# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 217186Orig1s000

# CLINICAL REVIEW(S)

# CLINICAL REVIEW

| | |
|---|---|
| **Application Type** | NDA Class 2 Resubmission |
| **Application Number(s)** | 217186 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | February 7, 2024 |
| **Received Date(s)** | February 7, 2024 |
| **PDUFA Goal Date** | August 7, 2024 |
| **Division/Office** | Division of Neurology 1 |
| **Reviewer Name(s)** | Elizabeth Haberfeld, MD |
| **Review Completion Date** | August 6, 2024 |
| **Established/Proper Name** | Carbidopa and levodopa (IPX203) |
| **(Proposed) Trade Name** | Crexont (carbidopa and levodopa) |
| **Applicant** | Impax Laboratories, LLC |
| **Dosage Form(s)** | Oral extended-release capsule |
| **Applicant Proposed Dosing Regimen(s)** | Flexible dosing. Starting dose is 35 mg/140 mg taken orally BID, increase gradually as needed, maximum daily dose is (b) (4) taken as divided doses (b) (4). |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. |
| **Recommended Dosing Regimen(s)** | Starting dose is 35 mg/140 mg taken orally BID, increase gradually as needed, maximum daily dose is 525 mg/2100 mg taken as divided doses TID to QID. |

**Table of Contents**

**Table of Tables**

## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AR | adverse reaction |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CDER | Center for Drug Evaluation and Research |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |

| | |
|---|---|
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Impax (the Applicant) resubmitted the 505(b)(2) new drug application (NDA) for IPX203 (Crexont-proposed) following a Complete Response Action from FDA. The deficiencies cited in the Complete Response Letter (CRL) included an inadequate scientific bridge based on the pharmacokinetic (PK) exposure between IPX203 and Sinemet or Rytary at the highest proposed dosage regimen of IPX203. Because the exposure of carbidopa in IPX203 is substantially higher than that from Sinemet or Rytary, it was not possible to rely on findings of safety for Sinemet or to cross-reference Rytary for safety for approval of IPX203. The Applicant established a bridge for the levodopa component of IPX203 to Sinemet and Rytary based on PK exposure.

The long-term safety database was insufficient to support the chronic safety of IPX203 in the absence of a bridge to Sinemet or Rytary, as there were only 67 subjects with a 12-month exposure to IPX203 when examined by modal daily dose and no subjects who had been exposed to IPX203 at the highest proposed dose regimen ( (b) (4) daily) for 12 months or more. In addition, because the Applicant was unable to rely on Sinemet or Rytary for safety, it was necessary to conduct a QT study to assess the potential effects of IPX203 on QTc, per ICH E14 section 1.3.

IXP203 is an extended-release formulation consisting of a mixture of immediate-release granules containing CD/LD and extended-release beads containing levodopa, inside an enteric-coated capsule. Each capsule consists of immediate-release granules (100% of the carbidopa and 25% of the levodopa) and extended-release beads (75% of the levodopa). The 1:4 ratio of carbidopa to levodopa in IPX203 is similar to that in other carbidopa-levodopa products. It is intended for the treatment of symptoms of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. IPX203 capsules are administered orally up to (b) (4) times daily. The Applicant submitted proposed dosage strengths of 35/240 mg, 52.5/210 mg, 70/280 mg and 87.5/350 mg and a maximum recommended daily dose of (b) (4).

Oral immediate release CD and LD have been marketed in the United States as tablets (Sinemet) for the treatment of PD and parkinsonism since 1974. There are several marketed immediate-release, extended-release, and three component combination products that include CD, LD plus entacapone and CD and LD enteral suspension (Duopa).

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided data from Study B16-02, a single double-blind, placebo-controlled, superiority trial comparing IPX203 to IR CD/LD, in subjects with advanced Parkinson's disease

(PD) with motor fluctuations. There was a statistically significant change favoring IPX203 on the primary efficacy endpoint, the change from baseline to the end of the double-blind treatment period for good "on" time. Study B16-02 also showed a statistically significant change favoring IPX203 compared to IR CD/LD on key secondary endpoints of decreased "off" time and Patient Global Impression of Change (PGI-C) at the end of the double-blind treatment period.

The results of this single, large, multicenter, adequate and well-controlled trial demonstrated an effect on a distinct and prespecified, clinically meaningful endpoint (relatively less decrease from baseline in good "on" time without troublesome dyskinesia and decrease from baseline in "off" time), complemented by a statistically significant difference in a key secondary patient-reported endpoint (the PGI-C), establishing internal consistency across results.

Additionally, the mechanism of action of carbidopa/levodopa is well-understood and well-established.

Detailed information regarding the review of efficacy can be found in the Clinical and Biometrics reviews of the original NDA.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Integrated Assessment**

The following is excerpted in part from the original NDA review.

Effectiveness of IPX203 was evaluated in a single, adequate, and well-controlled study, Study B16-02, which was a randomized, double-blind, flexible-dose, active-controlled study comparing treatment with IPX203 to IR CD/LD (immediate-release carbidopa/levodopa) in subjects with moderate to advanced PD with motor fluctuations. Long-term safety information from subjects treated with IPX203 was provided by open-label extension Study B16-03.

The primary efficacy endpoint in Study B16-02 was the change from baseline/Week 4 to end of treatment/Visit 7 (i.e., week 13 of the double-blind treatment period) in hours of good "on" time (i.e., "on" time without dyskinesia + "on" time with non-troublesome dyskinesia) assessed by the PD diary. The first key secondary endpoint was the change from baseline in hours of "off" during that same double-blind study period, also assessed by the PD diary. The second key secondary endpoint was the change in PGI-C score at end of treatment/Visit 7. The third and fourth key secondary endpoints were the change from baseline to Visit 7/ET of the double-blind treatment period on the MDS-UPDRS Part II (motor aspects of experiences of daily living) score and on the summed MDS-UPDRS Parts II + III (motor aspects of experiences of daily living + motor examination) scores.

The results for the primary endpoint (change from baseline in mean good "on" time) showed a statistically significant difference in favor of IPX203, with a least square mean difference of -0.53 hours or 31.8 minutes (p=0.0194) of good "on" time. For the primary endpoint, the difference was expressed as less decrease in good "on" time from baseline compared to IR CD/LD. The result of the first key secondary endpoint [change in "off" time in hours from baseline (Visit 4) to end of treatment (Visit 7/ET)] showed a statistically significant difference in favor of IPX203, with a least square mean difference of -0.48 hours or 28 minutes (p=0.025), indicating less increase in "off" time from baseline to Visit 7/ET. The result of the second key secondary endpoint (change in PGI-C score at Visit 7/ET) showed a statistically significant difference in "much improved" or "very much improved" PGI-C scores favoring IPX203 by 10% (p=0.0015) compared to IR CD/LD.

"On time without troublesome dyskinesia" is when subjects experience improvement in the hypokinetic symptoms of PD (bradykinesia, rigidity, +/- tremor primarily) unaccompanied by a disabling increase in the hyperkinetic side effects of levodopa supplementation therapy. Not all dyskinesia is disabling; therefore, the primary endpoint measure focuses on an improvement in the combination of "on" time without dyskinesia and "on" time with non-disabling / non-troublesome dyskinesia. An increase in good "on" time implies an accompanying decrease in

the inverse measure, "off" time, as seen here, and/or a decrease in troublesome dyskinesia, which is considered a clinically meaningful endpoint. Treatment effects for the primary and first key secondary endpoint moving in opposite directions provides additional confidence in the primary endpoint results. These results were overall modestly effective. The efficacy results were further supported by the second key secondary endpoint, the PGI-C, which likewise moved modestly (10%) in the direction of greater improvement with IPX203 treatment compared to IR CD/LD. Demographic subgroup analyses suggested that the majority of these effects occurred in subjects aged under 65 years and with age of disease onset under 65 years. Because the pivotal study was not powered to detect that difference, a definitive statement to that effect is not possible.

In pharmacokinetic analyses, the Applicant established an acceptable bridge to the cross-referenced and listed drugs Rytary and Sinemet only for the levodopa component of IPX203. Because the carbidopa exposures at maximal doses for IPX203 were substantially higher than those for Sinemet or Rytary, the Applicant failed to establish a scientific bridge to these drugs and could not rely on the safety findings for Sinemet or Rytary.

Therefore, the safety of IPX203 was evaluated primarily on the results of Study B16-02 and Study B16-03. Analysis of safety data in the original NDA submission demonstrated that the rates of serious adverse events in the double-blind treatment period of Study B16-02 were overall low although higher for the IPX203 group than for IR CD/LD (3.1% vs 1.6%). With respect to treatment emergent adverse events, compared to the IR CD/LD group, the IPX203 group reported more dyskinesia (2% vs 0.4%), more nausea (4.3% vs. 0.8%), more dizziness (2.3% vs 0.8%) and more anxiety (2.7% vs 0%) during the double-blind period of Study B16-02.

In the original NDA submission, the Applicant provided a safety database that was inadequate to support chronic dosing with IPX203. Based on the modal daily dose, there was an insufficient number of subjects with at least 12-month exposure at any single dose or at the proposed maximal daily dose of (b) (4) to support the safety of IPX203. In addition, because of the lack of a viable bridge to Sinemet or Rytary, there were insufficient QT/QTc data to support safety. FDA issued a Complete Response action based on these deficiencies.

The Applicant's resubmission adequately addressed these clinical deficiencies. A total of 179 subjects were exposed to IPX203 at any dose for at least 12 months. The data submitted in support of the maximum dosage requested were insufficient to support the maximum dosage requested ( (b) (4) LD); there were 11 subjects in who took this dose for at least 12 months during Studies B16-02 and B16-03. The exposure data, however, support a maximum daily dose of 525 mg CD / 2100 mg LD. A total of 32 subjects received IPX203 at or above this dose for at least 12 months, 41 subjects received this dose for at least 9 months, and 43 subjects received this dose for at least 6 months.

Safety findings for these subjects did not differ substantially from those for the pooled safety population. These figures constituted an acceptable proportion of subjects to support the safety conclusions, in the context of IPX203 not being a new molecular entity. Supplemental statistical analyses of the mITT population excluding subjects at modal daily doses higher than 2100 mg LD did not alter the efficacy findings. The QT-IRT team determined that the thorough QT study the Applicant included in the resubmission is adequate.

