 mg. • High-fat, high-calorie meal decreases both Cmax and $AUC_{0-\infty}$ by approximately 64%. *Levodopa* • Bioavailability: 88%-99% relative to IR CD-LD. • Dose proportional over IPX203 dosage strength range of 35 mg/140 mg to 87.5mg/350 mg. • High-fat, high-calorie meal increases Cmax by 19% and $AUC_{0-\infty}$ by 18%. • Alcohol induced dumping potential (based on *in vitro* studies) for levodopa is with 40% alcohol but not with 5% and 20% of alcohol concentrations.
Distribution	• Plasma protein binding of CD is ~ 36% • Plasma protein binding of LD is 10-30%
Metabolism	*Carbidopa* • Primary metabolites of CD are: α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxy-phenylpropionic acid.

	Levodopa • Levodopa is extensively metabolized to various metabolites. • The two major metabolic pathways are decarboxylation by dopa decarboxylase (DDC) and O-methylation by catechol-Omethyltransferase (COMT).
Excretion	• Unchanged carbidopa accounts for 30% of the total urinary excretion.
Elimination	• The terminal half-life of levodopa is approximately 2 hours in the presence of carbidopa. • The terminal half-life of carbidopa is approximately 2 hours.

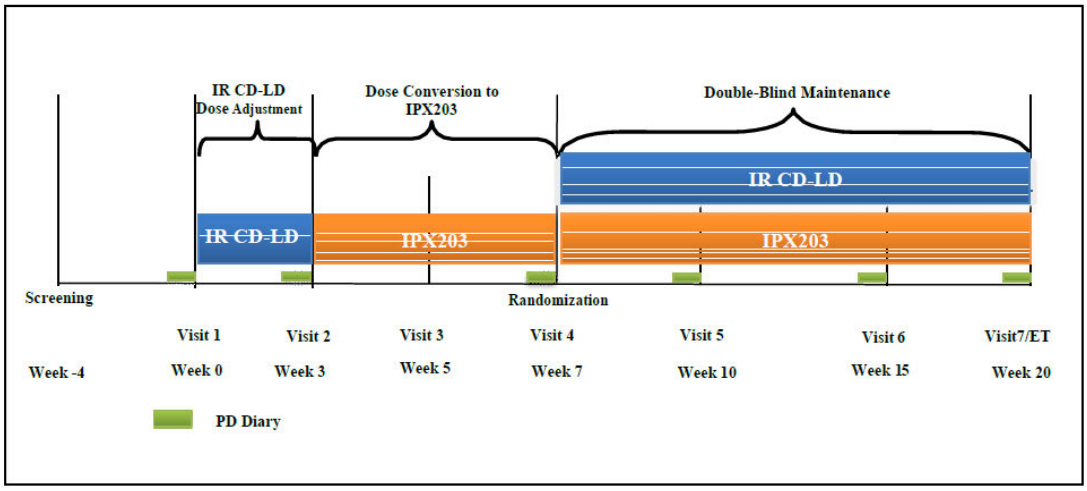
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness for Crexont is primarily based on the Phase 3 pivotal study IPX203-B16-02. This study was a randomized, double-blind, double-dummy, active-controlled study. After screening period, there was a 3-week open-label IR CD-LD dose adjustment period and a 4-week open-label period for conversion to IPX203. This was followed by a 13-week double-blind double-dummy treatment period in which a total of 630 subjects were randomized in a 1:1 ratio to receive either IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo). The study scheme is showed in Figure 1.

In the double-blind maintenance phase, the initial dosing regimen of IPX203 was based on the most frequent dose of the subject's stable dosing regimen of IR CD-LD at the end of the dose adjustment period (Table 2). As a result, each patient received a different total daily dose of IPX203 up to 5040 mg per day. IPX203 was mostly administered 3 times daily with a dosing interval of ~8 hours. For some patients the dosing interval varied from 6 hours to 12 hours based on individual adjustment.

Figure 1. Study IPX203-B16-02 flow chart



Source: Study Report IPX203-B16-02, Page 34, Figure 8

Table 2. (b) (4) starting dose of IPX203 (CD-LD) based on the dosing regimen of IR CD-LD at the end of the dose adjustment period

Most Frequent IR CD-LD Unit Dose (mg)	Recommended Starting IPX203 Daily Dosing Regimen CD-LD (mg) Every 8 Hours
25-100[a]	70-280 mg (2 × 35-140 mg)
>25-100 – 37.5-150	105-420 mg (3 × 35-140 mg)
>37.5-150 – 50-200	140-560 mg (4 × 35-140 mg)
>50-200	175-700 mg (5 × 35-140 mg)

Source: Study Report IPX203-B16-02, Page 36, Table 3

The primary efficacy endpoint was the mean change from baseline in "Good on" time in hours per day, averaged over the PD Diary days, at the end of the double-blind therapy (Visit 7/ ET). Per the applicant's analysis (Table 3), "Good on" time decreased less in the IPX203 group compared with IR CD-LD group, and IPX203 treatment resulted in significantly more hours of "Good on" time compared with IR CD-LD treatment. Please refer to the clinical review by Drs. Elizabeth Haberfeld and Natalie Getzoff, and statistical review by Drs. Minjeong Park and John Lawrence for further details.

Table 3. Analysis of Change from Baseline to Visit 7/ET in "Good on" Time (h) (mITT Analysis Set)

Statistic	IPX203 (N=249)	IR CD-LD (N=246)	Difference IPX203 – IR CD-LD
LS mean	-0.50	-1.03	0.53
Standard error	0.183	0.183	0.226
95% confidence interval	-0.86, -0.14	-1.39, -0.67	0.09, 0.97
p-value[a]			0.0194

Source: IPX203-B16-02, Page 106, Table 19

3.3.2 Is the PK bridging with previously approved CD/LD products adequately established to support the safety of IPX203 at the proposed maximum total daily dose?

NO. Exposure comparisons with Rytary or Sinemet cannot support the safety of IPX203 at more than half of the proposed maximum total daily dose. Carbidopa and levodopa exposure comparison with previously approved drug products comes from the following three studies:

Table 4. Studies that provided data for the evaluation exposure ratios of CD and LD between IPX203 and FDA approved products.

Study #	Test Formulation	Reference Formulation 1	Reference Formulation 2	Fasting
IPX203-B16-01	IPX203 (90/360)	IR CD-LD (25 /100)	-	8 hours[a]
IPX203-B16-05	IPX203 (70/280)	IR CD-LD (25 /100)	CR CD-LD (25 /100)	10 hours[b]
IPX203-B14-02	IPX203 (90/360)	IR CD-LD (25 /100)	Rytary (85/340)	8 hours[c]

[a]A low-protein breakfast was provided ~1 hour after dosing.
[b]Subjects received a standard meal at about 4, 8 and 12 hours after dosing
[c]A breakfast containing approximately 5 g of protein was served ~1 hour after dosing

Reviewer's Independent Analysis

The applicant compared carbidopa and levodopa exposures after normalizing to the dose conversion ratio used in each study. Because of the differences in dosing frequencies among the products, to compare the exposures, dose-normalized arithmetic $AUC_{0-\infty}$ were extrapolated to the maximum recommended total daily dose (MDD) for each product as showed in Tables 5-7.

Table 5. Dose-Normalized AUC0-∞ of carbidopa and levodopa following first dose on Day 1 extrapolated to maximum total daily dose of respective drug products (Study IPX203-B16-01). Refer to Section 4.3.2 for study design and results.

	Carbidopa		**Levodopa**	
	IPX203	IR CD-LD	IPX203	IR CR-LD
Normalized dose	70 mg	25 mg	280 mg	100 mg
AUC0-∞ (h* ng/mL)	1038	359	6925	2716
Relative Bioavailability	103%		91%	
Maximum Total Daily Dose (mg)	600	200	2400	2000
Extrapolated AUC0-∞ at MDD	8897	2872	59357	54320
$\frac{IPX203}{IR\ CD-LD}$	3.1		1.1	

IPX203-B16-05

Table 6. AUC0-∞ of carbidopa and levodopa extrapolated to maximum total daily dose of respective drug products (Study IPX203-B16-05). Refer to Section 4.3.1 for study details and results.

	Carbidopa			Levodopa		
	IPX 203	IR CD-LD	CR CD-LD	IPX 203	IR CD-LD	CR CD-LD
Dose (mg)	70	25	25	280	100	100
AUC0-∞ (h * ng/mL)	2247	655	510	7696	2776	2489
Relative Bioavailability	123%	-	78%	99%	-	90%
Maximum Total Daily Dose (mg)	600	200	600*	2400	2000	2400*
Extrapolated $AUC_{0-\infty}$ at MDD	19257	5236	-	65968	55518	59736

$\frac{IPX203}{IR\ CD-LD}$	3.7			1.2		
$\frac{IPX203}{CR\ CD-LD}$	1.6			1.1		

* According to the USPI of SINEMET CR, a dose of 400 to 1600 mg of levodopa per day is effective in most of the patients. Higher doses of SINEMET CR (2400 mg or more of levodopa per day) have been used but are not usually recommended. The CD/LD dose of 600 mg/ 2400 mg was used as the Maximum Total Daily Dose in this table for the purpose of comparison only.

IPX203-B14-02

Table 7. AUC0-∞ of carbidopa and levodopa extrapolated to maximum total daily dose of respective drug products (Study IPX203-B14-02). Refer to Section 4.3.3 for study design and results.

	Carbidopa			Levodopa		
	IPX 203	**IR CD-LD**	**Rytary**	**IPX 203**	**IR CD-LD**	**Rytary**
Normalized dose (mg)	90	25	85	360	*100*	*340*
AUC0-∞ (h * ng/mL)	1602	431	770	9800	*3108*	*8275*
Relative Bioavailability	103%		53%	88%		*78%*
Maximum Total Daily Dose (mg)	600	200	612.5	2400	*2000*	*2450*
Extrapolated $AUC_{0-\infty}$ at MDD	10680	3448	5549	65333	*62160*	*59629*
$\frac{IPX203}{IR\ CD-LD}$	3.1			1.1		
$\frac{IPX203}{Rytary}$	1.9			1.1		

Reviewer's Comments:

PK data from studies IPX203-B16-01, IPX203-B16-05 and IPX203-B14-02 demonstrated that IPX203 is not bioequivalent to IR CD-LD, CR CD-LD or Rytary.