The clinical team recommends an APPROVAL action based on the revised data contained in the resubmission, with a maximum recommended dose of 525 mg / 2100 mg per day in divided doses.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Parkinson's disease (PD) is a neurodegenerative disorder resulting from a progressive loss of dopaminergic neurons in the brain.<br>• The cardinal motor symptoms of PD include bradykinesia (slowness of movement), rigidity (stiffness), tremor, and postural instability.<br>• Patients with advanced PD experience episodes of immobility as the effective period for each dose of oral carbidopa and levodopa (CD/LD) wanes. Off times are episodes where the return of PD symptoms when the effects of medications diminish causing difficulty or disability in daily functioning.<br>• Dyskinesias are involuntary choreiform movements that if severe enough can interfere with daily function. Patients with advanced PD taking LD will at some point in their disease begin to experience dyskinesia at the time when LD reaches its' peak effects. | Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases world-wide. Recent estimates place the prevalence of PD at approximately 1 million patients in the U.S. As PD progresses, patients experience increasing disability from motor complications such as wearing off and dyskinesia. Additional late non-motor complications such as cognitive impairment and psychosis may cause profound disability and limit treatment with approved medications. |
| **Current Treatment Options** | • There is no treatment shown to slow or halt the progression of PD.<br>• The available treatments primarily act through increasing dopamine or its effects in the brain. The available treatment options include carbidopa-levodopa formulations (immediate and extended-release tablets and | There are no treatments that slow the progression of PD. The available medications effectively treat the motor symptoms of PD in early to middle stages of disease. As PD |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | capsules), dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase type -B inhibitors. Other classes of medications that treat the motor symptoms of PD are anticholinergic drugs, amantadine and adenosine receptor antagonists.<br>• Special formulations including CD/LD continuously delivered enteral suspension and orally inhaled levodopa are also available.<br>• Intermittently used medication for the treatment of OFF episodes such as apomorphine sublingual film or subcutaneous injection, orally inhaled CD/LD<br>• Surgical treatment for PD includes traditional lesioning surgery, MRI guided focused ultrasound and deep brain stimulation. | progresses, patients' response to medication is progressively limited by motor and non-motor complications reducing the ability to tolerate dopaminergic drugs.<br><br>In early to mid-stages of disease, after starting treatment with CD/LD patients may look and feel almost normal without experiencing dyskinesia. Advanced PD patients often must tolerate some dyskinesia from doses of CD/LD that provide relief from the motor symptoms of PD. Eventually, progressively lower doses of CD/LD evoke more severe dyskinesia.<br><br>Surgical treatments for PD are not appropriate for all patients with PD and each surgical treatment comes with some risks. The available surgical treatments have not been shown to delay the progression of PD. |
| **Benefit** | • Study B16-02 was a single, pivotal, randomized, double-blind, double-dummy, active-controlled, efficacy and safety study.<br>• The results for the primary endpoint (change from baseline in mean good "on" time), showed a statistically significant difference in favor of IPX203 compared to immediate release CD/LD (IR CD/LD). Both treatment groups showed a decline in good "on" time from baseline (Visit 4) to end of treatment (Visit 7); however, good "on" time decreased less in the IPX203 | The mechanism of action for CD and LD in treating PD is well-established and well-understood.<br><br>The results of this single, large, multicenter, adequate and well-controlled trial demonstrate that treatment with IPX203 was |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | treatment group compared to the IR CD/LD group. The difference in hours between the least square mean change from baseline in good "on" time between the IPX203 and IR CD/LD treatment groups from beginning (Visit 4) to end (Visit 7 or ET) of the double-blind treatment period was 0.53 hours or 31.8 minutes, a statistically significant result (p=0.0194).<br>• The results for the first key secondary endpoint [change in "off" time in hours from baseline (Visit 4) to end of treatment (Visit 7 /ET)] showed less increase in off time in the IPX203-treated group than in the IR CD/LD-treated group over the same double-blind treatment period. The least square mean difference between the IPX203-treated group and the IR CD/LD-treated group was -0.48 hours or -28 minutes, a statistically significant result (p=0.025).<br>• The difference of 31.8 minutes in the primary endpoint favoring IPX203 was modestly clinically meaningful yet supported by an also modest but statistically significant 10% (p=0.0015) difference in "much improved" or "very much improved" PGI-C scores favoring IPX203.<br>• Additional statistical analyses performed by the statistical reviewer on the mITT population demonstrated no change to the positive efficacy findings when the population was reanalyzed without the subjects who had taken doses higher than 525 mg / 2100 mg, the highest dose supported by the safety data. | effective in lessening a decline in good "on" time. This result represents a modestly clinically meaningful improvement of function in subjects with moderate to advanced PD with motor fluctuations.<br><br>The results of the single study plus confirmatory evidence of the well-understood mechanism of action of CD/LD and results of a trial of CD/LD-ER in a similar population are adequate to establish effectiveness of IPX203 in the treatment of advanced PD. |
| **Risk and Risk Management** | • The carbidopa exposure from IPX203 is substantially higher than that from Rytary or Sinemet, the listed drugs. The exposure to carbidopa from IPX203 at the maximal dose proposed was 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD).<br>• There were 5 deaths in subjects exposed to study drug, all during the | The Applicant demonstrated an acceptable bridge for safety to the levodopa component of IPX203 based on PK exposure at the maximum doses. The Applicant failed to establish a scientific bridge from IPX203 to |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | open-label safety study (Study B16-03). The causes were diverse, and the rate was not demonstrably higher than that for the moderate to advanced PD population at large. None of the deaths were clearly causally related to the study drug.<br>• Overall, more serious adverse events and more treatment emergent adverse events occurred with IPX203 than with IR CD/LD, although both rates were low. The serious adverse event rate was 3.1% in the IPX203 group and 1.6% in the IR CD/LD group during the double-blind period of Study B16-02. The treatment emergent adverse event rate in the IPX203 group was 49% vs the IR CD/LD group's 28% during the double-blind period. Compared to the IR CD/LD group, the IPX203 group reported more dyskinesia (2% vs 0.4%), more nausea (4.3% vs. 0.8%), more dizziness (2.3% vs 0.8%) and more anxiety (2.7% vs 0%) during the double-blind period of Study B16-02.<br>• The proposed maximum daily dosage of [redacted] (b) (4) is not actually achievable using any combination of dosages the Applicant proposes to manufacture. Therefore, the Applicant revised the maximum dose requested for labeling to [redacted] (b) (4) mg.<br>• Based on the modal daily dose, the resubmission contained a sufficient number of subjects with at least 12-month exposure at any dose (n=179); to support the safety of IPX203 for the proposed indication.<br>• There was an acceptable number of subjects (32) who received modal daily doses of 525 mg/2100 mg or higher for at least 12 months, supporting a maximum dose of 525 mg/2100 mg. This number was deemed acceptable to support long term safety findings, in the context of IPX203 not being a new molecular entity. | Sinemet or Rytary for the carbidopa component of IPX203. Therefore, the Applicant cannot rely on prior findings of safety from the listed drugs, Sinemet and Rytary. In the original submission, there was inadequate safety data to support the long-term safety of IPX203.<br><br>In the resubmission, the Applicant provided adequate exposure data to support a maximal daily dose of 525 mg/2100 mg. There were insufficient data to support the proposed maximal daily dose of [redacted] (b) (4) mg.<br><br>A thorough QT study was included in the resubmission, which was reviewed by the QT-IRT. The QT-IRT noted that clinically significant QTc interval prolongation was not observed and recommended approval for IPX203.<br><br>No unanticipated safety findings were identified during the clinical studies.<br><br>The known serious risks associated with IPX203 can be mitigated by the following:<br><br>• WARNINGS and PRECAUTIONS in labeling to describe hallucinations/psychosis and |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • In addition, a total of 41 subjects received the 525 mg/2100 mg dose for at least 9 months, and 43 subjects received this dose for at least 6 months. There were 11 subjects who received a modal daily dose of ≥ (b) (4) mg for ≥ 12 months, which is inadequate to support the maximum proposed dose in the labeling.<br>• There were no discordant safety findings in the subjects who took modal daily doses of ≥525 mg/2100 mg for at least 12 months compared to the pooled safety population.<br>• The QT-IRT team determined that the QT/QTc study the applicant supplied in the resubmission is adequate for approval. | dyskinesias, and<br><br>• Warnings for somnolence, impulse control compulsive behaviors, depression and suicidality, withdrawal-emergent hyperpyrexia and confusion, dyskinesia, cardiovascular ischemic events, and glaucoma should be included as they have been reported with other carbidopa/ levodopa products.<br><br>Additionally, the labeling should also include a dosage and administration statement that IPX203 should not be taken with alcohol.<br><br>The recommendation from the clinical team is for **APPROVAL for** NDA 217186 IPX203, with a maximum recommended daily dose of 525 mg / 2100 mg. |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Parkinson's disease (PD) is a neurodegenerative disorder resulting from a progressive loss of dopaminergic neurons in the brain, most notably in the substantia nigra, pars compacta. The core motor symptoms are bradykinesia, rigidity, rest tremor, and in moderate to advanced stages of PD, postural instability. A common non-motor prodrome, often noted in retrospect once the motor signs have appeared, may include REM sleep disturbance, restless legs, constipation, and sometimes olfactory deficit, that can precede the appearance of motor signs by years or decades, implying that the disease process and loss of striatal neurons has progressed significantly by the time motor signs are evident. The prevalence of PD is increasing and currently, it is estimated that approximately 1 million individuals in the U.S. have PD (Marras et al, 2018). Typically, within a few years after onset of motor signs, patients experience disability that requires symptomatic treatment. Approximately five to seven years after the appearance of motor signs, patients on levodopa treatment may begin to experience motor complications (motor fluctuations and dyskinesia) and many patients with Parkinson's disease will eventually develop some or all of the late non-motor complications (hallucinations, hypotension and cognitive loss), further increasing disability. Readers are referred to the original NDA review for a more detailed discussion of PD.

## 2.2. Analysis of Current Treatment Options

There is no treatment shown to slow or halt the progression of PD.

The available treatments primarily act through increasing dopamine or its effects in the brain. The available treatment options include CD/LD formulations (immediate and extended-release tablets and capsules), dopamine agonists, COMT inhibitors, monoamine oxidase type -B inhibitors. Other classes of medications that treat the motor symptoms of PD are anticholinergic drugs, amantadine, and adenosine receptor antagonists. Intermittently used medications for the treatment of "off" episodes include apomorphine sublingual film or subcutaneous injection. Special formulations, including CD/LD continuously delivered enteral suspension and orally inhaled levodopa, are also available. Surgical treatment for PD includes lesioning surgery in the basal ganglia, MRI guided focused ultrasound and deep brain stimulation.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Impax (the Applicant) resubmitted the 505(b)(2) NDA for IPX203 (Crexont-proposed) following a CR letter issued on June 30, 2023, from FDA. The deficiencies cited in the CR letter included the lack of a valid adequate scientific bridge between IPX203's carbidopa component and the proposed reference drugs Sinemet and Rytary; lack of an adequate safety database for long-term exposure; absence of safety data on a substantial proportion of subjects for 12 or more months at the highest dose proposed in labeling; and the necessity of a QT study in light of the inability to rely on Sinemet or cross-reference to Rytary for QT/QTc data.

There was a sufficient scientific bridge for the levodopa component of IPX203, therefore the Applicant is relying on aspects of FDA's findings for Sinemet immediate release oral tablets (NDA 17555), specifically the carcinogenicity and reproductive and developmental toxicity information for Sinemet.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

A Type A, End of Review Meeting was held between the FDA and representatives from Impax on October 4, 2023. The pre-meeting questions from Impax and the in-person meeting discussion involved requests for clarification or agreement on Impax's proposals to address the long-term safety data deficiencies and lack of QT/QTc data communicated in the FDA's CR letter. The meeting package for the Type A meeting contained a summary of a revised long-term safety calculation that brought the total exposed population from 67 people to 179 people. It also contained a request to evaluate the long-term exposure data by dividing the times exposed into quartiles, and to collapse all people exposed over the 2100 mg LD / day modal daily dose for ≥ 12 months into a single bin, which would then serve as the "substantial proportion of the population exposed for at least 12 months" subset for the maximum dose requested for labeling criterion. The Applicant also initially argued that a QT study was unnecessary and then suggested that one be done as a postmarketing requirement.

*Meeting Discussion:*
*The Agency noted that, based on the information provided in the meeting package, the Applicant's reanalysis of the long-term safety data using the FDA's definition of modal daily dose suggested that there were at least 100 patients exposed to IPX203 for at least 12 months, with the understanding that this reanalysis would be subject to review. The Agency further indicated that a reanalysis of all the data in the Integrated Summary of Safety (ISS) would not be required.*

*The Agency noted that the Applicant's request to use a modal dose range appeared reasonable to support long-term safety, but that it would not necessarily support labeling at the maximum dose proposed (* (b) (4) *daily). The Agency stated that this would be a matter of*

*review and might prompt sensitivity analyses of the primary efficacy endpoint at lower doses. The Agency requested that the Applicant's Resubmission should explain the discrepancy between the exposure numbers they cited in their April 2023 IR response (67 subjects with 12 month exposure by modal dose) vs in the Type A meeting package (179 subjects with 12 month exposure), and that they also include clear information on the number of subjects receiving the maximum dose. The Agency also proposed that the maximum dose proposed be amended to* (b) (4) *mg to reflect the maximum doses achievable with the proposed manufactured dosage strengths.*

*In discussions regarding the QT/QTc study, the Applicant initially maintained no study was necessary because of the bridge to Sinemet. Since no such bridge exists, they conceded, but proposed* (b) (4) (b) (4) *. The Agency noted that* (b) (4) *was unrealistic and instead requested a study comparing exposures of IPX203 maximum doses in fed and fasted states against Sinemet. Finally, the Agency agreed with the Applicant's subsequent proposal to conduct a TQT study with carbidopa alone, and recommended the Applicant submit a full TQT study protocol for review by the QT-IRT.*

The meeting concluded with agreement on the information needed to address the long-term safety data and QT/QTc data deficiencies, or clarification of how they could be addressed, with the understanding that the adequacy of information submitted by the Applicant after the NDA application and in the resubmission would be a matter of review. There were no unresolved questions posed by the Applicant.

### 3.3. Foreign Regulatory Actions and Marketing History

There are no foreign regulatory actions and no marketing history.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

No new information from clinical site inspections was submitted.

### 4.2. Product Quality

No Product Quality issues were identified in the original NDA review and no new information was submitted.

### 4.3. Clinical Microbiology

No new Clinical Microbiology information was submitted.

### 4.4. Nonclinical Pharmacology/Toxicology

No new Nonclinical Pharmacology/Toxicology information was submitted.

### 4.5. Clinical Pharmacology

No new Clinical Pharmacology information was submitted.

### 4.6. Devices and Companion Diagnostic Issues

There are no device or companion diagnostic issues. There are no consumer study reviews.

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

Table 1 shows the studies of IPX203 that contributed safety and exposure information in the original NDA. No new clinical studies were submitted in the Resubmission (apart from the QT study discussed in section 4.7 above).

**Table 1 Studies of IPX203 in NDA Resubmission**

| Analysis Set | Studies Included | Study Description | Treatment Duration | Treatment Groups (Number of Subjects) |
|---|---|---|---|---|
| Randomized Controlled Trial | IPX203-B16-02* | Randomized, double-blind, double-dummy, active-controlled, parallel-group, prospective, multicenter trial | 17 weeks (3-week, open-label IR CD-LD dose adjustment period, 4-week open-label conversion to IPX203, and 13-week double-blind treatment period) | IPX203 (N = 506 Randomized, 449 completed) |
| Open Label Extension Study | IPX203-B16-03* | Open-Label safety extension, multicenter study | 9 months | IPX203 (N=419 enrolled, 352 completed) |

| Analysis Set | Studies Included | Study Description | Treatment Duration | Treatment Groups (Number of Subjects) |
|---|---|---|---|---|
| Pooled exposure Population | IPX203-B16-02 and IPX203-B16-03 | | 52 weeks (17 weeks exposed to IPX203 in RCT plus 9 months in OLE) | N=179 |
| QT/QTc study | IPX203-102-23 | Three-way crossover QT/QTc study to evaluate the ECG effects of a supratherapeutic dose of carbidopa in healthy subjects. | 13 days (three separate 24 treatment days each separated by a 5-day washout period) | N=36 (6 cohorts of 6 subjects each, each randomized to a different one of six possible treatment sequences in the 3-way crossover design) |

*Studies IPX203-B16-02 and IPX203-B16-03 were completed prior to the original NDA submission, and the final CSRs submitted to the NDA 217186. No new safety concerns were identified in the resubmission from these studies. Study IPX203-102-23 was performed and submitted after the original NDA submission. No new safety concerns were identified in this study.