Using IR CD-LD as the reference product, the relative bioavailabilities of carbidopa and levodopa were as follows: 103%-123% and 88%-99% for IPX203, 78% and 90% for CR CD-LD, and 53% and 78% for Rytary. Carbidopa relative bioavailability following Rytary administration is approximately half of the IPX203.

The exposures of levodopa were similar between IPX203 and the approved products (IR CD-LD or Rytary) at the maximum total daily dose, with an extrapolated AUC0-∞ ratio around 1.1-folds (Tables 5-7). Considering the individualized dose adjustment, the review team did not have a concern on the scientific bridge for the safety of levodopa based on PK exposures.

However, at the maximum total daily dose of each product, the ratios of extrapolated $AUC_{0-\infty}$ of carbidopa for IPX203 was 1.9-folds compared to Rytary, and 3.1 to 3.7-folds compared to IR CD-LD. The increased exposures of carbidopa following IPX203 treatment are due to the higher amounts of the administered carbidopa compared to IR CD-LD product and the increased bioavailability of the carbidopa with IPX203 compared to Rytary. Hence, the review team concluded that the comparison of exposures with IR CD-LD or Rytary does not support the proposed maximum total daily dose of (b) (4) *for IPX203.*

3.3.3 Does the application support the proposed dose conversions and dosing frequency of 2-4 times a day?

Proposed dose conversion from IR CD-LD to IPX203 in Parkinson's disease patients is shown in Table 8. The proposed conversion is developed based on the results from the Phase 2 study IPX203-B14-02. It was used in the pivotal Phase 3 study IPX203-B16-02 and in the open label safety extension study, IPX203-B16-03.

Table 8. Conversion from Immediate-Release Carbidopa-Levodopa to Crexont

Most Frequent Immediate-Release Levodopa Single Dose	Recommended Starting CREXONT Dose of Levodopa	Recommended Starting CREXONT Dosing Frequency
100 mg	280 mg	3 times daily
150 mg	420 mg	3 times daily
200 mg	560 mg	3 times daily

For patients whose most frequent single dose of immediate-release levodopa is >200 mg, the recommended starting dosing regimen of IPX203 is 700 mg levodopa 3 times daily.

For patients who are on a total daily immediate-release levodopa dose of <500 mg, the recommended starting IPX203 dosing frequency is twice daily.

In the phase 3 studies, IPX203 dosing interval is allowed to decrease to every 6 hours if a patient appear to be benefit from a higher dosing frequency.

Overall, the proposed dosing regimen aligns with the completed Phase 3 dosing recommendations. Please refer to clinical review by Drs. Elizabeth Haberfeld and Natalie Getzoff for details on the efficacy and safety.

3.3.4 What is the effect of food on the bioavailability of IPX203?

Effect of a high-fat, high-calorie breakfast and sprinkling the IPX203 contents on apple sauce on the PK profiles of CD and LD from IPX203 were determined in a single-dose, open-label, randomized, three-treatment crossover study in healthy subjects (IPX203-B16-04). Refer to Section 4.3.5 for study details and the statistical analysis of the results.

High fat high calorie breakfast

Following oral administration of IPX203 to healthy subjects with a standard high fat high calorie breakfast, carbidopa exposures (Cmax and AUC) decreased by 64% compared to fasted state, while levodopa exposures (Cmax and AUC) were increased by 19% and 18%, respectively, compared to fasted state. The review team notes that PK bridging studies were conducted at fasted state (Table 4) and lack of food effect data on the CD pharmacokinetics from reference products did not allow comparison of exposure at high-fat meal condition.

Applesauce

Following oral administration of IPX203 capsules contents sprinkling on the applesauce to healthy subjects, the geometric mean ratios of carbidopa Cmax and AUC were 86% and 91%, respectively, compared to fasted state. The 90% CI for Cmax was 78%-97%, which was not contained in the standard bioequivalence limits of 80%-125%. Sprinkling the IPX203 capsule contents on applesauce did not affect the LD concentration time profile compared to the intact capsule under fasted condition.

However, IPX203 was administered with or without food in the pivotal efficacy study, IPX203-B16-02 and in the long-term safety study, IPX203-B16-03. The long-term safety of IPX203 administration with or without regard to food is not established yet. Please refer to Section 4.3.5 and the clinical review by Drs. Elizabeth Haberfeld and Natalie Getzoff for additional details.

3.3.5 Is the IPX203 clinical formulation manufactured at (b) (4) bioequivalent to the commercial formulation manufactured at Brookhaven, NY?

Treatment A and Treatment E of the study IPX203-B16-06 evaluated bioequivalence between the to-be-marketed formulation manufactured in USA and the clinical trial

formulation manufactured in [redacted] (b) (4) The 90% CIs of GMRs of carbidopa and levodopa exposures (Cmax, AUC0-∞) were within 80 to 125% range. Therefore, the to-be-marketed formulation manufactured at Brookahaven, NY is bioequivalent to the clinical trial formulation manufactured at [redacted] (b) (4). Please refer to the Section 4.3.6 for study details and statistical analysis. The OSIS have conducted a remote regulatory assessment (RRA) of the analytical portion of the study and concluded that data from the audited study is reliable[1].

[1] OSIS Memo. DARRTS dated 02/22/2023

4. Appendices

4.1 Summary of bioanalytical method validation

A total of three validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods were employed for determining the plasma concentrations of carbidopa and levodopa in the clinical development program for Crexont. The sample analysis was conducted in accordance with the FDA guidance for the industry, Bioanalytical Method Validation. Summary of the methods validation is provided in Table *9*

Table 9. Summary of bioanalytical method validation

Protocol No.:	**IPX203-B16-04, IPX203-B16-05 and IPX203-B16-06**	**IPX203-B14-02**	**IPX203-B16-01**
Validation Report Title:	Validation of a Liquid Chromatographic Method using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of LD (5 to 7500 ng/mL) and CD (0.5 to 750 ng/mL) in Stabilized Human EDTA K_2 Plasma	Determination of Carbidopa and Levodopa in Human Plasma by LC-MS/MS	Determination of Carbidopa and Levodopa in Plasma by LC-MS/MS
Analytes:	Levodopa (LD) and Carbidopa (CD)	Levodopa (LD) and Carbidopa (CD)	Levodopa (LD) and Carbidopa (CD)
Calibration Ranges:	LD: 5 to 7500 ng/mL CD: 0.5 to 750 ng/mL	LD: 10 to 2000 ng/mL CD: 2 to 400 ng/mL	LD: 10 to 2000 ng/mL CD: 2 to 400 ng/mL
Biological Matrix:	Stabilized Human EDTA K_2 Plasma	Human Plasma with EDTA K_2	Human Plasma with EDTA K_2
Sample Extraction:	Automated protein precipitation	Solid-phase extraction	Solid-phase extraction

Accuracy and Precision (Between-Run):	LD: Biases: -0.21 to 5.00% CV: 2.28 to 8.36% CD: Biases: -0.11 to 4.78% CV: 1.70 to 8.17%	LD: Precision (% CV): 1.9% to 6.2%, Accuracy (% Difference [%Nominal-100]): –1.9% to 1.8% CD: Precision (% CV): 1.2% to 4.1%, Accuracy (% Difference [%Nominal-100]): –2.3% to 2.0%	LD: Precision (%CV): 1.4% to 4.8% Accuracy (% Difference [%Nominal-100]): –1.9% to 2.0% CD: Precision (%CV): 1.3% to 3.7% Accuracy (% Difference [%Nominal-100]): –1.1% to 0.8%
Accuracy and Precision (Within-Run):	LD: Biases: -1.13 to 8.07% CV: 0.65 to 13.11% CD: Biases: -6.67 to 7.33% CV: 0.65 to 8.21%	LD: % Nominal values: 100.0 to 104.7%, %CV: <6.1% CD: % Nominal values: 100.2 to 107.5%, %CV: <4.3%	LD: % Nominal values: 100.0 to 104.7%, %CV: <6.1% CD: % Nominal values: 100.2 to 107.5%, %CV: <4.3%
Short-Term Stability of Analytes in Matrix:	24 h 19 min at 4°C	LD and CD: At least 8.1 h in an ice-water bath At least 17.8 h in an ice-water bath in K_3EDTA	LD and CD: At least 8.1 h in an ice/water bath; At least 12.1 h in an ice/water bath in hemolyzed plasma; At least 12.1 h in an ice/water bath in lipemic plasma; At least 17.8 h in an ice/water bath in K_3EDTA.
Long-Term Stability of Analytes in Matrix:	LD: 109 days at -80°C CD: 102 days at -80°C	LD and CD: At least 741 days when stored at -70±15°C At least 33 days when stored at -20±10°C At least 10 days when stored at -70±15°C in K_3EDTA	LD and CD: At least 741 days when stored at -70±15°C; At least 17 days when stored at -70±15°C in hemolyzed plasma; At least 23 days when stored at -70±15°C in lipemic plasma; At least 33 days when stored at -20±10°C; At least 10 days when stored at -70±15°C in K_3EDTA.

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Reviewer's Comments

The validation and performance of the assay was reviewed individually for the key clinical pharmacology studies. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within the accepted limits.

4.2 Tabular listing of all clinical studies

Clinical development program for Crexont include three Phase 1 studies, two Phase 2 studies and two Phase 3 studies.

Study No.	Study Objective(s)	Study Design and Type Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatments
IPX203-B16-06 N=40 healthy adults	To assess the bioequivalence of IPX203 capsules manufactured at two sites (Brookhaven, New York (b) (4) (b) (4)) To assess the dose proportionality of IPX203 capsules (35-140 mg CD-LD, 52.5-210 mg CD-LD, 70-280 mg CD-LD, 87.5-350 mg CD-LD)	Randomized (first 2 treatment periods only), single-site, open-label, single-dose, 5-treatment, 5-period, crossover bioequivalence (Treatments A and E) and dose proportionality (Treatments A through D) study	**Treatment A:** IPX203 ER CD-LD 35-140 mg, 1 capsule **Treatment B:** IPX203 ER CD-LD 52.5-210 mg, 1 capsule **Treatment C:** IPX203 ER CD-LD 70-280 mg, 1 capsule **Treatment D:** IPX203 ER CD-LD 87.5-350 mg, 1 capsule **Treatment E:** IPX203 ER CD-LD 35-140 mg, 1 capsule Treatments A through D made in the US. Treatment E made in (b) (4) Treatments A and E were given during the first 2 treatment periods (randomized sequence). Then, Treatments B, C, and D were given in Treatment Periods 3, 4, and 5. Oral under fasted conditions	Single doses of each study treatment with 5- day washout between treatments
IPX203-B16-04	To assess the effect of a standardized high-fat meal on the PK of IPX203	Randomized, single center, open-label,	**IPX203 Fed:**	Single doses of each study treatment,

N = 27 healthy adults	To characterize the PK of IPX203 after sprinkling the capsule contents on apple sauce as a representative soft food.	single-dose, 3-treatment, 3-period, crossover study.	IPX203 ER CD-LD 87.5-350 mg, 1 capsule after initiating a standardized high-fat, high-calorie breakfast **IPX203 Sprinkled on Applesauce:** IPX203 ER CD-LD 87.5-350 mg, 1 capsule of IPX203 contents sprinkled on 1 tablespoon of Applesauce and swallowed without chewing. **IPX203 Fasted:** IPX203 ER CD-LD 87.5-350 mg, 1 capsule under fasted conditions Oral	separated by a 6-day washout between first and second periods and a 7-day washout between second and third periods.
IPX203-B16-05 N = 27 healthy Adults	To compare the single-dose Pharmacokinetics (PK) of IPX203 (carbidopalevodopa extended-release [ER] capsules) with immediate release (IR) CD-LD (Sinemet®) and controlled-release (CR) CD-LD (Sinemet CR®)	Randomized, single center, open-label, single-dose, 3-treatment, 3-period, crossover study	**Treatment A:** IPX203 ER CD-LD 70mg/280mg Capsule **Treatment B:** IR CD-LD [SINEMET® (CD-LD) Tablets 25mg/100mg] **Treatment C:** CR CD-LD [SINEMET® CR (CD-LD) SR Tablets 25mg/100mg] The subjects received 1 capsule each of Treatments A, B and C Oral administration	Single-dose over a 2-week period with a 6-day washout period between dosing periods
IPX203-B14-02 N = 26 advanced	To assess the pharmacodynamics and PK of single doses of IPX203 in subjects with advanced Parkinson's	Randomized, open label, rater-blinded, multi center, 3-treatment, 3-period, single-dose, crossover	**IPX203 capsules:** 180 mg (containing 45 mg CD/180 mg LD) and 270 mg (containing 67.5 mg CD/270 mg LD) **ER CD-LD (Rytary) capsules:**	Single doses of each study treatment, with washout periods of

idiopathic Parkinson's disease patients	disease using Rytary and IR CD-LD as References To characterize the safety of single doses of IPX203 in subjects with Advanced Parkinson's disease		145 mg (containing 36.25 mg CD/145 mg LD) and 195 mg (containing 48.75 mg CD/195 mg LD) **IR CD-LD (Sinemet IR) tablets:** 100 mg (Containing 25 mg CD/100 mg LD) Oral administration	~1 week between doses
IPX203-B16-01 N = 28 advanced idiopathic Parkinson's disease patients	To compare the PK of single and multiple doses of IPX203 with IR CD-LD in subjects with advanced Parkinson's disease To compare the pharmacodynamics of single and multiple doses of IPX203 with IR CD-LD To compare the efficacy of IPX203 with IR CD-LD following multiple doses To evaluate the safety of IPX203	Randomized, multicenter open-label, rater-blinded, multiple dose, 2-treatment, 2-period, crossover	Subjects randomized to 1 of 2 dosing sequences: IR CD-LD (Sinemet IR) followed by IPX203, and IPX203 followed by IR CD-LD. Variable dosing, 15 days per treatment period, using: **IPX203 capsules:** 180 mg (containing 45 mg CD/180 mg LD) and 270 mg (containing 67.5 mg CD/270 mg LD) **IR CD-LD (Sinemet IR) tablets:** 100 mg (Containing 25 mg CD/100 mg LD) Oral administration	Two 15-day treatment periods, one for each study treatment, with a washout period of approximately 1 week (±2 days) between the two treatment periods
IPX203- B16-02 N = 630 Parkinson's disease with motor fluctuations	To evaluate the safety and efficacy of IPX203 in comparison to IR CD-LD in the treatment of subjects with Parkinson's disease with motor fluctuations	Randomized, double-blind, double- dummy, active controlled, parallel-group, prospective, multicenter study	**IPX203 (CD-LD) ER capsules:** 35 mg CD-140 mg LD **IR CD-LD tablets:** 25 mg CD-100 mg LD Matching IPX203 and IR CD-LD placebo Individualized based on incoming IR CD-LD dose. Oral administration	13 weeks of double-blind treatment preceded by a 3-week dose adjustment period on IR CD-LD and a 4-week open label dose conversion

				period on IPX203
IPX203-B16-03 N = 419 Subjects who successfully completed Study IPX203-B16-02	To evaluate the long-term safety and clinical utility of IPX203 in subjects with Parkinson's disease with motor fluctuations	Multicenter open label safety extension study	**IPX203(CD-LD) capsules:** 35-140 mg CD-LD 52.5-210 mg CD-LD 70-280 mg CD-LD 87.5-350 mg CD-LD Individualized based on the final IPX203 dosing regimen that was determined during the IPX203 dose conversion period of Study IPX203-B16-02. Oral administration	9 months

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4.3 Individual Study Summary

4.3.1 IPX203-B16-05

IPX203-B16-05 was a Phase 1 comparative pharmacokinetic study. The objective of the study was to evaluate the relative bioavailability of IPX203 compared with the FDA approved CD-LD products, IR CD-LD(Sinemet®) and CR CD-LD (Sinemet® CR). This was a randomized, single-center, open-label, single-dose, 3-treatment, 3-period, crossover study in healthy, adult, human subjects. All subjects who have completed the study (N = 25) received treatments (A, B and C) with 240 mL of water after an overnight fast of 10 hours at room temperature as per randomized schedule.

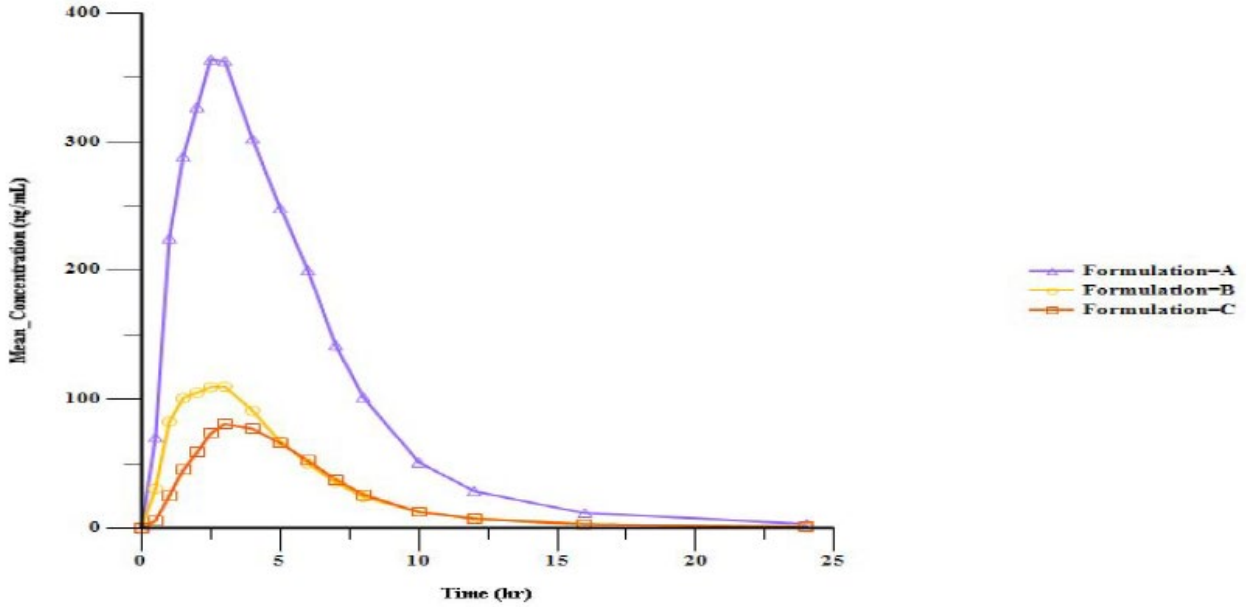
Treatment A: IPX203 ER CD-LD 70 mg/280 mg per Capsule manufactured by Amneal Pharmaceuticals 50 Horseblock Road, Brookhaven, NY 11719, USA

Treatment B: IR CD-LD [SINEMET® (CD-LD) Tablets 25 mg/100 mg] manufactured by Mylan Pharmaceuticals Inc. Morgantown WV 26505 USA

Treatment C: CR CD-LD [SINEMET® CR (CD-LD) SR Tablets 25 mg/100 mg] manufactured by Mylan Pharmaceuticals Inc. Morgantown WV 26505 USA

The mean carbidopa plasma concentration-time profiles for Test Product (A), Reference Product (B), and Reference Product (C) are presented in Figure 2. The mean pharmacokinetic parameters estimated for Test Product (A), Reference Product (B), and Reference Product (C) for Carbidopa are presented in Table *10*.

Figure 2. Linear plot of mean plasma carbidopa concentration -time profiles of Formulation A (IPX203), Formulation B (CR CD-LD) and Formulation C (CR CD-LD)



Source: Study Report IPX203-B16-05, Page 70, Figure 03.