### 5.2. Review Strategy

Calculations for total number of subjects exposed for at least 12 months were based on the revised datasets the Applicant described in the Type A meeting package in October 2023, and submitted on March 4, 2024, in response to the Agency's March 1, 2024, information request (IR). Calculations for the total number of subjects exposed at doses at or above the highest doses requested for labeling were based on the revised datasets the Applicant submitted in March 2024 and the additional revised datasets the Applicant submitted on July 5, 2024, in response the Agency's IR from June 28, 2024.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

The NDA resubmission did not include new efficacy studies/data.

A comprehensive discussion of the efficacy analysis for IPX203-B16-02 is in the original clinical review of the NDA and is summarized in the Benefit/Risk Section above.

For the resubmission, the statistical reviewer for the original NDA, Dr. Minjeong Park, performed additional analyses assessing whether removing those subjects whose doses were above the 525 mg/2100 mg maximum dose threshold supported by the safety analysis, would change the efficacy results. These analyses are summarized in Tables 2-5 below.

**Table 2: Summary of Study Drug Exposure in the Double-Blind Period, Study B16-02**

| Characteristic statistic | Randomized analysis set | | mITT analysis set | |
|---|---|---|---|---|
| Average Daily Dose of Levodopa (mg) | IPX203 (N=256) n (%) | IR CD-LD (N=250) n (%) | IPX203 (N=249) n (%) | IR CD-LD (N=246) n (%) |
| < 400 | 0 | 0 | 0 | 0 |
| 400 - < 800 | 29 (11.3) | 115 (46.0) | 29 (11.6) | 112 (45.5) |
| 800 - < 1200 | 50 (19.5) | 91 (36.4) | 48 (19.3) | 91 (37.0) |
| 1200 - < 1600 | 57 (22.3) | 24 (9.6) | 55 (22.1) | 23 (9.4) |
| 1600 - ≤2100 | 86 (33.6) | 20 (8.0) | 84 (33.7) | 20 (8.1) |
| > 2100 | 34 (13.3) | 0 | 33 (13.3) | 0 |

Source: Statistical reviewer

**Table 3: Primary Efficacy Endpoint: Change from Baseline to Visit7/ET in "Good on" Time during DBP by Randomized Treatment Group (mITT Analysis Set) – Excluding 33 subjects who received an average daily dose of LD >2100**

| | Randomized Treatment Group | |
|---|---|---|
| Statistics (hour) | IPX203 (N=249) | IR CD-LD (N=246) |
| LS Mean change (SE) at Week 12 from baseline | -0.4262 (0.1943) | -1.0383 (0.1834) |
| LS Mean difference (95% CI) (IPX203 vs. IR CD-LD) | 0.6122 (0.1466, 1.0777) | |
| p-value | 0.0101 | |

Abbreviations: DBP=double-blind treatment period, ET=early termination, mITT=modified intent-to-treat, IR CD-LD=immediate-release carbidopa-levodopa, N=number, SE=standard error, CI=confidence interval.
The LS mean, SE, LS Mean Difference, 95% CIs and p-values have been obtained from the MMRM with treatment, visit as fixed effects, pooled center as a random effect, baseline assessment as a continuous fixed covariate, and a treatment-by-visit interaction.
*Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt. adex.xpt*
* Wilcoxon rank sum test with LOCF in this subgroup showed a statistically significant difference between groups

**Table 4: Key Secondary Efficacy Endpoint 1: Change from Baseline to Visit7/ET in "Off" Time during DBP by Randomized Treatment Group (mITT Analysis Set) – After excluding 33 subjects who received an average daily dose of LD >2100**

| | Randomized Treatment Group | |
|---|---|---|
| Statistics (hour) | IPX203 (N=249) | IR CD-LD (N=246) |
| LS Mean change (SE) at Week 12 from baseline | 0.3891 (0.1852) | 0.8685 (0.1750) |
| LS Mean difference (95% CI) (IPX203 vs. IR CD-LD) | -0.4794 (-0.9244, -0.0344) | |
| p-value | 0.0348 | |

Abbreviations: DBP=double-blind treatment period, ET=early termination, mITT=modified intent-to-treat, IR CD-LD=immediate-release carbidopa-levodopa, N=number, SE=standard error, CI=confidence interval.
The LS mean, SE, LS Mean Difference, 95% CIs and p-values have been obtained from the MMRM with treatment, visit as fixed effects, pooled center as a random effect, baseline assessment as a continuous fixed covariate, and a treatment-by-visit interaction.
*Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt, adex.xpt*
* Wilcoxon rank sum test with LOCF in this subgroup showed a statistically significant difference between groups (p=0.0412)

**Table 5: Key Secondary Efficacy Endpoint 2: PGI-C Scores by Randomized Treatment Group (ITT Analysis Set) – After excluding 34 subjects who received an average daily dose of LD >2100**

| PGI-C Score | IPX203 (N=256) n (%) | IR CD-LD (N=250) n (%) |
|---|---|---|
| Much or very much improved | 65 (29.3) | 47 (18.8) |
| Percent difference (95% CI) | 10.5 (2.8, 18.2) | |
| p-value* | 0.0038 | |

Abbreviations: PGI-C=patient global impression of change, ITT= intent-to-treat, IR CD-LD=immediate carbidopa-levodopa, n=number.

* p-value from Cochran-Mantel-Haenszel test stratified by pooled center comparing the proportion of much or very much improved subjects between the treatment groups.

Note: For subjects with missing PGI-C, the data will be imputed as non-responders (i.e., not being "much improved" or "very much improved").
*Source: Statistical Reviewer Analysis; adqseff.xpt, adsl.xpt, adex.xpt*

Dr. Park concluded: *Results from additional efficacy analyses demonstrated that the impact of 33 subjects who received overdose of daily average levodopa (> 2100) in mITT analysis set did not change the conclusion from the primary analysis result.*

# 7. Review of Safety

## 7.1. Safety Review Approach

There were no new clinical study reports included in this NDA resubmission. The data reviewed consisted of re-tabulations of previously collected and reviewed data from Studies B16-02 and B16-03.

## 7.2. Review of the Safety Database

### 7.2.1. Overall Exposure

The Complete Response letter noted that the overall exposure database the Applicant submitted in response to the March 14, 2023, IR and March 17, 2023, IR clarification requesting a database describing exposures by modal daily dose, contained only 67 subjects who had received IPX203 at any dose for at least 12 months. Impax subsequently identified an error in

their own approach to the database. Specifically, Impax explained in their Type A briefing package (Supporting Information for Question 1, page 12), that they had erroneously included only those subjects who had taken exclusively their modal dose for at least 12 months, resulting in an undercount. In both the Type A Meeting package and in the datasets submitted with the resubmission, they corrected the exposure database to include all subjects who had been exposed to IPX203 at any modal daily dose for at least 12 months (179 people). These subjects exposed to IPX203 for at least 12 months were the subjects who had been randomized to IPX203 in the B16-02 study (4 week open-label conversion to IPX203 followed by 13-week double blind treatment period) and went on to complete the open-label extension study (9 months) for a total of 52-53 weeks exposure to IPX203. Although some subjects randomized to IPX203 during Study B16-02 had (when the IPX203 conversion period was included) continuous exposure for >53 weeks, inclusion of these exposure data did not change the overall number of subjects with 12-month exposure.

Among the subjects in the uncontrolled OLE study (Table 7), 352 completed the study, 179 of whom had received IPX203 during the controlled study's double-blind phase (Table 6).

**Table 6: Analysis Populations, Study B16-02**

| | Dose Adjustment Period | Conversion Period | Double-Blind Period | | |
|---|---|---|---|---|---|
| | IR CD/LD | IPX203 | IPX203 | IR CD/LD | All |
| **Enrolled Population** | 630 | 589 | 256 | 250 | 506 |
| **Randomized Population** | 506 | 506 | 256 | 250 | 506 |
| **Treated in DB Period** | 506 | 506 | 256 | 250 | 506 |
| **Intent-To-Treat Population** | 506 | 506 | 256 | 250 | 506 |
| **Modified Intent-to-Treat Population** | 495 | 495 | 249 | 246 | 495 |
| **Completers Population** | 446 | 446 | 220 | 226 | 446 |
| **Per-Protocol Population** | 313 | 313 | 155 | 158 | 313 |

Source: FDA Analysis

**Table 7: Analysis Populations, Study B16-03**

| | Dose Adjustment Period | Conversion Period | Double-Blind Period | | |
|---|---|---|---|---|---|
| | IR CD/LD | IPX203 | IPX203 | IR CD/LD | All |
| **Enrolled Population** | 419 | 419 | 206 | 213 | 419 |
| **Completers Population** | 352 | 352 | 179 | 173 | 352 |

Source: FDA Analysis

In the Type A meeting, the Agency informed the Applicant that it was not necessary to reanalyze the information in the ISS based on the modal dose exposure and therefore no new analyses of the AEs, laboratory findings or vital signs were submitted. The ISS in the original review contains a complete discussion of the safety findings based on the Applicant's prior submission of the controlled and open-label safety populations.

With respect to the Applicant's support of the highest dose requested for labeling ( (b) (4) mg LD), analysis of the modal daily dose data submitted in the original NDA submission

had identified only 14 subjects who took at least 2000 mg for 1 year, with no subjects exposed to IPX203 for at least 12 months at doses of 2400 mg or greater. In the Complete Response letter, the Agency informed the Applicant that they would need to provide long-term safety data "…with a substantial proportion of subjects using the highest dose intended for labeling based on modal dose." In the Type A Meeting package that included the revised count of 179 subjects exposed for at least 12 months, the Applicant presented summary of the distribution of modal doses for these subjects, as seen in Table 8 below.

**Table 8: Distribution of Modal Dose for Subjects with Exposure to IPX203 ≥ 12 months**

| Modal Dose of LD (mg) | Subjects with 12-month exposure to IPX203 (N = 179) n (%) |
|---|---|
| 560 | 14 (7.8%) |
| 700 | 7 (3.9%) |
| 770 | 1 (0.6%) |
| 840 | 20 (11.2%) |
| 980 | 4 (2.2%) |
| 1050 | 2 (1.1%) |
| 1120 | 11 (6.1%) |
| 1260 | 23 (12.8%) |
| 1400 | 7 (3.9%) |
| 1470 | 3 (1.7%) |
| 1540 | 9 (5.0%) |
| 1680 | 24 (13.4%) |
| 1820 | 4 (2.2%) |
| 1890 | 1 (0.6%) |
| 1960 | 3 (1.7%) |
| 2030 | 1 (0.6%) |
| 2100 | 15 (8.4%) |
| 2240 | 9 (5.0%) |
| 2380 | 11 (6.1%) |
| 2520 | 5 (2.8%) |
| 2660 | 1 (0.6%) |
| 2940 | 1 (0.6%) |
| 3360 | 2 (1.1%) |
| 5040 | 1 (0.6%) |

Source: from Table 1 Type A Briefing Package [NDA 217186, 1.2.2]

Based on the information included in the briefing package, there was still an insufficient number of subjects (n=21) exposed to the highest requested levodopa dose (b) (4) for at least 12 months. Therefore, the Applicant proposed evaluating the exposures in four quartiles using a "highest modal dose range," rather than a highest modal dose cutoff, placing all the subjects who had received LD dose of 2100 mg or more in a single bin for analysis. Using this approach, the Applicant identified 45 subjects who had taken doses of at least 2100 mg for at

least 12 months to support the "substantial proportion" requirement. The Agency noted during the meeting that this approach would be a matter of review.

The Applicant submitted the same exposure data from the Type A briefing package in the NDA resubmission. During review of the resubmission, the exposure data were analyzed with specific attention to the question of number of subjects with exposures to carbidopa of at least 525 mg carbidopa modal daily dose (i.e., 2100 mg levodopa) and their duration of exposure. This examination found that the Applicant had reported the most-frequently-taken dose for each subject as the modal daily dose. However, this method obscured some subjects who took one dose most frequently (modal dose), but at other times might have taken a dose above that dose. For example, a subject whose modal daily dose of carbidopa was 525 mg, may have taken higher doses during the study, but in the Applicant's calculation, that subject would only be counted as having been exposed to the 525 mg dose for the duration of time for which they took that modal dose.

The data tables provided in the resubmission did not permit calculation of the actual number of days that a subject took their modal dose, or of the number of days they took a modal daily dose of carbidopa ≥525 mg. The Agency therefore sent an IR requesting this information on June 28, 2024, and on July 5, 2024, received revised tables including columns showing the number of days each subject was on their modal daily dose, and the number of days any subject was on a modal daily dose of carbidopa ≥525 mg.

The Applicant again identified 45 subjects who had received a modal daily carbidopa dose ≥525 mg (= ≥2100 mg levodopa) for at least 12 months. However, Agency review of the datasets identified 32 subjects exposed at the modal daily dose of at least 525 mg CD / 2100 mg LD, for at least 12 months (Table 9). Only 11 subjects were exposed for at least 12 months at the maximum dose proposed in the labeling ( (b) (4) mg LD); which is insufficient to support the proposed maximum dose.

**Table 9: Resubmission Update, Duration of Exposure to IPX203 by Modal Daily Dose Category**

| | Number of subjects exposed | | |
|---|---|---|---|
| **Dose** | **≥ 6 months** | **≥ 9 months** | **≥ 12 months** |
| ≥ 2100 mg / 525 mg | 43 | 41 | 32 |
| ≥ (b) (4) | 25 | 21 | 11 |

A review of the adverse events for the subjects with ≥ 12 months exposure found no pattern of unusual adverse events compared to the adverse event rates observed in the rest of the safety population.