Table 10. Pharmacokinetic parameters of Carbidopa

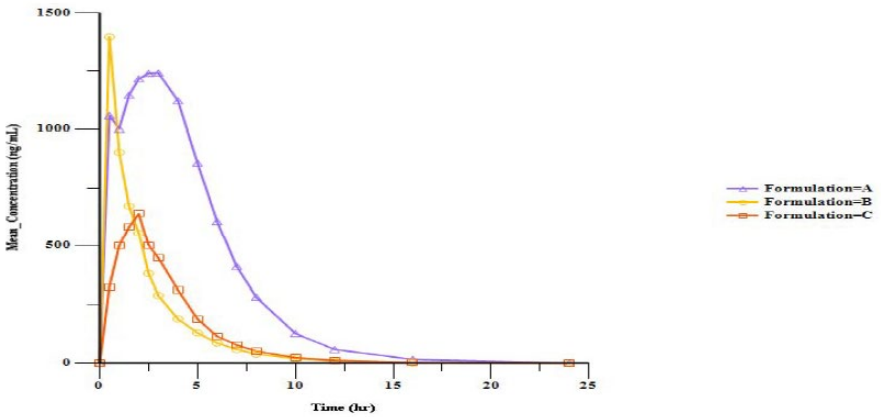
Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV)		
	Test Product (A) (N = 25)	Reference Product (B) (N = 25)	Reference Product (C) (N = 25)
C_{max} (ng/mL)	403.416 ± 144.6802 (35.86%)	120.441 ± 42.4375 (35.24%)	92.572 ± 44.5244 (48.10%)
#t_{max} (hr)	3.000 (1.50 - 6.00)	2.500 (1.00 - 4.00)	3.000 (1.50 - 6.00)
AUC_{0-t} (hr*ng/mL)	2228.936 ± 891.8502 (40.01%)	648.964 ± 296.1805 (45.64%)	504.663 ± 303.1730 (60.07%)
$AUC_{0-\infty}$ (hr*ng/mL)	2246.617 ± 900.5074 (40.08%)	654.554 ± 298.7243 (45.64%)	510.106 ± 304.8641 (59.76%)
$t_{½}$ (hr)	3.886 ± 0.4117 (10.60%)	3.956 ± 0.8071 (20.40%)	3.483 ± 0.7935 (22.79%)
K_{el} (1/hr)	0.181 ± 0.0213 (11.82%)	0.183 ± 0.0429 (23.37%)	0.209 ± 0.0463 (22.18%)
AUC_%Extrap_obs (%)	0.768 ± 0.2623 (34.14%)	0.880 ± 0.3109 (35.33%)	1.328 ± 0.8479 (63.83%)

For $t_{max,}$ Median (min – max),

Source: Study Report IPX203-B16-05, Page 68, Table 29

The mean levodopa plasma concentration-time profiles for Test Product (A), Reference Product (B), and Reference Product (C) are presented in Figure *3*. The mean pharmacokinetic parameters estimated for Test Product (A), Reference Product (B), and Reference Product (C) for levodopa are presented in Table *11*.

Figure 3. Linear plot of mean plasma levodopa concentration -time profiles Formulation A (IPX203), Formulation B (CR CD-LD) and Formulation C (CR CD-LD)



Source: Study Report IPX203-B16-05, Page 69, Figure 01.

Table 11. Pharmacokinetic parameters of levodopa

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV)		
	Test Product (A) (N = 25)	Reference Product (B) (N = 25)	Reference Product (C) (N = 25)
C_{max} (ng/mL)	1621.360 ± 494.9552 (30.53%)	1600.146 ± 804.4910 (50.28%)	735.869 ± 221.7016 (30.13%)
#t_{max} (hr)	2.000 (0.50 - 5.00)	0.500 (0.50 - 2.00)	2.000 (0.50 - 2.50)
AUC_{0-t} (hr*ng/mL)	7662.313 ± 2039.5995 (26.62%)	2752.742 ± 607.9932 (22.09%)	2459.708 ± 655.6731 (26.66%)
$AUC_{0-\infty}$ (hr*ng/mL)	7696.203 ± 2041.1585 (26.52%)	2775.919 ± 607.9711 (21.90%)	2489.391 ± 664.1034 (26.68%)
$t_{½}$ (hr)	1.997 ± 0.2620 (13.12%)	2.094 ± 0.3239 (15.47%)	2.021 ± 0.3929 (19.44%)
K_{el} (1/hr)	0.353 ± 0.0442 (12.53%)	0.338 ± 0.0475 (14.07%)	0.355 ± 0.0650 (18.32%)
AUC_%Extrap_obs (%)	0.458 ± 0.2845 (62.17%)	0.872 ± 0.3112 (35.69%)	1.190 ± 0.7287 (61.23%)

For t_{max}, Median (min – max)

Source: Study Report IPX203-B16-05, Page 67, Table 28

4.3.2 IPX203-B16-01

Comparison of carbidopa and levodopa exposures following single dose and multiple doses of IPX203 and listed drug (IR CD-LD) were studies in IPX203-B16-01. This study was a Phase 2, multicenter, open-label, randomized, rater-blinded, 2-treatment, 2-period, multiple-dose crossover study. Approximately 30 eligible LD-experienced subjects with advanced PD were randomized with equal probability to one of two dosing sequences: IPX203 followed by IR CD-LD or IR CD-LD followed by IPX203.

Subjects received oral doses of either IPX203 or IR CD-LD according to their randomized sequence for Periods 1 and 2. The initial dosing regimen of IPX203 was according to *Table 12*, which was based on each individual's prestudy IR CD-LD morning dose and daily dosing regimen. The dosing regimen for IPX203 was 3 times a day, approximately every 7 to 8 hours.

Table 12. Initial IPX203 LD dosing regimen subsequent to IPX203 morning dose based on prestudy regimen of LD

Most Frequent Afternoon and Evening LD Unit Dose (mg)	IPX203 Regimen Post Morning Dose
100 – 125 mg	270 mg every 7 to 8 hours (270 mg × 1)
150 – 175 mg	450 mg every 7 to 8 hours (180 mg × 1 + 270 mg × 1)
200 – 225 mg	540 mg every 7 to 8 hours (270 mg × 2)
250 – 275 mg	720 mg every 7 to 8 hours (270 mg × 2 + 180 mg × 1)
300 mg	810 mg every 7 to 8 hours (270 mg × 3)

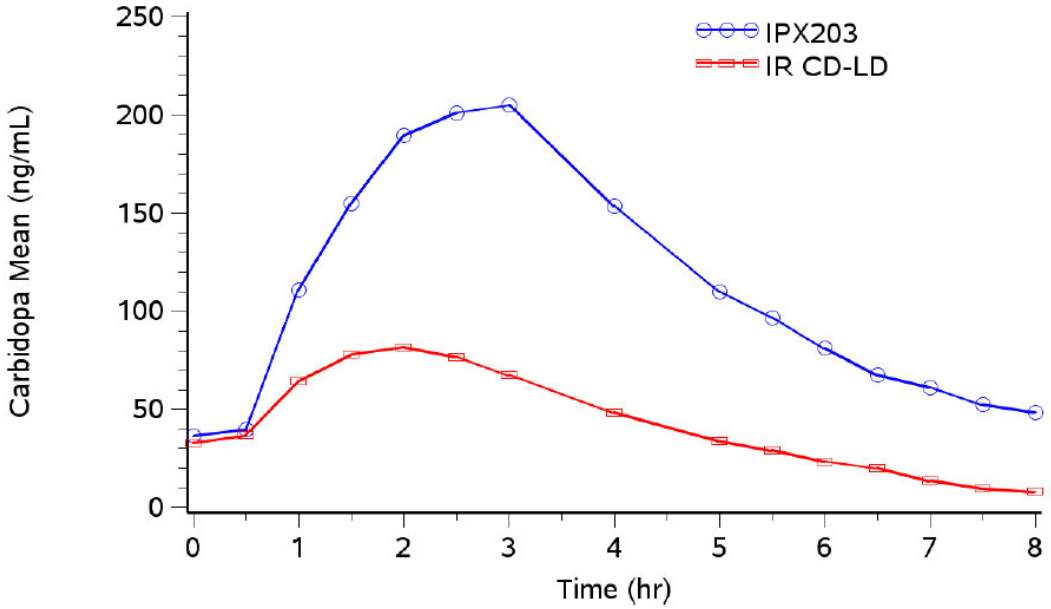
Note: A 100-mg unit dose of IR LD converts approximately to a 270-mg unit dose of IPX203.
Abbreviations: LD = levodopa

Source: Study Report IPX203-B16-01, Page 23, Table 4

Pharmacokinetics of Carbidopa at steady State following multiple doses of IPX or IR for 15 days

PK analyses were conducted using data from the 27 subjects in the PK completer analysis set. Mean dose-normalized carbidopa plasma profiles for the 2 study treatments on Day 15 are shown in *Figure 4* and mean dose-normalized carbidopa PK parameters following first dose on day 15 are shown in *Table 13*. Following the first dose of IPX203 on Day 15, CD was absorbed with a median Tmax of 2.5 hours. The mean dose-normalized CD Cmax following IPX203 treatment was 227±86 ng/mL and approximately 2.6-fold greater than that of IR CD-LD. The mean dose-normalized CD AUCtau value following IPX203 treatment was 918±319 h·ng /mL and approximately 3.7-fold greater than that of IR CD-LD, consistent with the higher CD dose and formulation characteristics.

Figure 4. Mean dose-normalized carbidopa plasma concentration-time profiles for first dose on Day 1



Source: Study Report IPX203-B16-01, Final Post Text Report, Page 681, Figure 14.2.7.3-11

Table 13. Dose-normalized carbidopa PK parameters following first dose on Day 1

Parameter	IPX203 (N = 27)	IR CD-LD (N = 27)
C_{max} (ng/mL)	229 ± 99	91 ± 45
AUC_t (h·ng/mL)	898 ± 339	265 ± 126
AUC_∞ (h·ng/mL)	1038 ± 384[a]	359 ± 164[b]

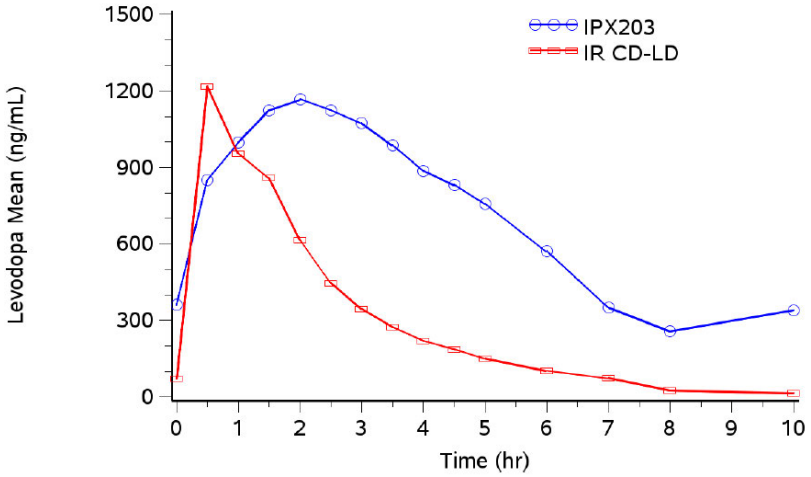
[a] N = 26
[b] N = 20

Source: Study Report IPX203-B16-01, Page 61, Table 18
PK parameters are normalized to 25 mg CD for IR CD-LD and 70 mg CD for IPX203

Pharmacokinetics of Levodopa at steady State following multiple doses of IPX or IR for 15 days

The concentration-time profiles following dose normalization of LD to 100 mg in IR CD-LD and 280 mg in IPX203 are shown in *Figure 5*. The associated dose-normalized PK parameters following first dose on Day 1 are listed in *Table 14*. Mean Cmax values following IPX203 dosing were comparable between IPX203 and IR CD-LD. The mean dose-normalized LD AUCtau value following IPX203 treatment on Day 15 was 5752±1772 h·ng /mL and approximately 2.36-fold greater than that of IR CD-LD, consistent with the higher LD dose and formulation characteristics. Fluctuation index of levodopa from IPX203 was decreased by 37% (1.7 ± 0.5) compared to IR CD-LD (2.7 ± 1.0).

Figure 5. Mean dose-normalized levodopa plasma concentration-time profiles for first dose on Day 1



Source: Study Report IPX203-B16-01, Final Post Text report, Page 675, Figure 14.2.7.3-5

Table 14. Dose-normalized levodopa PK parameters following first dose on Day 1

Parameter	IPX203 (N=27)	IR CD-LD (N=27)
C_{max} (ng/mL)	1425 ± 527	1367 ± 613
AUC_t (h·ng/mL)	6037 ± 2648	2343 ± 761
AUC_∞ (h·ng/mL)	6925 ± 3467	2716 ± 903[a]
$AUC_{0\text{-}2}$ (h·ng/mL)	1698 ± 792	1512 ± 661[a]
$AUC_{2\text{-}8}$ (h·ng/mL)	4574 ± 2018	1124 ± 387[a]

[a] N=26. AUC_∞ could not be calculated for Subject No. (b) (6) due to insufficient data points.

Source: Study Report IPX203-B16-01, Page 56, Table 15
Values are normalized to 100 mg LD for IR CD-LD and 280 mg LD for IPX203

4.3.3 IPX203-B14-02

IPX203-14-02 was a Phase 1 study, it assessed PK of single doses of IPX203 in subjects with advanced PD, using Rytary and IR CD-LD as the references. This was a randomized, open-label, rater-blinded, multicenter, 3-treatment, 3-period, single-dose crossover study. Approximately 51 qualified subjects with advanced PD with motor fluctuations who were receiving IR CD-LD at study entry were randomized to one of three dosing sequences of IPX203, IR CD-LD, and Rytary. Dosing is based on the prestudy morning dose of LD in IR CD-LD as shown in *Table 15*. All treatments were administered with 240 mL of room-temperature water to subjects in fasted state.

Table 15. Study Dosing Scheme based on Prestudy IR LD dose for Study IPX203-B14-02

Prestudy Morning Dose of LD in IR CD-LD (mg)	Study Treatments					
	IR CD-LD		Rytary		IPX203	
	LD (mg)	Tablets	LD (mg)	Capsules	LD (mg)	Capsules
100	100	1 (1×100)	340	2 (1×195 plus 1×145)	360	2 (2×180)
150	150	1.5 (1.5×100)	485	3 (1×195 plus 2×145)	540	3 (3×180)
200	200	2 (2×100)	630	4 (1×195 plus 3×145)	720	3 (2×270 plus 1×180)
250	250	2.5 (2.5×100)	780	4 (4×195)	810	3 (3×270)

CD and LD were present at a fixed ratio of 1:4 in each strength and treatment

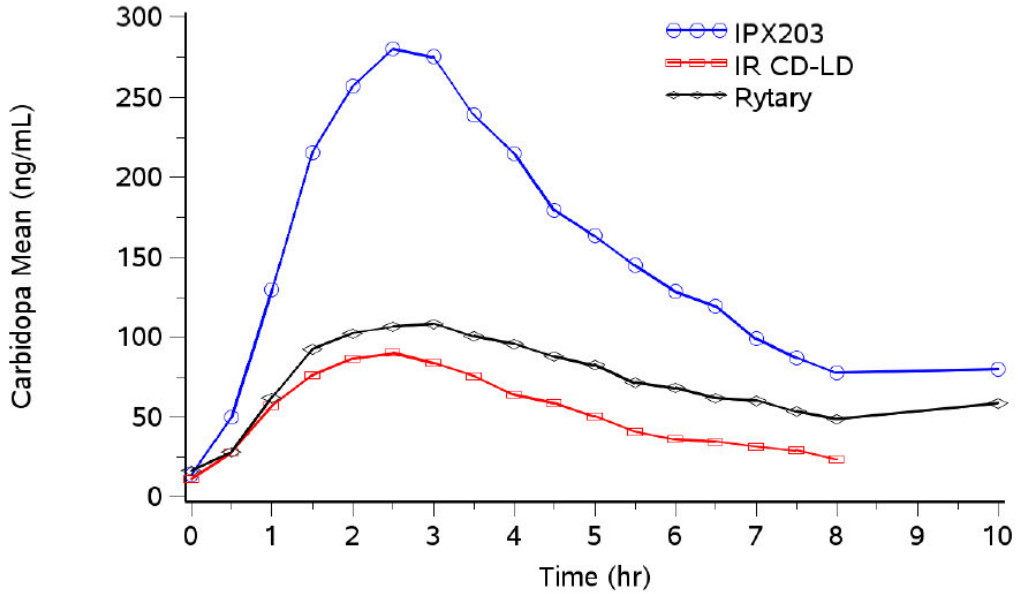
Source: Clinical Study Report – IPX203-B14-02, Page 18, Table 4

Blood samples (6 mL) were collected in each treatment period at nominal times (predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, and 10 hours postdose) for measurement of LD and CD plasma concentrations. PK analyses were conducted using data from the 24 subjects who completed all three treatments and in whom any plasma concentrations were available.

Carbidopa pharmacokinetics

The carbidopa concentration-time profiles following **dose normalization to the lowest dose in each treatment** are shown in *Figure 6* and the associated dose-normalized PK parameters are listed in *Table 16*

Figure 6. Mean Dose-Normalized CD Plasma Concentration-Time Profiles (N =24)



Source: IPX203-B14-02 Tables and Figures, Page 710, Figure 14.2.6.3-4

Table 16. Dose-Normalized Carbidopa Pharmacokinetic Parameters for PK Completers in Study IPX203-B14-02 (N =24)

Parameter	IPX203	IR CD-LD	Rytary
C_{max} (ng/mL)	331 ± 159	101 ± 48	132 ± 56
AUC_t (ng·h/mL)	1271 ± 534	333 ± 175	555 ± 268
$AUC_{0-\infty}$ (ng·h/mL)	1602 ± 725	431 ± 223	770 ± 334

Values are mean ± SD. PK parameters are normalized to lowest dose in each treatment, ie, 90 mg CD (IPX203), 25 mg CD (IR CD-LD), 85 mg CD (Rytary).

Source: Clinical Study Report – IPX203-B14-02, Page 48, Table 16

Bioavailability values of CD based on dose-normalized natural-log-transformed $AUC_{0-\infty}$ for IPX203 and Rytary were approximately 112% and 55%, respectively, relative to IR CD-LD. *Table 17*

Table 17. Carbidopa Bioavailability Assessment for PK Completers in Study IPX203-B14-02

Comparison	% Ratio of Geometric Mean Estimates (90% Confidence Interval)		
	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
IPX203 / IR CD-LD	97.60 (83.59, 113.95)	118.51 (99.84, 140.67)	112.07 (92.40, 135.92)
Rytary / IR CD-LD	40.09 (34.33, 46.80)	51.53 (43.41, 61.16)	55.37 (45.50, 67.38)

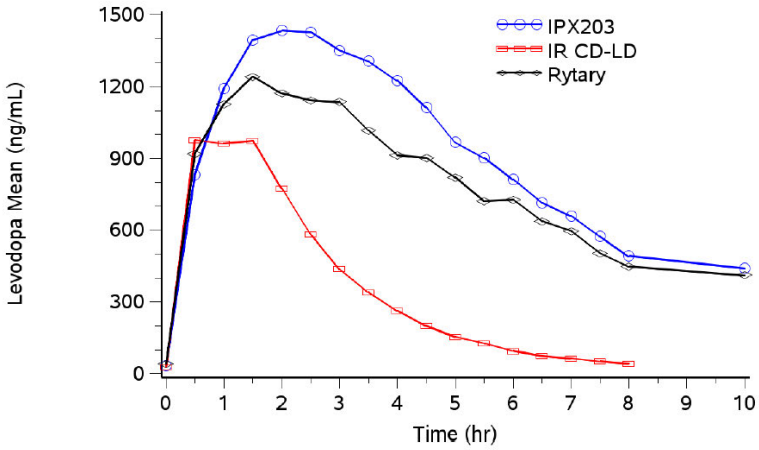
Data reported are ratios of dose-normalized ln-transformed geometric means for Test/Reference expressed as a percentage and 90% confidence intervals.

Source: Clinical Study Report – IPX203-B14-02, Page 44, Table 14

Levodopa Pharmacokinetics

Levodopa concentration-time profiles following dose normalization to the lowest dose in each treatment are shown in *Figure 7*and the associated dose-normalized PK parameters are listed in *Table 18*.

Figure 7. Mean Dose-Normalized LD Plasma Concentration-Time Profiles (N =24)



Source: IPX203-B14-02 Tables and Figures, Page 708, Figure 14.2.6.3-2

Table 18. Dose-Normalized Levodopa Pharmacokinetic Parameters for PK Completers in Study IPX203-B14-02

Parameter	IPX203	IR CD-LD	Rytary
C_{max} (ng/mL)	1868 ± 658	1415 ± 567	1715 ± 905
AUC_t (ng·h/mL)	7809 ± 3077	2774 ± 972	6358 ± 3205
$AUC_{0-\infty}$ (ng·h/mL)	9800 ± 4068	3108 ± 988	8275 ± 4032

Values are normalized to the lowest dose in each treatment, ie, 100 mg LD (IR CD-LD), 360 mg LD (IPX203), and 340 mg LD (Rytary). Values are mean ± SD.