*Reviewer's comment:*
*The exposure data included in the NDA resubmission support the chronic safety of IPX203 at a maximal daily dose of 525 mg CD / 2100 mg LD, based on 32 subjects with 12-month exposure, 41 subjects with 9-month exposure, and 44 subjects with 6-month exposure at this modal dose.*

*In addition, there were no notable adverse events (or increase in adverse event rates) reported in the subjects who received this dose or greater for >6 months as compared to those treated for ≤6 months. There are inadequate exposure data to support the maximal dose proposed by the Applicant.*

#### 7.2.2. Relevant characteristics of the safety population

The safety demographics of the safety population in the resubmission were unchanged from that in the original NDA review as it is the same population.

#### 7.2.3. Adequacy of the safety database

The safety database included the data listed in the protocol and is well organized and searchable. The datasets are compliant with CDISC standards and analyzable. The Applicant's safety analyses are reproducible although with differences in interpretation. No new safety narratives were submitted with the resubmission.

### 7.3. Adequacy of Applicant's Clinical Safety Assessments

#### 7.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns about data integrity raised during the review of the original NDA or during the review of the resubmission. The issues with the ways that the Applicant counted subjects who were exposed at modal dose, and the way they calculated the total number of days each subject was exposed to a modal daily dose, are described above. These were addressed and corrected in the Applicant's reply to the June 28, 2024, IR, with further analyses of their data performed by the Agency as described above.

### 7.4. Safety Results

See the clinical review of the original NDA submission for a full description of the safety results of Studies B16-02 and B16-03. For a summary of the adverse reactions that occurred in at least 2% of subjects with Parkinson's disease who received Crexont and at a higher rate than subjects who received immediate-release carbidopa-levodopa, see Section 8.4.4 and Table 23 in the clinical review of the original NDA submission.

#### 7.4.1. QT

On February 7, 2024, the Applicant submitted clinical study IPX203-102-23, a three-way crossover thorough QT/QTc study to evaluate the electrocardiographic effects of a supratherapeutic (single) dose of carbidopa in healthy subjects. The highest dose evaluated was 400 mg which provided 1.1-fold therapeutic exposure. The study was reviewed by the QT-IRT team. There were no deaths or SAEs in the study. There were no AEs reported in Cardiac Disorders SOC in the study. Four subjects (11.4%) dropped out of the study. One of these was because of fever, another because of a positive urine drug screen. The remaining two dropped out because of abnormal ECGs; both occurred prior to receiving the first dose of IPX203. The

QT-IRT team recommended including the following language in the Crexont label:

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

Additional details of the study and review can be found in the QT Study Review from the Interdisciplinary Review Team for Cardiac Safety Studies, dated April 23, 2024.

## 7.5. Safety in the Postmarket Setting

### 7.5.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarket experience.

### 7.5.2. Expectations on Safety in the Postmarket Setting

The most commonly reported adverse events, nausea, dyskinesia, and dizziness, are likely to remain the most common events, with anxiety, constipation, headache, vomiting and insomnia occurring less commonly. Adverse events associated with levodopa are expected.

## 7.6. Additional Safety Issues From Other Disciplines

There are no outstanding safety concerns from other review disciplines.

## 7.7. Integrated Assessment of Safety

There were at least 100 subjects with PD treated for at least 12 months with doses of IPX203 that would be used clinically. There is a sufficient number of subjects with 12-month exposure to a total daily dose of at least 525 mg carbidopa / 2100 mg levodopa to support this as the maximum recommended daily dose in the product labeling.

The QT/QTc study adequately addresses the concerns about possible effects of Crexont on the QT. The QT-IRT team has recommended approval of this NDA.

No additional safety signals were identified during the review of the Resubmission Safety Update.

**Safety Conclusions:**

- The oral administration of the formulation of carbidopa/levodopa in IPX203 capsules is reasonably safe and can be monitored with routine pharmacovigilance.
- The increased bioavailability of carbidopa from IPX203 is predicted to significantly exceed that of the referenced products Sinemet and Rytary. However, the Applicant provided exposure data from clinical studies to support the long-term safety of IPX203 at a maximal dose of 525 mg CD / 2100 mg LD.
- There were no clinically significant QTc interval prolongations at exposures

corresponding to the maximum recommended dose of carbidopa in Crexont.

- The label should contain a statement that oral administration of Crexont with a high fat, high calorie meal may delay absorption by approximately 2 hours and overall absorption may be decreased, compared to absorption in a fasted state.
- Patients should be advised to swallow the pill whole and not to chew or crush it.
- The label should contain the same usual warnings that appear on the Sinemet label.
- Based on the review of the clinical information, the recommendation of the clinical review team is for **APPROVAL** of IPX-203 (Crexont).

# 8. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not deemed necessary.

# 9. Labeling Recommendations

## 9.1. Prescription Drug Labeling

The main concerns in labeling are the clinical team finds long-term safety data supports a maximum recommended total levodopa daily dose of 2100 mg/day which is less than the Applicant requested in the draft label. The long-term safety experience from the Applicant's clinical trials did not meet the requirement for 50 subjects treated for 12 months with a higher modal dose; however, the Division determined that 32 subjects with 12-month exposure would be adequate, given the long-experience with CD/LD and the number of subjects with 6- and 9-month exposure at ≥2100 mg of levodopa daily.

## 9.2. Nonprescription Drug Labeling

Not Applicable

# 10. Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary.

# 11. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments were considered necessary.

# 12. Appendices

## 12.1. References

Marras, C., Beck, J., Bower, J., Roberts, E., Ritz, B., Ross, G., ... Willis, A. (2018). Prevalence of Parkinson's disease across North America. NPJ Parkinson's disease, 4(1), 1-7.

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

ELIZABETH HABERFELD
08/06/2024 05:06:08 PM

NATALIE B GETZOFF
08/06/2024 05:07:48 PM

# CLINICAL REVIEW

| | |
|---|---|
| **Application Type** | NDA |
| **Application Number(s)** | 217186 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | 10/17/2022 |
| **Received Date(s)** | 10/17/2022 |
| **PDUFA Goal Date** | 06/30/2023 |
| **Division/Office** | DN1/OND |
| **Reviewer Name(s)** | Elizabeth Haberfeld, MD |
| **Review Completion Date** | 6/25/2020 |
| **Established/Proper Name** | IPX203 |
| **(Proposed) Trade Name** | Crexont |
| **Applicant** | Impax, Inc |
| **Dosage Form(s)** | Oral extended-release capsules |
| **Applicant Proposed Dosing Regimen(s)** | Variable dosing, interval approximately every (b) (4). Available strengths: carbidopa/levodopa ER: 35/140mg; (b) (4)/210mg; 70/280mg; 87.5/350mg. |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of Parkinson's disease, post-encephalitic parkinsonism and (b) (4) parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. |
| **Recommendation on Regulatory Action** | **Complete Response** |
| **Recommended Indication(s)/Population(s)** (if applicable) | N/A |

**Table of Contents**

**Table of Tables**

**Table of Figures**

## Glossary

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AR | adverse reaction |
| AST | aspartate aminotransferase |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CD | carbidopa |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COMT | catechol-O-methyltransferase |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DBS | deep brain stimulation |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ER | extended-release |
| ET | end of treatment |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GPi | globus pallidus interna |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IDSMC | Independent Data Safety Monitoring Committee |
| IND | Investigational New Drug Application |
| INR | international normalized ratio |
| IR | immediate-release |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |

| | |
|---|---|
| LD | levodopa |
| LDP | levodopa phosphate |
| LED | levodopa equivalent dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDS-UPDRS | The Movement Disorders Society-Unified Parkinson's Disease Rating Scale |
| mITT | modified intent to treat |
| MAOB-I | monoamine oxidase type-B inhibitor |
| MRgFUS | MR-guided focused ultrasound |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCP | Office of Clinical Pharmacology |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PD | Parkinson's disease |
| PGI-C | Patient Global Impression of Change |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| PV | pharmacovigilance |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SI | suicidal ideation |
| SOC | standard of care |
| STN | subthalamic nucleus |
| TEAE | treatment emergent adverse event |

# 1. Executive Summary

## 1.1. Product Introduction

Impax (the Applicant) submitted an original 505(b)(2) new drug application (NDA) for IPX203 (CREXONT-proposed). The Applicant is relying on FDA's findings of safety and effectiveness for Sinemet immediate release carbidopa/levodopa oral tablets (NDA 17555) and cross-referencing Rytary, a carbidopa/levodopa extended-release formulation, which the Applicant also owns.

IPX203 is an extended-release formulation of carbidopa/levodopa (CD/LD). The Applicant's stated overall objective was to develop an extended-release product that can attain therapeutic levodopa plasma concentrations rapidly and maintain constant levodopa plasma concentrations for a longer duration than currently approved products with minimal peak-to-trough fluctuations. The intended dosing for IPX203 is every (b) (4).

The proposed indication is for the treatment of Parkinson's disease, post-encephalitic parkinsonism and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication, which is identical to the indication statements for both Sinemet and Rytary. The formulation is a mixture of immediate-release granules containing CD/LD and extended-release beads containing levodopa, inside an enteric-coated capsule. Each capsule consists of immediate-release granules (100% of the carbidopa and 25% of the levodopa) and extended-release beads (75% of the levodopa).

Carbidopa is an aromatic amino acid decarboxylation inhibitor and levodopa is an aromatic amino acid. Carbidopa blocks the peripheral metabolism of levodopa, minimizing levodopa's gastrointestinal adverse effects, while increasing levodopa's central bioavailability, plasma levels and plasma half-life. The Applicant proposes a combination product in a 1:4 ratio (similar to the ratio in existing varieties of carbidopa/levodopa) with proposed dosage strengths of 35/(b) (4), 52.5/210mg, 70/280mg and 87.5/350mg and a maximum recommended daily dose of (b) (4)

Oral immediate release CD and LD have been marketed in the United States as tablets (Sinemet) for the treatment of PD and parkinsonism since 1974. There are several marketed immediate-release (IR) and extended-release (ER) formulations of CD/LD, a CD and LD intestinal gel, and three component combination products that include CD, LD plus a catechol-O-methyltransferase (COMT) inhibitor.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided data from a single double-blind, placebo-controlled, superiority trial comparing IPX203 to IR CD/LD, Study B16-02 in patients with advanced Parkinson's disease (PD) with motor fluctuations. There was a statistically significant change favoring IPX203 on the primary efficacy endpoint, the change from baseline to the end of the double-blind treatment

period for good "on" time. Study B16-02 also showed a statistically significant change favoring IPX203 compared to IR CD/LD on key secondary endpoints of decreased "off" time and Patient Global Impression of Change (PGI-C) at the end of the double-blind treatment period.

The results of this single, large, multicenter, adequate and well-controlled trial demonstrate an effect on a distinct and prespecified, clinically meaningful endpoint (relatively less decrease from baseline in good "on" time without troublesome dyskinesia and decrease from baseline in "off" time), complemented by a statistically significant difference in a key secondary patient-reported endpoint (the PGI-C), establishing internal consistency across results.

Additionally, the mechanism of action of carbidopa/levodopa is well-understood and well-established.

The results from Study B16-20 meet the standard of a positive, single adequate and well-controlled clinical investigation together with confirmatory evidence in the form of compelling mechanistic evidence, in the setting of a well-understood disease pathophysiology; well-documented natural history of disease; and support by scientific knowledge about the effectiveness of other drugs in the same pharmacologic class. The Applicant has met the regulatory requirement for substantial evidence of effectiveness of IPX203 for the treatment of advanced PD.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Integrated Assessment**

**IPX203 is an extended-release formulation of carbidopa/levodopa (CD/LD) intended to treat Parkinson's Disease. It is developed to attain therapeutic levodopa plasma concentrations rapidly and maintain constant levodopa plasma concentrations for a longer duration than currently approved products with minimal peak-to-trough fluctuations. The intended dosing for IPX203 is every (b) (4). The formulation is a mixture of immediate-release granules containing CD/LD and extended-release beads containing levodopa, inside an enteric-coated capsule. Each capsule consists of immediate-release granules (100% of the carbidopa and 25% of the levodopa) and extended-release beads (75% of the levodopa).**

**Parkinson's disease (PD) is a neurodegenerative disorder resulting from a progressive loss of dopaminergic neurons in the brain. The cardinal motor symptoms of PD include bradykinesia (slowness of movement), rigidity (stiffness), tremor and postural instability.**

**There is no treatment shown to slow or halt the progression of PD. The available treatments primarily act through increasing available dopamine or its effects in the brain. The available medical treatment options include CD/LD formulations (immediate and extended-release tablets and capsules), dopamine agonists, catechol-O-methyltransferase inhibitors and monoamine oxidase type-B inhibitors.**

**Effectiveness of IPX203 was evaluated in a single, adequate, and well-controlled study, Study B16-02 which was a randomized, double-blind, flexible-dose, active-controlled study comparing treatment with IPX203 to IR CD/LD (immediate-release carbidopa/levodopa) in subjects with moderate to advanced PD with motor fluctuations. Long-term safety information from subjects treated with IPX203 was provided by open-label extension Study B16-03.**