Source: Clinical Study Report – IPX203-B14-02, Page 43, Table 12

The bioavailability of LD based on dose-normalized natural-log-transformed $AUC_{0-\infty}$ was higher following IPX203 (85.5%) than following Rytary (71.8%) (*Table 19*) relative to IR CD-LD.

Table 19. Levodopa Bioavailability Assessment for PK Completers in Study IPX203-B14-02

Comparison	% Ratio of Geometric Mean Estimates (90% Confidence Interval)		
	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
IPX203 / IR CD-LD	37.76 (32.59, 43.75)	77.50 (71.25, 84.31)	85.50 (77.89, 93.85)
Rytary / IR CD-LD	34.03 (29.38, 39.43)	62.81 (57.74, 68.32)	71.79 (65.26, 78.97)

Data reported are the ratios of the ln-transformed dose-normalized geometric means for Test/Reference expressed as a percentage and 90% confidence interval.

Source: Clinical Study Report – IPX203-B14-02, Page 43, Table 13

Reviewer's Comments:

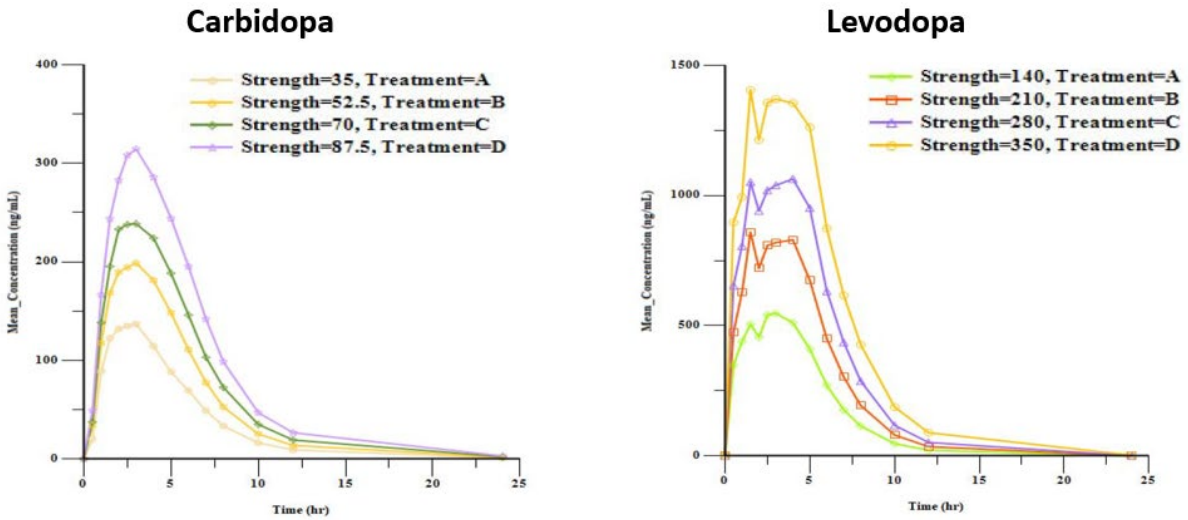
Dose-normalized levodopa exposures following IPX203 and Rytary are in the same range. However, carbidopa exposures from IPX203 are >2-folds higher than those of Rytary. These higher carbidopa levels are a safety concern.

4.3.4 IPX203-B16-06 (Dose proportionality)

Study IPX203-B16-06 assessed the dose proportionality of IPX203 capsules (Treatment A: 35-140 mg CD-LD, Treatment B: 52.5-210 mg CD-LD, Treatment C: 70-280 mg CD-LD, and Treatment D: 87.5-350 CD-LD) in healthy volunteers. Drug products for Treatments A-D were manufactured at Amneal Pharmaceuticals 50 Horseblock Road, Brookhaven, NY 11719, USA

All subjects who completed the study, were administered Treatments A to D in sequence with 240 mL of water after overnight fast for 10 hours. A total of 39 subjects completed the dose proportionality part of the study. The mean plasma concentration time profiles for carbidopa and levodopa following oral administration of Treatments A-D are presented in Figure 8. The pharmacokinetic parameters of Carbidopa and Levodopa are tabulated in *Table 20* and Table 21, respectively.

Figure 8. Mean plasma concentration time profiles of carbidopa (left) and levodopa (right) following Treatments A, B, C, and D



Source: Carbidopa- Study Report IPX203-B16-06, Page 81, Figure 07. Levodopa- Study Report IPX-203-B16-06, Page 80, Figure 05

Table 20. Pharmacokinetic parameters of Carbidopa for the dose proportionality

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 39)			
	Treatment A (35 mg)	Treatment B (52.5 mg)	Treatment C (70 mg)	Treatment D (87.5 mg)
C_{max} (ng/mL)	154.539 ± 68.6283 (44.41%)	226.091 ± 74.5566 (32.98%)	275.088 ± 88.8305 (32.29%)	352.127 ± 121.9104 (34.62%)
#T_{max} (hr)	2.500 (1.00 - 4.00)	2.500 (1.00 - 7.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.00)
AUC_{0-t} (hr*ng/mL)	825.510 ± 317.1635 (38.42%)	1254.431 ± 423.6325 (33.77 %)	1588.500 ± 575.8140 (36.25%)	2073.312 ± 702.4142 (33.88%)
$AUC_{0-\infty}$ (hr*ng/mL)	831.147 ± 318.1727 (38.28%)	1263.268 ± 425.7902 (33.71 %)	1600.377 ± 579.8454 (36.23%)	2089.468 ± 706.0206 (33.79%)
$t_{½}$ (hr)	3.684 ± 0.5868 (15.93%)	3.770 ± 0.3606 (9.56%)	3.712 ± 0.3791 (10.21%)	3.756 ± 0.4152 (11.06%)
K_{el} (1/hr)	0.193 ± 0.0363 (18.76%)	0.186 ± 0.0187 (10.05%)	0.189 ± 0.0183 (9.70%)	0.187 ± 0.0200 (10.73%)
AUC_%Extrap_ obs (%)	0.749 ± 0.4060 (54.19%)	0. 731 ± 0.2403 (32.89%)	0.755 ± 0.1743 (23.08%)	0.821 ± 0.2693 (32.81%)

For T_{max}, median (min – max)

Source: Study Report IPX203-B16-06, Page 76, Table 32

Table 21. Pharmacokinetic parameters of Levodopa for the dose proportionality

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 39)			
	Treatment A (140 mg)	Treatment B (210 mg)	Treatment C (280 mg)	Treatment D (350 mg)
C_{max} (ng/mL)	664.228 ± 180.9922 (27.25%)	1082.458 ± 278.5233 (25.73%)	1312.182 ± 290.9092 (22.17%)	1757.309 ± 503.4004 (28.65%)
#T_{max} (hr)	2.500 (0.50 - 5.00)	2.500 (0.50 - 5.02)	3.000 (0.50 - 5.00)	2.500 (0.50 - 5.00)
AUC_{0-t} (hr*ng/mL)	3211.613 ± 55.2400 (20.40%)	5106.955 ± 989.4288 (19.37%)	6829.669 ± 1251.1643 (18.32%)	9364.931 ± 1547.5314 (16.52%)
$AUC_{0-\infty}$ (hr*ng/mL)	3263.490 ± 59.6983 (20.21%)	5188.386 ± 013.9887 (19.54%)	6948.185 ± 1275.9628 (18.36%)	9528.881 ± 1582.4031 (16.61%)
$t_{½}$ (hr)	1.668 ± 0.1629 (9.77%)	1.692 ± 0.3685 (21.78%)	1.731 ± 0.5015 (28.98%)	2.113 ± 0.6700 (31.70%)
K_{el} (1/hr)	0.420 ± 0.0444 (10.58%)	0.422 ± 0.0632 (14.99%)	0.419 ± 0.0684 (16.33%)	0.356 ± 0.0940 (26.44%)

Source: Study Report IPX203-B16-06, Page 76, Table 33

Dose proportionality of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for both CD and LD were assessed using a power model ($Y = \alpha*[Dose]^{\beta}$). The statistical model included terms for subject and dose. Values of β and its corresponding 90% CI were estimated and compared with the acceptance intervals. The Slope Acceptance Range of C_{max}, AUC_{0-t} and AUC_{0-inf}, Calculated slope and 90% confidence interval of Slope obtained from the analysis of ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for carbidopa and levodopa are presented in *Table 22* and *Table 23*, respectively.

Table 22. Statistical results for pharmacokinetic parameters of Carbidopa for dose proportionality

PK Parameters (Unit)	Slope Acceptance Range	Calculated Slope	90% Confidence Interval of Slope
C_{max} (ng/mL)	0.7565% - 1.2435%	0.9000	0.8214% - 0.9862%
AUC_{0-t} (hr*ng/mL)	0.7565% - 1.2435%	0.9967	0.9124% - 1.0888%
$AUC_{0-\infty}$ (hr*ng/mL)	0.7565% - 1.2435%	0.9974	0.9134% - 1.0891%

Source: Study Report IPX203-B16-06, Page 88, Table 39

Table 23. Statistical results for pharmacokinetic parameters of Levodopa for dose proportionality

PK Parameters (Unit)	Slope Acceptance Range	Calculated Slope	90% Confidence Interval of Slope
C_{max} (ng/mL)	0.7565% - 1.2435%	1.0335	0.9672% - 1.1045%
AUC_{0-t} (hr*ng/mL)	0.7565% - 1.2435%	1.1673	1.1224% - 1.2136%
$AUC_{0-\infty}$ (hr*ng/mL)	0.7565% - 1.2435%	1.1687	1.1239% - 1.2150%

Source: Study Report IPX203-B16-06, Page 87, Table 38

Reviewer's Comments:

PK data from IPX203-B16-06 demonstrated that carbidopa and levodopa exposures increase in dose proportional manner between 35-140 mg CD-LD and 87.5-350 CD-LD.

4.3.5 IPX203-B16-04

Effect of a standardized high-fat meal on the pharmacokinetics of IPX203 as well as characterization of the pharmacokinetics of IPX203 after sprinkling the capsule contents on applesauce as a representative soft food was conducted in IPX203-B16-04. This study was a

randomized, single-site, open-label, single-dose, 3-treatment, 3-period, crossover study in healthy, adult, human subjects. A total of 27 healthy, adult, human male subjects were enrolled in the study.

Subjects received Treatments A, Treatment B, or Treatment C with 240 mL of water in a randomized fashion after an overnight fast of at least 10 hours in each study period. All enrolled (27) subjects completed the study.

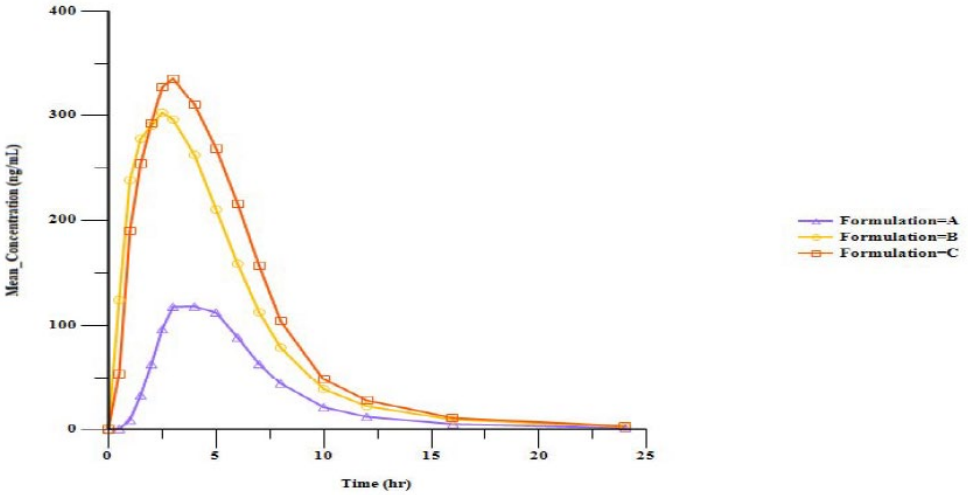
Treatment A − IPX203 Fed: One IPX203 capsule containing 87.5 – 350 mg CD-LD administered orally with 240 mL of water approximately 30 minutes after initiating a standardized high-fat, high-calorie breakfast.

Treatment B − IPX203 Sprinkled on Applesauce: Contents of one IPX203 capsule containing 87.5 – 350 mg CD-LD sprinkled on 1 tablespoon of applesauce and swallowed without chewing.

Treatment C − IPX203 Fasted: One IPX203 capsule containing 87.5 – 350 mg CD-LD IPX203 administered orally with 240 mL of water.

Linear plot of mean carbidopa plasma concentration – time profiles *Figure 9* and the mean carbidopa pharmacokinetic parameters estimated for Treatment A, Treatment B and Treatment C are presented in *Table 24*.

Figure 8. Linear plot of mean concentration vs. time for carbidopa



Source: Study Report IPX203-B16-04, Page 68, Figure 03

Table 24. Pharmacokinetic parameters of Carbidopa following Treatments A-C

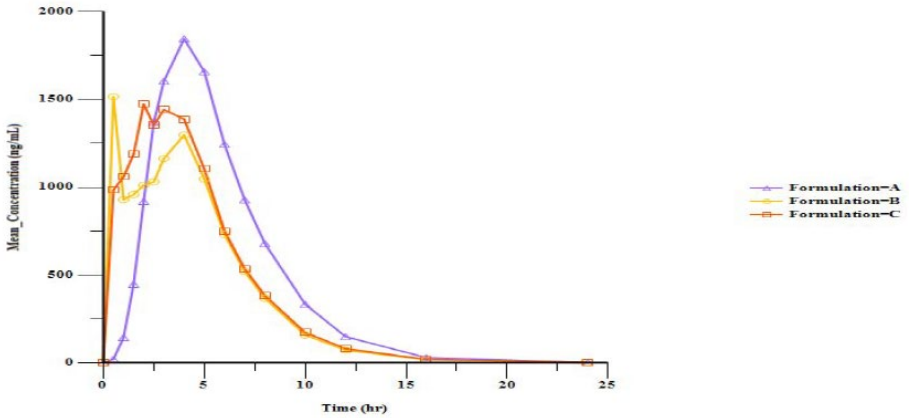
Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 27)		
	Treatment A	Treatment B	Treatment C
C_{max} (ng/mL)	140.767 ± 41.1239 (29.21%)	338.559 ± 91.7557 (27.10%)	403.573 ± 156.7192 (38.83%)
#t_{max} (hr)	4.000 (2.00 - 6.00)	2.500 (1.50 - 5.00)	3.000 (1.00 - 6.00)
AUC_{0-t} (hr*ng/mL)	751.026 ± 205.1475 (27.32%)	1909.196 ± 618.2405 (32.38%)	2174.983 ± 905.8102 (41.65%)
$AUC_{0-\infty}$ (hr*ng/mL)	758.932 ± 205.3838 (27.06%)	1923.482 ± 620.8102 (32.28%)	2191.336 ± 910.6846 (41.56%)
$t_{½}$ (hr)	3.861 ± 0.7780 (20.15%)	3.948 ± 0.6684 (16.93%)	3.903 ± 0.5606 (14.36%)
K_{el} (1/hr)	0.185 ± 0.0311 (16.77%)	0.181 ± 0.0317 (17.58%)	0.181 ± 0.0265 (14.63%)
AUC_%Extrap_obs (%)	1.091 ± 0.6127 (56.15%)	0.790 ± 0.3816 (48.29%)	0.786 ± 0.2262 (28.79%)

For T_{max}, Median (min – max),

Source: Study Report IPX203-B16-04, Page 66, Table 23

Linear plot of mean levodopa plasma concentration – time profiles *Figure 10* and the mean levodopa pharmacokinetic parameters estimated for Treatment A, Treatment B and Treatment C are presented in Table 25.

Figure 9. Linear plot of mean levodopa concentration vs. time following Treatments A-C



Source: Study Report IPX203-B16-04, Page 67, Figure 01

Table 25. Pharmacokinetic parameters of Levodopa following Treatments A-C

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 27)		
	Treatment A	Treatment B	Treatment C
C_{max} (ng/mL)	2185.564 ± 472.7236 (21.63%)	1634.170 ± 409.3129 (25.05%)	1826.947 ± 385.3425 (21.09%)
#t_{max} (hr)	4.000 (2.00 - 5.00)	0.500 (0.50 - 5.00)	2.000 (0.50 - 5.00)
AUC_{0-t} (hr*ng/mL)	10552.789 ± 1425.5710 (13.51%)	8330.925 ± 1965.0426 (23.59%)	9124.960 ± 2149.7628 (23.56%)
$AUC_{0-\infty}$ (hr*ng/mL)	10611.158 ± 1433.6441 (13.51%)	8371.116 ± 1969.8153 (23.53%)	9161.364 ± 2153.0025 (23.50%)
$t_{½}$ (hr)	1.786 ± 0.3135 (17.56%)	2.024 ± 0.3079 (15.21%)	1.988 ± 0.3000 (15.09%)
K_{el} (1/hr)	0.397 ± 0.0559 (14.07%)	0.350 ± 0.0517 (14.76%)	0.356 ± 0.0515 (14.47%)
AUC_%Extrap_obs (%)	0.548 ± 0.3488 (63.60%)	0.493 ± 0.3266 (66.23%)	0.409 ± 0.2109 (51.57%)

For $T_{max,}$ Median (min – max)

Source: Study Report IPX203-B16-04, Page 66, Table 22

The geometric least squares mean of Treatment (A and B) and treatment (C), its ratio (A/C)% and (B/C)%), intra-subject variability, 90% confidence intervals the Geometric least square mean ratio (A/C and B/C) and power obtained from the analysis of ln transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ are summarized for carbidopa (*Table 26*) and levodopa (*Table 27*).

Table 26. Statistical results for Pharmacokinetics of Carbidopa

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 27)			ISCV (%)	90% CI	Power (%)
	Treatment A	Treatment C	(A/C) (%)			
C_{max} (ng/mL)	135.800	376.056	36.11	24.56	32.34% - 40.33%	95.35
AUC_{0-t} (hr*ng/mL)	724.914	1992.757	36.38	23.85	32.68% - 40.50%	96.18
$AUC_{0-\infty}$ (hr*ng/mL)	732.926	2008.543	36.49	23.75	32.79% - 40.61%	96.29

For Treatment B vs. Treatment C:

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 27)			ISCV (%)	90% CI	Power (%)
	Treatment B	Treatment C	(B/C) (%)			
C_{max} (ng/mL)	326.725	376.056	86.88	24.56	77.80% - 97.02%	95.35
AUC_{0-t} (hr*ng/mL)	1811.573	1992.757	90.91	23.85	81.66% - 101.20%	96.18
$AUC_{0-\infty}$ (hr*ng/mL)	1826.015	2008.543	90.91	23.75	81.70% - 101.16%	96.29

Source: Study Report IPX203-B16-04, Page 71, Table 26

Table 27. Statistical results for pharmacokinetic parameters of Levodopa

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 27)			ISCV (%)	90% CI	Power (%)
	Treatment A	Treatment C	(A/C) (%)			
C_{max} (ng/mL)	2136.723	1792.049	119.23	16.93	110.43% - 128.74%	99.88
AUC_{0-t} (hr*ng/mL)	10455.621	8873.210	117.83	12.04	111.56% - 124.46%	100.00
$AUC_{0-\infty}$ (hr*ng/mL)	10513.344	8909.675	118.00	11.95	111.76% - 124.58%	100.00

For Treatment B vs. Treatment C:

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 27)			ISCV (%)	90% CI	Power (%)
	Treatment B	Treatment C	(B/C) (%)			
C_{max} (ng/mL)	1586.094	1792.049	88.51	16.93	81.97% - 95.56%	99.88
AUC_{0-t} (hr*ng/mL)	8112.302	8873.210	91.42	12.04	86.56% - 96.57%	100.00
$AUC_{0-\infty}$ (hr*ng/mL)	8152.544	8909.675	91.50	11.95	86.67% - 96.61%	100.00

Source: Study Report IPX203-B16-04, Page 70, Table 24

Reviewer's Comments

When IPX203 is administered with a standard high fat high calorie breakfast, carbidopa exposures (Cmax and AUC) decreased by 64% compared to fasted state. When IPX203 is administered with a standard high fat, high calorie breakfast, levodopa exposures, Cmax and AUC, were increased by 19% and 18%, respectively, compared fasted state. Sprinkling the IPX066 capsule contents on applesauce did not affect the overall LD concentration time profile compared to the intact capsule under fasted condition.