**The primary efficacy endpoint in Study B16-02 was the change from baseline/Week 4 to end of treatment/Visit 7 (= week 13 of the double-blind treatment period) in hours of good "on" time (= "on" time without dyskinesia + "on" time with non-troublesome dyskinesia) assessed by the PD diary. The first key secondary endpoint was the change from baseline in hours of "off" during that same double-blind study period, also assessed by the PD diary. The second key secondary endpoint was the change in PGI-C score at end of treatment/Visit 7. The third and fourth key secondary endpoints were the change from baseline to Visit 7/ET of the double-blind treatment period on the MDS-UPDRS[1] Part II (motor aspects of experiences of daily living) score and on the summed MDS-UPDRS Parts II + III (motor aspects of**

[1] Movement Disorders Society-Unified Parkinson's Disease Rating Scale

**experiences of daily living + motor examination) scores.**

**The results for the primary endpoint (change from baseline in mean good "on" time) showed a statistically significant difference in favor of IPX203, with a least square mean difference of -0.53 hours or 31.8 minutes (p=0.0194) of good "on" time. For the primary endpoint, the difference was expressed as less decrease in good "on" time from baseline compared to IR CD/LD. The result of the first key secondary endpoint [change in "off" time in hours from baseline (Visit 4) to end of treatment (Visit 7/ET)] showed a statistically significant difference in favor of IPX203, with a least square mean difference of -0.48 hours or 28 minutes (p=0.025), indicating less increase in "off" time from baseline to Visit 7/ET. The result of the second key secondary endpoint (change in PGI-C score at Visit 7/ET) showed a statistically significant difference in "much improved" or "very much improved" PGI-C scores favoring IPX203 by 10% (p=0.0015) compared to IR CD/LD.**

**"On time without troublesome dyskinesia" is when patients experience improvement in the hypokinetic symptoms of PD (bradykinesia, rigidity, +/- tremor primarily) unaccompanied by a disabling increase in the hyperkinetic side effects of levodopa supplementation therapy. Not all dyskinesia is disabling; therefore, the primary endpoint measure focuses on an improvement in the combination of "on" time without dyskinesia and "on" time with non-disabling / non-troublesome dyskinesia. An increase in good "on" time implies an accompanying decrease in the inverse measure, "off" time, as seen here, and/or a decrease in troublesome dyskinesia, which is considered a clinically meaningful endpoint. Treatment effects for the primary and first key secondary endpoint moving in opposite directions provides additional confidence in the primary endpoint results. These results were overall modestly effective. The efficacy results were further supported by the second key secondary endpoint, the PGI-C, which likewise moved modestly (10%) in the direction of greater improvement with IPX203 treatment compared to IR CD/LD. Demographic subgroup analyses suggested that the majority of these effects occurred in subjects aged under 65 years and with age of disease onset under 65 years. Because the pivotal study was not powered to detect that difference, a definitive statement to that effect is not possible.**

**The safety and effectiveness of IPX203 is intended to rely, in part, on prior findings of safety and effectiveness of levodopa and carbidopa from two listed drugs (Sinemet [IR CD/LD] and Rytary [CD/LD-ER]. However, in pharmacokinetic analyses, the Applicant established an acceptable bridge to the cross-referenced and listed drugs Rytary and Sinemet only for the levodopa component of IPX203. The carbidopa exposures at maximal doses for IPX203 are substantially higher than those for Sinemet or Rytary. Thus, the Applicant failed to establish a scientific bridge to the cross-referenced and listed drugs Rytary and Sinemet, based on the carbidopa exposures, in this 505(b)(2) application, and therefore cannot rely on the safety findings for Sinemet or Rytary.**

**Therefore, the safety of IPX203 was evaluated solely on the results of Study B16-02 and Study B16-03. The rates of serious adverse events in the double-blind treatment period of Study B16-02 were overall low in both the treatment group and active control group; however, they**

**were higher for the IPX203 group than for IR CD/LD (SAE 3.1% vs 1.6%). With respect to treatment emergent adverse events, compared to the IR CD/LD group, the IPX203 group reported more dyskinesia (2% vs 0.4%), more nausea (4.3% vs. 0.8%), more dizziness (2.3% vs 0.8%) and more anxiety (2.7% vs 0%) during the double-blind period of Study B16-02.**

**The safety database provided by the Applicant is inadequate to support chronic dosing with IPX203. Based on the modal daily dose, there was an insufficient number of subjects with at least 12-month exposure at any single dose (n=67); and no subjects with 12-month exposure at the proposed maximal dose of (b) (4) per day to support the safety of IPX203. There are insufficient exposure data to support the long-term safety of IPX203 in the treatment of moderate to advanced PD with motor fluctuations.**

**This review recommends a Complete Response action based on these deficiencies.**

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Parkinson's disease (PD) is a neurodegenerative disorder resulting from a progressive loss of dopaminergic neurons in the brain.<br>• The cardinal motor symptoms of PD include bradykinesia (slowness of movement), rigidity (stiffness), tremor, and postural instability.<br>• Patients with advanced PD experience episodes of immobility as the effective period for each dose of oral carbidopa and levodopa (CD/LD) wanes. Off times are episodes where the return of PD symptoms when the effects of medications diminish causing difficulty or disability in daily functioning.<br>• Dyskinesias are involuntary writhing movements that if severe enough can interfere with daily function. Patients with advanced PD taking LD will at some point in their disease begin to experience dyskinesia at the time when | Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases world-wide. Recent estimates place the prevalence of PD at approximately 1 million patients in the U.S. As PD progresses, patients experience increasing disability from motor complications such as wearing off and dyskinesia. Late non-motor complications such as cognitive impairment and psychosis may cause profound disability and limit treatment with approved medications. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | LD reaches its peak effects. | |
| **Current Treatment Options** | • There is no treatment shown to slow or halt the progression of PD.<br>• The available treatments primarily act through increasing dopamine or its effects in the brain. The available treatment options include CD/LD formulations (immediate and extended-release tablets and capsules), dopamine agonists, COMT inhibitors, monoamine oxidase type -B inhibitors. Other classes of medications that treat the motor symptoms of PD are anticholinergic drugs, amantadine, and adenosine receptor antagonists.<br>• Special formulations including CD/LD continuously delivered enteral suspension and orally inhaled levodopa are also available.<br>• Intermittently used medication for the treatment of "off" episodes such as apomorphine sublingual film or subcutaneous injection, orally inhaled CD/LD<br>• Surgical treatment for PD includes lesioning surgery in the brain, MRI guided focused ultrasound and deep brain stimulation. | There are no treatments that slow the progression of PD. The available medications effectively treat the motor symptoms of PD in early to middle stages of disease. As PD progresses, patients' response to medication is progressively limited by motor and non-motor complications reducing the ability to tolerate dopaminergic drugs.<br><br>In early to mid-stages of disease, after starting treatment with CD/LD patients may look and feel almost normal without experiencing dyskinesia. Patients with advanced PD often must tolerate some dyskinesia from doses of CD/LD that provide relief from the motor symptoms of PD. Eventually, progressively lower doses of CD/LD evoke more severe dyskinesia.<br><br>Surgical treatments for PD are not appropriate for all patients with PD and each surgical treatment comes with some risks. The available surgical treatments have not been shown to delay the progression of PD.<br><br>There is a continued need for additional well-tolerated, safe, and effective treatment options. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Benefit** | • Study B16-02 was a single, pivotal, randomized, double-blind, double-dummy, active-controlled, efficacy and safety study.<br>• The results for the primary endpoint (change from baseline in mean good "on" time), showed a statistically significant difference in favor of IPX203 compared to immediate release CD/LD (IR CD/LD). Both treatment groups showed a decline in good "on" time from baseline (Visit 4) to end of treatment (Visit 7); however, good "on" time decreased less in the IPX203 treatment group compared to the IR CD/LD group. The difference in hours between the least square mean change from baseline in good "on" time between the IPX203 and IR CD/LD treatment groups from beginning (Visit 4) to end (Visit 7 or ET) of the double-blind treatment period was 0.53 hours or 31.8 minutes, a statistically significant result (p=0.0194).<br>• The results for the first key secondary endpoint [change in "off" time in hours from baseline (Visit 4) to end of treatment (Visit 7 /ET)] showed less increase in off time in the IPX203-treated group than in the IR CD/LD-treated group over the same double-blind treatment period. The least square mean difference between the IPX203-treated group and the IR CD/LD-treated group was -0.48 hours or -28 minutes, a statistically significant result (p=0.025).<br>• The difference of 31.8 minutes in the primary endpoint favoring IPX203 was modestly clinically | The mechanism of action for CD and LD in treating PD is well-established and well-understood.<br><br>The results of this single, large, multicenter, adequate and well-controlled trial demonstrate that treatment with IPX203 was effective in lessening a decline in good "on" time. This result represents a modestly clinically meaningful improvement of function in patients with moderate to advanced PD with motor fluctuations.<br><br>The results of the single study plus confirmatory evidence of the well-understood mechanism of action of CD/LD and results of a trial of CD/LD-ER in a similar population are adequate to establish effectiveness of IPX203 in the treatment of advanced PD. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | meaningful, yet supported by an also modest but statistically significant 10% (p=0.0015) difference in "much improved" or "very much improved" PGI-C scores favoring IPX203. | |
| **Risk and Risk Management** | • The carbidopa exposure from IPX203 is substantially higher than that from Rytary or Sinemet, the listed drugs. The exposure to carbidopa from IPX203 at the maximal dose proposed was 1.9x that of Rytary, and 3.1x to 3.7x that of Sinemet (IR CD/LD).<br>• Based on the modal daily dose, there was an insufficient number of subjects with at least 12-month exposure at any dose (n=67); and no subjects with 12-month exposure at the proposed maximal dose to support the safety of IPX203 for the proposed indication.<br>• There were 5 deaths in subjects exposed to study drug, all during the open-label safety study (Study B16-03). The causes were diverse, and the rate was not demonstrably higher than that for the moderate to advanced PD population at large. None of the deaths were clearly causally related to the study drug.<br>• Overall, more serious adverse events and more treatment emergent adverse events occurred with IPX203 than with IR CD/LD, although both rates were low. The serious adverse event rate was 3.1% in the IPX203 group and 1.6% in the IR CD/LD group during the double-blind period of Study B16-02. The treatment emergent adverse event rate in the IPX203 group was 49% vs the IR CD/LD group's 28% during the double-blind period. Compared to the IR CD/LD group, the IPX203 | The Applicant failed to establish an adequate scientific bridge between IPX203 and Rytary or Sinemet for the carbidopa component of IPX203, using PK exposures at the highest proposed doses of IPX203. The Applicant demonstrated an acceptable bridge for safety to the levodopa component of IPX203 based on PK exposure at the maximum doses. Therefore, the Applicant cannot rely on prior findings of safety from the listed drugs, Sinemet and Rytary.<br><br>There are insufficient exposure data from the completed studies to support the safety of chronic IPX203 dosing in the treatment of moderate to advanced PD with motor fluctuations.<br><br>Additionally, a thorough QT study is necessary to assess the effects of IPX203 on QT, since it results in significantly higher carbidopa exposure (i.e., Cmax and AUC) compared to the already approved drugs.<br><br>Recommendation is for Complete Response. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | group reported more dyskinesia (2% vs 0.4%), more nausea (4.3% vs. 0.8%), more dizziness (2.3% vs 0.8%) and more anxiety (2.7% vs 0%) during the double-blind period of Study B16-02.The proposed maximum daily dosage of (b) (4) is not actually achievable using any combination of dosages the Applicant proposes to manufacture.<br>• There are no data to assess the effects of IPX203 on QT given that there is no adequate scientific bridge to the listed drugs for the high exposures of carbidopa. | |

### 1.4. Patient Experience Data

The primary endpoint for the pivotal trials is based on patient diaries, which were recorded by subjects and/or caregivers in a diary and reported to the Applicant. Additional patient and/or caregiver reported outcome measures in the trials included the patient global impression of change.

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| X | The patient experience data that was submitted as part of the application include: | | | |
| | X | Clinical outcome assessment (COA) data, such as | | |
| | | X | Patient reported outcome (PRO) | See Sections 6.1 and 6.2 Study endpoints |
| | | X | Observer reported outcome (ObsRO) | See Sections 6.1 and 6.2 Study endpoints |

## 2. Therapeutic Context

### 2.1. Analysis of Condition

Parkinson's disease (PD) is a neurodegenerative disorder resulting from a slowly progressive loss of dopaminergic neurons in the striatum, specifically in the substantia nigra pars compacta in the midbrain. These affected neurons characteristically contain abnormal deposits of alpha-synuclein protein, which are hypothesized to cause neuronal cell death. Pathologists have long observed that the progression of these depositions proceeds in a rostral to caudal manner, ascending the brain stem, through the midbrain, and ultimately reaching the cortex in advanced stages of the disease. This progression is thought to be responsible for the evolving sequence of clinical features of PD.

Currently the prevalence of Parkinson disease in the US is estimated to be about 1 million people, making it the second most common neurodegenerative disease after Alzheimer disease. The main risk factor for PD is age, with most cases occurring over age 65, and about 4% below age 50. The incidence of PD is therefore rising along with aging population, with current incidence estimated at around 90,000 people diagnosed annually. There is an approximately 1.5x greater frequency in men than women. (Willis et al, 2022)[2]

The disease remains a clinical diagnosis. The hallmark motor signs of bradykinesia, rigidity and/or resting tremor are usually the reason patients come to medical attention. Bradykinesia is required for diagnosis, plus a resting tremor, rigidity, or both. The classic clinical triad includes

[2] [2] Willis, A.W., Roberts, E., Beck, J.C. et al. Incidence of Parkinson disease in North America. npj Parkinsons Dis. 8, 170 (2022). https://doi.org/10.1038/s41531-022-00410-y

all three of these cardinal motor features. These typically present relatively early in the disease course. These symptoms of dopaminergic deficit characteristically respond to treatment with levodopa and other medications that increase available dopamine at the D2 receptor and synapse.