Following oral administration of IPX203 capsules contents sprinkling on the applesauce to healthy subjects, the geometric mean ratios of carbidopa Cmax and AUC were 87% and 91%, respectively, compared to fasted state. The 90% CI for Cmax was 78%-97%, which was not contained in the standard bioequivalence limits of 80%-125%. Sprinkling the IPX203 capsule contents on applesauce did not affect the LD concentration time profile compared to the intact capsule under fasted condition

4.3.6 IPX203-B16-06 (Bioequivalence)

The study IPX203-B16-06 was designed as a single-site, open-label, single-dose, five-treatment, five period, crossover bioequivalence (Treatments A and E) and dose proportionality (Treatments A through D) study in healthy adult human male and female subjects. In the first two periods; the subjects received either Treatment A or Treatment E of the same strength manufactured at two different sites in a randomized fashion during the first 2 periods.

Treatment A: IPX203 ER CD-LD 35 mg/140 were manufactured at Amneal Pharmaceuticals 50 Horseblock Road, Brookhaven, NY 11719, USA.

Treatment E: IPX203 ER CD-LD 35 mg/140 mg were manufactured at (b) (4) .

Subjects received Treatments A and E orally with 240 mL of water at room temperature after an overnight fast of at least 10 hours in respective periods. A total of forty (40) subjects were enrolled in the study. All forty (40) subjects completed Treatment A and Treatment E.

The plasma carbidopa concentration- time profiles, pharmacokinetic parameters of carbidopa, and statistical analysis results for bioequivalence following Treatments A and E are presented in Figure 11, *Table 28*, and *Table 29*, respectively.

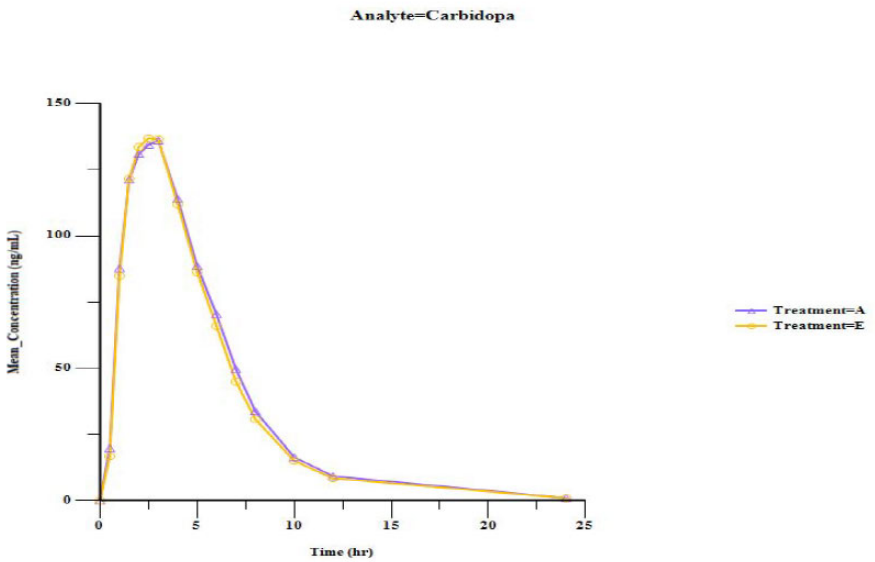


Figure 10. Linear plot of mean carbidopa concentration vs. time (Treatment A and Treatment E)
Source: Study Report IPX203-B16-06, Page 79, Figure 03

Table 28. Pharmacokinetic parameters of Carbidopa following Treatments A and E

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 40)	
	Treatment (A) (35 mg)	Treatment (E) (35 mg)
C_{max} (ng/mL)	153.484 ± 68.0712 (44.35%)	154.918 ± 63.0400 (40.69%)
#T_{max} (hr)	2.500 (1.00 - 4.00)	2.500 (1.00 - 5.00)
AUC_{0-t} (hr*ng/mL)	824.626 ± 313.1209 (37.97%)	797.201 ± 313.7050 (39.35%)
$AUC_{0-\infty}$ (hr*ng/mL)	830.253 ± 314.1179 (37.83%)	803.160 ± 314.2826 (39.13%)
$t_{½}$ (hr)	3.680 ± 0.5797 (15.75%)	3.679 ± 0.6076 (16.51%)
K_{el} (1/hr)	0.193 ± 0.0358 (18.51%)	0.195 ± 0.0440 (22.56%)
AUC_%Extrap_obs (%)	0.747 ± 0.4010 (53.69%)	0.913 ± 0.7933 (86.90%)

#For $T_{max,}$ median (min – max)

Source: Study Report IPX203-B16-06, Page 75, Table 30

Table 29. Statistical analysis results of Carbidopa.

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 40)			Intra subject %CV	90% Confidence Interval	Power (%)
	Treatment (A) (35 mg)	Treatment (E) (35 mg)	(A/E) (%)			
C_{max} (ng/mL)	142.080	141.310	100.55	23.04	92.28% - 109.55%	99.49
AUC_{0-t} (hr*ng/mL)	767.395	727.619	105.47	21.19	97.45% - 114.14%	99.81
$AUC_{0-\infty}$ (hr*ng/mL)	773.176	734.346	105.29	20.95	97.37% - 113.84%	99.83

Source: Study Report IPX203-B16-06, Page 85, Table 34

The plasma levodopa concentration- time profiles, pharmacokinetic parameters, and statistical analysis results of levodopa following Treatments A and E are presented in Figure 12, *Table 30*, and Table 31., respectively.

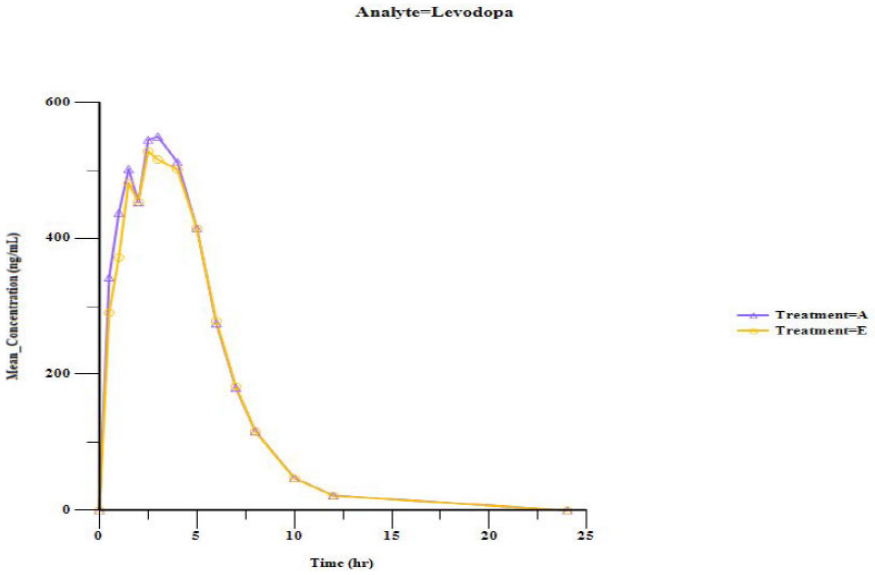


Figure 11. Linear plot of mean levodopa concentration vs. time following Treatment A and Treatment E
Source: Study Report IPX203-B16-06, Page 79, Figure 01

Table 30. Pharmacokinetic parameters of Levodopa following Treatment A and Treatment E

Pharmacokinetic Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 40)	
	Treatment (A) (140 mg)	Treatment (E) (140 mg)
C_{max} (ng/mL)	664.606 ± 178.6727 (26.88%)	636.216 ± 135.2782 (21.26%)
#T_{max} (hr)	2.500 (0.50 - 5.00)	2.750 (0.50 - 5.00)
AUC_{0-t} (hr*ng/mL)	3225.528 ± 652.7447 (20.24%)	3115.380 ± 579.6287 (18.61%)
$AUC_{0-\infty}$ (hr*ng/mL)	3277.899 ± 657.5317 (20.06%)	3166.765 ± 596.7841 (18.85%)
$t_{½}$ (hr)	1.665 ± 0.1621 (9.74%)	1.640 ± 0.1772 (10.80%)
K_{el} (1/hr)	0.420 ± 0.0441 (10.49%)	0.427 ± 0.0448 (10.50%)
AUC_%Extrap_obs (%)	1.630 ± 0.6637 (40.72%)	1.580 ± 0.5852 (37.04%)

#For t_{max}, median (min – max)

Source: Study Report IPX203-B16-06, Page 75, Table 31

Table 31. Statistical analysis results of Levodopa

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 40)			Intra subject %CV	90% Confidence Interval	Power (%)
	Treatment (A) (140 mg)	Treatment (E) (140 mg)	(A/E) (%)			
C_{max} (ng/mL)	641.571	622.042	103.14	12.72	98.33% - 108.19%	100.00
AUC_{0-t} (hr*ng/mL)	3159.217	3062.886	103.15	7.92	100.12% - 106.27%	100.00
$AUC_{0-\infty}$ (hr*ng/mL)	3211.629	3112.110	103.20	7.98	100.14% - 106.35%	100.00

Source: Study Report IPX203-B16-06, Page 86, Table 36

Reviewer's Comments

- *The office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspection for the pivotal bioequivalence study, IPX203-B16-06. The OSIS have conducted a remote regulatory assessment (RRA) of the analytical portion of the study and concluded that data from the audited study is reliable.*[2]
- *The geometric mean ratios of Cmax and AUC0-∞ of carbidopa following Treatment A are 100 and 105, respectively., compared to Treatment E. The 90% CIs of carbidopa PK parameters (Cmax and AUC0-∞) were contained within the BE limits of 80 to 125% range. The geometric mean ratios of Cmax and AUC0-∞ of levodopa following Treatment A is compared to Treatment E. The 90% CIs of levodopa PK parameters (Cmax and AUC0-∞) were contained within BE of 80 to 125% range. Therefore, the clinical trial formulation manufactured at* (b) (4) *and the to be marketed formulations manufactured at Amneal Pharmaceuticals 50 Horseblock Road, Brookhaven, NY 11719, USA are bioequivalent in terms of carbidopa and levodopa exposures.*

[2] Bioequivalence Establishment Inspection Report Review. DARRTS dated 02/22/2023

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/s/

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