With time, clinicians and researchers have identified a host of non-motor features of Parkinson disease. There is a common prodrome, often noted in retrospect once the motor signs have appeared, of REM sleep disturbance, restless legs, constipation, and sometimes olfactory deficit, that can precede the appearance of motor signs by years or decades, implying that the disease process and loss of striatal neurons has progressed significantly by the time motor signs are evident.

After an initial period of 1-3 years with no or minimal need for supplemental levodopa, during which time patients frequently can function well with milder dopamine-enhancing medication, most patients are sufficiently disabled by their motor symptoms to require supplemental levodopa. After 3-5 years of levodopa exposure many people with PD develop complications from the medication. These are motor fluctuations (distinct “on” and “off” periods that are time-locked with wearing on and off the dose of medication) and dyskinesias, which are painless involuntary hyperkinetic movements that can occur at peak dose or when the medication is wearing on or off. Although usually harmless, severe dyskinesia can be disabling. A major goal of treatment is to increase and consolidate the daily amount of good “on” time, aka time when patients are neither “off” nor bothered by troublesome dyskinesia.

With time, additional features of the disease develop. Moderate to advanced motor signs generally appear 8-15 years into the disease course. These include freezing and postural instability (leading ultimately to falls). Moderate to advanced non-motor features include orthostatic hypotension, urinary and sexual dysfunction, executive dysfunction, and dementia with or without hallucinations. These features are typically not responsive or only minimally responsive to dopaminergic augmentation.

The most commonly prescribed treatments work by restoring dopamine’s effects in the brain, such as dopamine ($D_2$ family) receptor agonists, monoamine type B inhibitors that prolong the presence of dopamine in the synapse, or various formulations of levodopa, which is metabolized to dopamine. Because of its potent effects on the gastrointestinal system, levodopa is nearly always administered in combination with carbidopa, which both blocks levodopa’s peripheral metabolism and increases the proportion of levodopa that is centrally metabolized.

For those who are levodopa responsive but cannot tolerate the necessary doses of levodopa, or whose motor fluctuations and/or dyskinesias are sufficiently advanced, there is a functional neurosurgical treatment option of either microelectrode deep brain stimulation neuromodulation of the subthalamic nucleus or globus pallidum. These targets can also be lesioned non-invasively using high frequency ultrasound. Patients who undergo functional

neurosurgery, however, typically continue to require some degree of supplemental medication. There is general agreement that life expectancy is reduced in patients with PD but estimates of life expectancy vary by country. Availability and quality of subspecialty care, as well as caregiving, have a significant effect on longevity. Life expectancy in PD is also influenced by age at disease onset and the presence of dementia and postural instability.

## 2.2. Analysis of Current Treatment Options

**Carbidopa and Levodopa:**
Levodopa (LD) is a large neutral amino acid that is absorbed in the small intestine by active transport. An increase in dietary proteins may interfere with the absorption of LD by competition from other neutral amino acids for transporter binding sites. Once in circulation, LD is rapidly and extensively metabolized to dopamine by aromatic L-amino acid decarboxylase (AADC). Dopamine in the periphery is not able to cross the blood brain barrier because of a lack of lipid solubility and lack of necessary transport carriers in the capillary endothelial cells; levodopa, however, can cross the blood brain barrier.

Carbidopa (CD) is an AADC inhibitor that decreases the peripheral conversion of levodopa to dopamine, allowing more levodopa to cross the blood-brain barrier and enter the brain where it is converted by AADC into dopamine. Carbidopa is often added to levodopa to block levodopa's adverse systemic effects, allowing a lower dose of levodopa and increasing levodopa's tolerability

There are several available oral, immediate release (IR) and extended release (ER) CD and LD products, including generic products. Immediate release carbidopa and levodopa (CD/LD) in a 1 to 4 ratio (Sinemet) was first approved in the U.S. in 1975. Although, products containing only levodopa were marketed in the U.S. prior to 1975, oral levodopa-only tablets are no longer marketed in the United States. CD/LD is considered the most effective oral treatment for the motor symptoms of PD.

Sinemet CR was the first extended-release CD/LD product (CD/LD ER) approved in the United States in 1991. CD/LD ER is less bioavailable compared with the immediate release product. Sinemet CR uses a slowly eroding matrix to sustain plasma levels of CD and LD (1 to 4 ratio) which is somewhat longer than with the IR product. Rytary was the next CD/LD ER product approved in 2015. Rytary is an oral capsule containing microbeads of CD and LD in various amounts and containing a mixture of release properties also in a 1 to 4 ratio of CD to LD for all capsule strengths.

CD/LD enteral suspension (Duopa) was approved in 2015. Duopa is a drug/device combination product. The drug product is a viscous suspension of CD/LD in a 1 to 4 ratio delivered by a continuous enteral infusion pump through a tube placed in the jejunum. Patients initially receive Duopa through a temporary naso-jejunal tube to evaluate their response before undergoing endoscopic surgery for placement of the jejunal tube. Duopa is continuously pumped to the jejunum for 16 hours/day and patients take oral CD/LD during the remaining 8

hours overnight. The most serious adverse effects associated with Duopa are related to infections including peritonitis.

Levodopa without carbidopa is available as an orally inhaled powder (Inbrija) approved in 2018. Inbrija is a drug/device combination product indicated "for the intermittent treatment of 'off' episodes in patients with Parkinson's disease treated with carbidopa/ levodopa." Inbrija may be inhaled using the oral inhaler up to five times per day.

Chronic treatment with CD/LD has been associated with peripheral neuropathy, although the underlying mechanism is not fully understood.

**Catechol-O-Methyltransferase (COMT) inhibitors**
Members of the drug class Catechol-O-Methyltransferase (COMT) inhibitors include entacapone (Comtan) approved in 1999, tolcapone (Tasmar) approved in 1998 and opicapone (Ongentys) approved in 2020. In the presence of a decarboxylase inhibitor such as carbidopa, COMT becomes the major metabolizing enzyme for levodopa catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery. By blocking the metabolism of LD via catecholamine-O-methyl transferase in the periphery allows more LD to cross the blood brain barrier. COMT inhibitors are always administered to patients taking CD/LD to increase the relative bioavailability (AUC) of levodopa. COMT-inhibitors have been associated with severe diarrhea (entacapone) and drug induced hepatic injury (tolcapone).

**Dopamine receptor agonists**
The class of dopamine receptor agonists includes bromocriptine (Parlodel) approved in 1978, ropinirole (Requip) approved in 1997, pramipexole (Mirapex) approved in 1997, rotigotine (Neupro) approved in 2007 and apomorphine (Apokyn) injection approved in 2004. The approved dopamine agonists primarily stimulate the D2 family of dopamine receptors with apomorphine having greater effects on D1 dopamine receptors compared with other dopamine agonists. Bromocriptine, ropinirole, and pramipexole are all tablets administered three times daily for the treatment of patients with PD. These three dopamine agonists may be used alone or as adjunctive therapy in patients taking CD/LD products. Rotigotine is a transdermal patch that is changed once daily. Apomorphine injection is approved for the treatment of Off episodes associated with advanced PD and is administered as a subcutaneous injection as needed, up to five times per day. Ropinirole and pramipexole are also both available as extended-release oral tablets administered once daily. The primary endpoint in the pivotal studies of patients treated for early PD was the Unified Parkinson's Disease Rating Scale (UPDRS), Part III and/or Part II. In studies of advanced PD, the Parkinson's Disease Diary was used to evaluate efficacy. The change in Off hours and hours spent in the "on" state were used to evaluate efficacy in patients with advanced PD. The primary outcome measure in pivotal trials of ropinirole was the proportion of patients experiencing a decrease (compared with baseline) of at least 30% in the UPDRS motor score. In advanced PD, the primary outcome was the proportion of responders, defined as patients who were able both to achieve a decrease

(compared with baseline) of at least 20% in their L-dopa dosage and a decrease of at least 20% in the proportion of the time awake in the Off condition

**Monoamine oxidase type-B inhibitors**
The class of monoamine oxidase type-B inhibitors (MAOB-I) includes selegiline (Eldepryl) approved in 1996, rasagiline (Azilect) approved in 2006, safinamide (Xadago) approved in 2017. All the MAOB-I drugs are approved for adjunctive treatment of PD in patients receiving CD/LD. Rasagiline is also approved as monotherapy and as adjunctive treatment with CD/LD in PD patients. In the brain, MAOB-I blocks the catabolism of catecholamines and dopamine available in the synaptic cleft increasing stimulation of postsynaptic dopamine receptors. Aside from the expected dopaminergic neuropsychiatric adverse events, MAOB-I taken in higher than recommended doses can interfere with the metabolism of dietary tyramine, causing hypertension.

**Adenosine $A_{2a}$ receptor antagonists**
Adenosine A2a receptor antagonist is the newest class of medications approved for adjunctive treatment to CD/LD in adult patients with PD experiencing Off episodes. The first and only approved member of the class is istradefylline (Nourianz) approved in 2019. Members of the class potentiate the effects of levodopa but the mechanism of action of istradefylline is unknown. The primary efficacy endpoint was the change in total daily On Time without troublesome dyskinesia

**Amantadine**
Amantadine (Symmetrel) was first approved for prophylaxis of influenza A. In the early 1970s amantadine was approved for the treatment of “idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis.” Amantadine is also approved for the treatment of drug-induced extrapyramidal reactions, but the clinical trials supporting this indication were limited to patients treated for tardive dyskinesia. The mechanism of action for the treatment of PD or extrapyramidal reaction is unknown.

Amantadine extended release (Gocovri) was approved in 2017 “For the treatment of dyskinesia in patients with Parkinson’s disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications,” and “As adjunctive treatment to levodopa/carbidopa in patients with Parkinson’s disease experiencing “off” episodes.” Gocovri is taken once daily compared to the recommended two to three times daily for immediate release amantadine. Osmolex ER is another extended-release amantadine product which has the original indication for the treatment of PD as the immediate release products but does not include the indication for the treatment of dyskinesia. The indication for both amantadine ER products does not include the prophylaxis of influenza-A.

Amantadine is eliminated by the kidneys and the dose must be reduced in patients with renal

impairment. Improper dosing in patients with renal impairment can lead to accumulation of amantadine causing cardiac arrhythmia and sudden death. Other adverse events associated with amantadine include hallucinations, psychosis, orthostatic hypotension and livedo reticularis.

**Anticholinergic medications**

Anticholinergic medications were among the first medications used for the treatment of PD. Trihexyphenidyl (approved in 1949), benztropine (approved in 1954), orphenadrine, procyclidine, and biperiden were approved for the treatment of PD; however, procyclidine, and biperiden have been discontinued according to the FDA Orange Book. Anticholinergic medications are prescribed less frequently to patients with PD because of common side effects that include urinary retention, cognitive impairment, hallucinations, blurred vision and constipation. Patients above 70 years of age are susceptible to adverse reactions affecting the central nervous system. Some PD patients receive anticholinergic medications to treat tremor or off dystonia.

**Other Treatments for Parkinson's Disease**

Surgical treatments for PD have advanced from traditional stereotactic lesioning surgery (e.g., thalamotomy or pallidotomy) to Deep Brain Stimulation (DBS) and MRI-guided Focused Ultrasound (MRgFUS). DBS with electrode placement in the subthalamic nucleus (STN) or the globus pallidus interna (GPi) to treat dyskinesia and improve the motor symptoms of PD has been used in clinical practice over the last 20 years. DBS has been described as the surgical procedure of choice for treatment of patients with advance PD experiencing dyskinesia and "off" episodes. Successfully implanted patients experience significant improvement of motor fluctuations with a reduced need for dopaminergic medications, AND with a reduced risk for dysarthria compared with traditional STN lesioning surgery.[3] DBS is associated with surgical risks of intracranial hemorrhage, infection and hardware complications. Patients may also experience cognitive loss and behavioral changes following DBS surgery. Careful pre-operative screening is necessary to minimize the risk of these complications.

MRgFUS targeting the ventral intermediate nucleus of the thalamus is used for the treatment of medically refractory Essential Tremor (ET) and tremor predominant PD (Eisenberg et al., 2020). Delivery of focused ultrasound is the transcranial delivery of high intensity ultrasound energy to a small area of targeted tissue deep within the brain. The ultrasound energy heats the tissue causing thermal destruction (lesioning) of the targeted tissue. Studies of MRgFUS targeting the GPi have been completed and the results on reducing dyskinesia are promising. In the post-procedure period, patients may experience headache, nausea and vomiting. Because tissue loss caused by MRgFUS is irreversible, unintended spread to surrounding areas may cause persistent neurologic deficits such as impaired balance, dysarthria, or fine motor impairments.

[3] Faggiani E, Benazzouz A. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: From history to the interaction with the monoaminergic systems. Prog Neurobiol. 2017 Apr;151:139-156. doi: 10.1016/j.pneurobio.2016.07.003. Epub 2016 Jul 10. PMID: 27412110.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

IPX203 does not have marketing approval in the United States.

## 3.2. Summary of Pre-submission/Submission Regulatory Activity

The Applicant described a program with the overall objective to develop an extended-release product that can attain therapeutic LD plasma concentrations rapidly and maintain constant LD plasma concentrations for a longer duration than currently approved products with minimal peak-to-trough fluctuations. The intended dosing for IPX203 is every (b) (4)

This section of the review is focused on key clinical advice and agreements between the Applicant and the FDA. There are additional topics relating to other important areas of product development (e.g., product quality, manufacturing, clinical pharmacology studies, biostatistics) that were discussed in Type B meetings, (February 8, 2017; February 2, 2020) and teleconference (October 1, 2017). In total there were six formal meetings and two advice letters between the Applicant and the FDA, and the FDA also provided feedback in multiple emails.

October 22, 2014: IND 122793 Submitted by Sponsor for the product IPX203 carbidopa/levodopa extended-release capsules.

January 6, 2015: Study May Proceed issued

December 19, 2016: Sponsor submitted a draft protocol for Study IPX203-B16-02 in the meeting package for an End of Phase 2 (EOP2) Meeting. The face-to-face EOP2 meeting about this protocol took place on February 8, 2017.

February 27, 2017: Final written response meeting minutes, in response to Meeting between FDA & Sponsor on February 8, 2017, for discussion of the Phase 3 development plan:

> In this meeting the Division accepted the use of "'on' time without troublesome dyskinesia" or "good 'on' time" as a primary endpoint.
>
> This meeting addressed two main clinical and regulatory/administrative questions:
>
> Question 8: The Sponsor estimated that approximately 300 of the completers in Study IPX203-B16-02 would enter the 9-month open-label extension (OLE) Study IPX203-B16-03. The Sponsor queried whether the Division agreed that this proposed OLE study would provide adequate long-term patient safety database to support an NDA filing as a 505(b)(2) application.

The Division responded that was acceptable on face, unless unexpected safety findings were identified that required further testing, or the daily exposure to carbidopa or levodopa exceeded the exposure for the reference product. The determination of the adequacy of the safety database was also to be subject to review.

Question 14: The Sponsor asked whether the Division agreed that the proposed development program was sufficient to support a 505(b)(2) NDA for the proposed indication ("treatment of Parkinson's disease, postencephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication").

The Division responded that while on face it appeared that the proposed plan would support an indication for the treatment of advanced Parkinson's disease, a final decision on its adequacy is subject to FDA review of the actual application. The Division noted whereas a global indication for the treatment of symptoms of Parkinson's disease (PD) usually requires adequate and well-controlled trials supporting its use in both early and advanced PD, the proposed protocol only supported this indication in advanced disease. The Division further reminded the Sponsor that in the NDA submission, they would need to list specifically the sections and information in the labeling for each listed drug upon which the Sponsor intend to rely. The Division instructed the Sponsor that if the Sponsor intended to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), which is considered reliance on FDA's finding of safety and/or effectiveness for the listed drug(s), they should identify in the NDA the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54.

May 26, 2017: Pediatric waiver

July 15, 2017: Special Protocol Assessment (SPA): No Agreement (in response to 05/25/17 SPA request). This communication contained multiple pharmacologic and biostatistical concerns.

October 17/2017: Special Protocol Assessment: Agreement. This Agreement addressed non-clinical concerns raised in a letter on July 7, 2017 and a teleconference meeting with the Division on October 10, 2017.

The SPA concerned the proposed Study B16-02, a pivotal Phase 3 trial proposed to provide the primary basis of an efficacy claim for IPX203 (carbidopa/levodopa) extended-release capsules via the 505(b)(2) pathway. The Study was titled "A Randomized Controlled Study to Compare the Safety and Efficacy of IPX203 with Immediate-Release Carbidopa-Levodopa in Parkinson's Disease Patients with Motor Fluctuations." The Sponsor proposed a randomized, double blind, double-dummy, active-controlled, parallel-group multicenter study enrolling 501 adult subjects and employing variable dosing with a 13-week double-blind treatment period. The study began

with a double-blind treatment period were a 3-week, open-label, immediate release CD/LD dose adjustment period, followed by a 4-week open-label period for conversion to IPX203. Then followed a double-blind treatment maintenance period with subjects randomized 1:1 to IR CD/LD or IPX203, at fixed doses established in the preceding dose adjustment and dose conversion periods. The proposed primary endpoint was good "on" time without troublesome dyskinesia. This study would be followed by Study B16-03, a 9-month open-label extension study.

The SPA addressed the following concerns:

- The primary efficacy endpoint became good "on" time without troublesome dyskinesia averaged over 3 PD diary days
- Baseline was defined as the data collected immediately prior to randomization (Visit 4)
- The original efficacy endpoint, change from baseline in "off' time in hours/day averaged over 3 PD diary days, as measured at the end of the double-blind treatment prior or study termination, became a Secondary efficacy endpoint.
- Additional secondary endpoints included: change from baseline in average number of motor fluctuations per day averaged over 3 PD diary days; proportion of subjects with "improved" or "much improved" PGI-C scores; and change from baseline in the sum of MDS-UPDRS parts II and III scores at the end of the double-blind treatment period or study termination.
- revised initial dose conversion algorithm from IR CD/LD to IPX203
- updated strategy for pooling centers
- updated sensitivity analyses
- strategy for handling of missing data and discontinuation of subjects requiring rescue medications during the study – patients with at least one valid e-diary entry at baseline and during treatment to be included in the mITT population for primary analysis of efficacy.

April 12, 2021: Proprietary Name Granted

October 12, 2021: Type C meeting WRO

This summarized the following recommendations:

- The Sponsor is required to submit an Integrated Summary of Effectiveness (ISE) as part of the NDA.
- Data from double-blind, placebo-controlled, randomized trial B16-02 intended to support the efficacy of IPX203 in PD should not be combined with data from open-label extension study B16-03 or other studies in the development program.
- The Sponsor was required to submit separate SDTM and ADaM datasets that contain the efficacy and safety data from Study IPX203-B16-02 by itself. They were required to employ USUBJID that was CDIC-compliant and allowed subjects to be tracked across studies B16-02 and B16-03, because both studies were used to calculate exposure.

- Sponsor was instructed to identify subjects with a gap in exposure to IPX203 and the duration of any gap.
- Sponsor was instructed to include a summary table of exposure listing individual studies with the number of subjects by dose and duration in days and to include the dose a subject was receiving at the start of any adverse event.
- The Sponsor was advised that the exposure in support of chronic use in Parkinson's disease should include at least 100 patients on continuous treatment for 12 months exposed to the dose range intended for approval with a substantial majority of these patients maintained at the highest proposed dose for the entire year.

April 8, 2022: Final Meeting Minutes Type B Pre-NDA meeting (these minutes summarized the Teleconference between the Sponsor and the Division that occurred on 3/8/22). At this time the pivotal trial Study B16-02 had been completed and the open-label extension Study B16-03 was ongoing. Key points from this teleconference were the following:

- The Division indicated that based on the information provided at the time, the proposal to rely on Sinemet, Sinemet CR and to reference information in the Sponsor's own Rytary® NDA appeared acceptable.

- The Sponsor suggested a broad indication "Treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication." The Division found this reasonable but with the final determination to be made once the NDA was submitted.

- The Sponsor stated that they had established a PK bridge to Rytary®, Sinemet and Sinemet CR as the Listed Drugs for the application. They stated that pharmacokinetic data from a comparative clinical pharmacokinetic study with IPX203 and the Listed Drugs and reliance on relative bioavailability revealed that the systemic exposure of levodopa and carbidopa from IPX203 was similar to the Listed Drugs, and that there were no new safety issues identified. The Division responded that if an adequate bridge had been established and no new safety concerns identified, further nonclinical studies would not be needed to support the NDA.

- The Division advised the Sponsor that the acceptability of the proposed maximum daily dose (MDD) of (b) (4) CD and (b) (4) LD would depend on the adequacy of the pharmacokinetic (PK) bridging to the MDD of the highest approved daily dosing regimen for the reference product and the actual MDD tested in the pivotal clinical study.

- The Division advised the Sponsor that their conclusion on the dose proportionality and bioequivalence of the four proposed strengths of IPX203 would be a matter of review.

- The Division advised the Sponsor that based on the FDA analysis, exposures of carbidopa for proposed MDD of IPX203 is expected to be higher than the exposure of

carbidopa for the highest approved dosing regimen of the reference products. They advised the Sponsor that in order to rely on the FDA's finding of safety on the listed drug(s) to establish the safety of their product, the exposure of levodopa/carbidopa (Cmax and AUC) at the highest proposed regimen at steady state for the test product should be equal to or less than the exposure of the highest approved dosing regimen. The Division noted that the dose-normalized AUC of the proposed and reference products appeared comparable for levodopa when compared to Sinemet IR and is slightly higher when compared to Sinemet CR. However, carbidopa exposure and bioavailability seemed to be much higher for IPX203 when compared to listed drugs (Sinemet, Sinemet CR). The Division recommended that the sponsor conduct a pharmacokinetic (PK) simulation to compare the exposure at the highest proposed regimen of the proposed drug product versus the highest approved dosing regimen of the listed product(s) they planned to use as a reference.

The Sponsor then presented a comparison of exposure of the proposed product versus (b) (4) based on information available in summary basis of approval (SBOA), labeling, and literature. The sponsor proposed referencing (b) (4) as a listed drug in addition to Sinemet IR. The Agency recommended that if (b) (4) were to be used as a listed drug, a study would need to be conducted to establish the bridge. The Agency also advised the sponsor to conduct a simulation to confirm that (b) (4) is the most appropriate reference product to establish the bridge.

The Sponsor further asked, if a PK bridge is not possible, could the proposed highest dose of carbidopa (b) (4) be supported by clinical safety data. The Agency recommended that the 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. The Agency stated that based on the information provided, it was unclear if the number of patients receiving the highest dose of carbidopa (b) (4) met the recommended exposures for a safety database and requested that the sponsor provide updated information on distribution of patients by carbidopa dose and duration of exposure in the completed Phase 3 trial and ongoing open-label extension study.

The Sponsor subsequently submitted a table showing showed that 169 patients were exposed to IPX203 for at least 12 months with 76 patients exposed at the highest dosage range of CD (>400 mg). They also discussed reducing the maximum recommended daily dose (MRDD) of IPX203 to (b) (4) CD/LD in order to further assure the safety of its proposed drug product. The Division acknowledged the sponsor's updated CD exposure data and noted that the exposure of (b) (4) of CD in IPX203 would likely still be greater than the exposure of CD at the highest approved regimen of listed drugs, and that both this and the adequacy of a reduced dose to support efficacy would be a matter of review. The Division also advised the Sponsor that nonclinical studies cannot be used as a substitute for adequate clinical safety data.

The Division advised the Sponsor to submit a complete safety database at the time of submission.

October 17, 2022: NDA filed for IPX203.

### 3.3. Foreign Regulatory Actions and Marketing History

IPX203 is not approved for use in any country.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted in depth inspections of two study sites:

1) Site 115, Kevin Klos MD, The Movement Disorder Clinic of Oklahoma, 7134 S. Yale Avenue, Suite 205, Tulsa, OK 74136; Inspection Dates: 1/3/2023 – 1/5/2023

2) Site 163, Manuel F. Fernanadez Medical Professional Clinical Research Center, Inc. 3850 SW 87 Ave Suites 201 and 202 Miami, FL 33165; Inspection Dates: 2/9/2023 – 2/17/2023.

The OSI concluded that Study B16-02 study "appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication."

See the OSI report by Drs. Alfaro, Kronstein and Sellers for details.

### 4.2 Product Quality

The Office of Product Quality (OPQ) reviewed the application and recommended approval NDA 217186 for Crexont (carbidopa and levodopa) extended-release capsules): "Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements."

### 4.3 Clinical Microbiology

Not applicable.

### 4.4 Nonclinical Pharmacology/Toxicology

Please see the nonclinical review. Per their report no new studies were needed to support this application.

## 4.5 Clinical Pharmacology

During the pre-NDA meeting, described in Section 3.2 above, The Office of Clinical Pharmacology raised concerns regarding the ability of IPX203 to bridge to its predecessors Sinemet, Rytary and Duopa. Specifically, they raised concern that the AUC for carbidopa in IPX203 exceeds that in any prior formulation of carbidopa/levodopa. Please refer to the Clinical Pharmacology review by Dr. Ramakrishna Samala, Ph.D., Yifei Zhang, Ph.D., Bilal AbuAsal, Ph.D., excerpted below, for their detailed analysis.

> The Division of Neuropsychiatric Pharmacology reviewed the submitted application and found that the carbidopa exposures between 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…
>
> 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...
>
> 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...
>
> 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… Therefore, exposure comparison with IR CD-LD or Rytary cannot support the safety of IPX203 at the proposed maximum total daily dose.

## 4.6 Devices Issues

There are no devices associated with this application.

## 4.7 Consumer Study Reviews

There were no human factor studies to review.

### 4.8 Interdisciplinary Review Team for Cardiac Safety Studies (QT-IRT)

QT-IRT reviewed the submission and recommended that the Applicant should conduct a thorough QT study to assess the effects of Crexont, since the new formulation results in significantly higher carbidopa exposure (i.e., Cmax and AUC) compared to the already approved drugs.

## 5. Sources of Clinical Data and Review Strategy

### 5.1 Table of Clinical Studies

**Table 1: Listing of Clinical Trials Relevant to IPX203 for PD**

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| ***Controlled Studies to Support Efficacy and Safety*** | | | | | | | |
| IPX203-B16-02- | Phase 3, randomized 1:1, double-blind, double-dummy, active-controlled, parallel-group, prospective, multicenter study evaluating safety and efficacy of IP 203 vs. IR CD-LD. | Up to 2400m/day in divided doses 35/140mg capsules ER vs 25/100 IR, individualized based on incoming regimen.<br><br>Doses:<br>35/140<br>52.5/210<br>70/280<br>87.5/350<br><br>Starting Dose (lowest):<br>35/140 po BID<br>Max daily dose:<br>600/2400mg | Efficacy:<br>Primary: Change from baseline to visit 7 in "good on" time as expressed through Patient Diaries of on time/off time<br>Secondary:<br>Change from baseline to visit 7 in "off" time<br><br>PGIC (Patient Global Impression of Change)<br>MDS-UPDRS part III<br>MDS-UPDRS Part II + III<br>Subjects who were "on" upon awakening at visit 7<br>Subjects who were "good on" upon awakening at Visit 7 | 20 weeks:<br><br>4w screening<br>3w open label dose adjustment<br>13w double-blinded treatment | 630 enrolled in dose adjustment<br>589 in IPX203 conversion period<br>506 randomized 1:1 | CD-LD experienced patients with moderate to advanced PD with motor fluctuations. | 105 sites in the United States, Western and Eastern Europe. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Studies to Support Safety*** | | | | | | | |
| IPX203-B16-03 | Phase 3, multicenter, open-label extension study evaluating long-term safety and clinical utility. | 35/140 ER, 52.5/210 ER, 70/280 ER, 87.5/350 ER Individualized based on final IPX203 dose from B16-02 | Safety: Adverse Events, Vital signs, EKG, Labs, Physical Exam, Medications, GCSI C-SSRS | 9 months:<br><br>Baseline visit followed by 3 visits at ~3 month intervals | 419 enrolled and treated | CD-LD experienced PD patients with motor fluctuations who completed study IPX203-B16-02. | |

## 5.2 Review Strategy

The evidence supporting the efficacy of IPX203 in treating the symptoms of Parkinson's Disease in patients with motor fluctuations rests primarily on the pivotal Phase 3 study IPX203-B16-02 (Study B16-02), with additional information from Phase 3 study IPX203-B16-03 (Study B16-03), an open-label extension. The former provides information for both efficacy and safety. The Applicant also conducted three Phase 1 PK studies in healthy volunteers (Studies B16-04, B16-05 and B16-06), a Phase 2 single-dose PK/PD/efficacy and safety study in advanced PD patients (Study B14-02) and a safety study of single and multiple doses of IPX203 in advanced PD patients (Study B16-01).

The Applicant performed safety analyses on Studies B16-01, B16-02, B16-03, B16-04, B14-04 and B16-05 separately, as well as on pooled datasets. They pooled the datasets by study phase, specifically:

- Phase 1 studies in healthy volunteers, 1 day dosing: B16-04, B16-05, B16-06
- Phase 2 studies in advanced PD, 1-14 days of dosing: B14-02, B16-01
- Phase 3 studies in advanced PD with motor fluctuations, long-term dosing: B16-02, B16-03
- Plus one pool of all the studies above combined.

Studies B16-02 and B16-03 are submitted to evaluate the safety of IPX203 in the treatment of people with Parkinson's disease with motor fluctuations. Study B16-03 provides information on safety in longer-term use (9 months). As the second study is contiguous with the first study and enrolled patients who completed the first study, the treatment time frame of both studies combined (13 weeks + 9 months) potentially provides 12 months of safety data (counting only those patients who were randomized to study medication in the first trial and then completed the second).

In keeping with usual practice for levodopa-based medications, the Applicant relies in their submission on extensive prior experience and approvals for existing forms of carbidopa/levodopa, primarily Sinemet, which serves as the active control in the pivotal trial. The exposures of levodopa in IPX203 are comparable to those found in Sinemet (IR CD/LD), the active-control in the Phase 3 trial, and Rytary (CD/LD-ER). However, the maximal exposure of carbidopa in IPX203 is not comparable to those of IR CD/LD or CD/LD-ER. For this reason, the proposed product cannot rely on the findings of safety for carbidopa for either IR CD/LD or CD/LD-ER (see Section 4.5 above). As IPX203 is a combination product consisting of two drugs, one component of which inhibits the peripheral metabolism of the other, it is not possible to separate out the disparate effects of the two active components in the administered form. Rather the adverse event review necessarily looks at the effects of both components in the doses proposed.

# 6. Review of Relevant Individual Trials Used to Support Efficacy

## 6.1.Study IPX203-B16-02

### 6.1.1. Study Design

**Title:**

"A Randomized Controlled Study to Compare the Safety and Efficacy of IPX203 with Immediate-Release Carbidopa-Levodopa in Parkinson's Disease Patients with Motor Fluctuations."

**Overview and Objective**

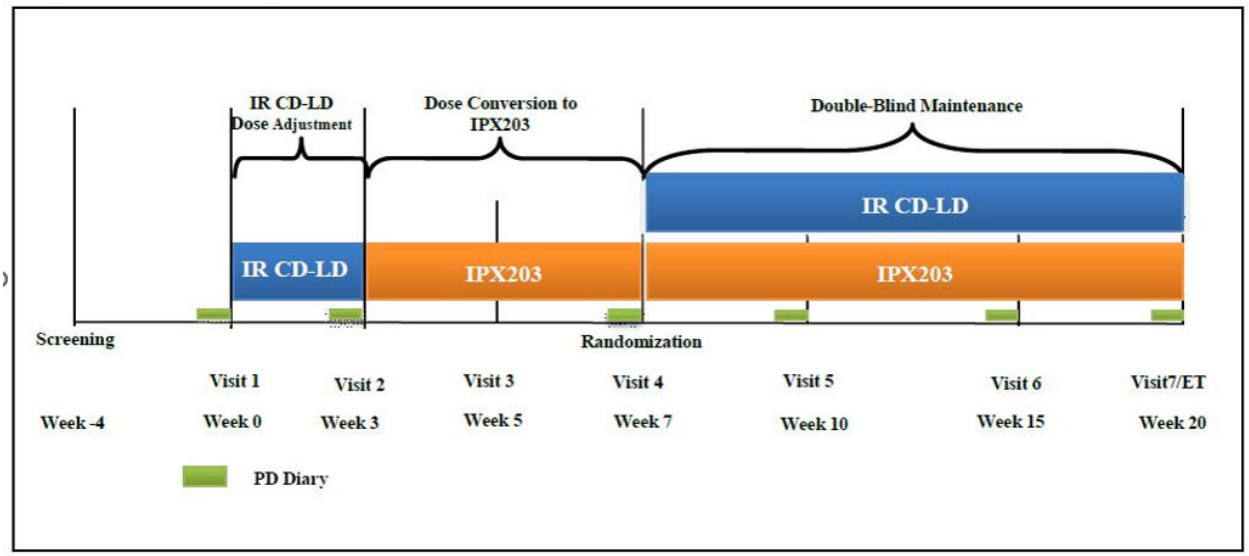
The objective of this trial is to evaluate the safety and efficacy of IPX203 in the symptomatic treatment of patients with moderate to advanced Parkinson's disease with motor fluctuations and prior CD/LD experience, in comparison to the existing option of IR CD/LD.

**Trial Design**

This was a Phase 3, randomized 1:1, double-blind, double-dummy, active-controlled, parallel-group, prospective, multicenter study comparing the safety and efficacy of IPX203 to IR CD/LD in people with Parkinson's disease with motor fluctuations.

The study had four periods: a 4-week Screening Period, a 3-week Dose Adjustment Period (IR CD/LD), a 4-week Dose Conversion Period (IPX203), and a 13-week Double-Blind Maintenance Period. Following the Screening there were seven planned Visits beginning four weeks after screening (Week -4). These occurred at Weeks 0, 3, 5, 7 10, 15, and 20. The maximum anticipated study duration, including screening, adjustment and conversion periods, was 24 weeks. The flow chart below illustrates the study design:

**Figure 1: Study B16-02 Flow Chart**




Abbreviations: IR=immediate-release, CD=carbidopa, LD=levodopa, ET=early termination

Source: Applicant; Protocol IPX203-B16-02

Following an initial screening appointment, subjects completed three days of a Patient Diary immediately preceding their study entry visit (Visit 1).

During the dose adjustment period, subjects entered a three-week open-label process of achieving best medical therapy using adjustable doses of IR CD/LD, in combination with stable doses of their other dopaminergic and anticholinergic medications, to optimize their "on" time without troublesome dyskinesia and minimize their "off" periods. Subjects were required to be on stable doses of all medications without rescue medications for five days prior to entering the dose conversion period. They completed three days of Patient Diaries immediately preceding their entry to the dose conversion period (Visit 2). Use of rescue medications triggered discontinuation from the study.

Subjects who successfully completed the dose adjustment period criteria entered the dose conversion period (Visit 2). In this period, the doses of IR levodopa established in the dose adjustment period were converted to equivalent doses of IPX203 at a ratio of 1:2.8. Dosing interval could range from a minimum of 6 to a maximum of 12 hours with the recommended interval being 8 hours. All other medications remained stable. They completed three days of Patient Diaries immediately preceding their entry to the dose conversion period (Visit 4). Use of rescue medications triggered discontinuation from the study. Subjects were required to be on stable doses of all medications without rescue medications for five days prior to entering the subsequent Randomization Period.

Subjects who successfully completed the dose conversion period then entered the randomization period (Visit 4). In this period, each subject was stratified 1:1 by center and

received either IPX203 and placebo IR CD/LD; or IR CD/LD and placebo IPX203 (double dummy design). Subjects took their assigned drug at the stable dose established in the preceding periods of the trial. Dose adjustments were not allowed during the double-blind period. Subjects returned for clinic visits 5 (week 10), 6 (week 15), and 7 (week 20), and completed three days of Patient Diaries immediately preceding each visit. Use of rescue medication triggered discontinuation from the study.

**Diagnostic Criteria:** Male or female subjects diagnosed at ≥40 years old with Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria (bradykinesia + at least one of muscular rigidity, 4-6Hz rest tremor, or postural instability not from another primary cause), and treated with stable regimens of CD/LD on which they experience motor fluctuations. See Section 13.3 for full definition.

**Key Inclusion Criteria:**
Patients were required to:

- Have idiopathic PD according to the UK PD Society Brain Bank clinical criteria
- Hoehn & Yahr Stages 1 to 4 when "On" ("on" as defined by the MDS-UPDRS Part III).
- MoCA ≥ 24 at Screening when "on"
- Daily "wearing-off" with periods of bradykinesia + rest tremor or rigidity, "off" on awakening most mornings, and at least 2,5 cumulative hours of "off" time daily while awake
- CD/LD responsive and on a stable regimen that requires at least 100mg LD at the first morning dose; a total daily dose of at least 400mg with a maximum of 2400mg, a dosing frequency of 4-9 times daily; with efficacy typically lasting <4 hours.
- MDS-UPDRS Part III score ≥ 20 in the "off state."

**Key Exclusion Criteria:**

- Using CR CD/LD apart from a single bedtime dose within 4 weeks prior to Visit 1
- Used ER CD/LD (i.e., Rytary) within that period or failed ER LD/CD; used additional carbidopa or benserazide, COM-t inhibitors, or MAO inhibitors or antidopaminergic medications within 4 weeks of Visit 1.
- Prior surgery for PD or surgery that would interfere with LD absorption
- History of peptic ulcer disease with upper gastrointestinal bleed within 5 years, glaucoma, seizure within 12m, myocardial infarction (MI) with residual uncontrolled arrhythmia, or any MI within 12m, Neuroleptic Malignant Syndrome (NMS) rhabdomyolysis, LFTs ≥ 2.5 upper limit of normal (ULN), Cr ≥ 1.75 ULN or dialysis, melanoma, cancer within 5 years
- Drug or alcohol abuse within 5 years
- Any history of non-iatrogenic or non-PD associated psychosis within 10y (mild PD illusions accepted)
- Treatment with a DA antagonist for psychosis or bipolar disorder within 2 years
- Inability to comply with the Patient Diary requirements

**Investigators and Administrative Structure**

The study initiated at 122 sites and ultimately enrolled at 105 sites in the United States (U.S.) and Eastern and Western Europe (Germany, the United Kingdom, France, Italy, Spain, the Czech Republic, and Poland). The results appear applicable to the US population.

The subjects were enrolled between November 2018 and June 2021.

*Reviewer Comment:*

*These enrollment criteria were acceptable.*

**Dose Selection:**

This was a flexible dose trial. The initial regimen of IPX203 was based on the most frequent dose of the subject's dosing regimen at the end of the dose adjustment period (Visit 2). The Applicant used the following dose conversion table to convert subjects from the most frequent dose of IR CD/LD in the dose adjustment phase to the recommended starting IPX203 daily dosing regimen:

| **Most frequent IR CD/LD Unit Dose (mg)** | **Recommended Starting IPX203 Daily Dosing Regimen CD/LD mg every 8 hours** |
|---|---|
| 25/100 | 70/280mg (2x 35/140) |
| >25/100 – 37.5/150 | 105-420mg (3x 35/140) |
| >37.5/150-50/200 | 140/560mg (4x 35/140) |
| >50/200 | 175/700 (5x 35/140) |

IPX203 was administered every 8 hours for most subjects and was not to be more frequent than every 6 hours. An exception was that if a subject was taking a total daily dose of less than 125-500mg IR CD/LD at the end of the dose adjustment period, they would be initially administered IPX203 every 12 hours. The dose of IPX203 was adjustable during the dose conversion period to optimize effectiveness and tolerability. The dose and regimens of subjects' other non-CD/LD Parkinson's Disease medications remained stable during this time.

**Study Treatments**

For the double-blind treatment period, subjects received either the study drug IPX203 ER capsules containing 35mg of CD and 140mg of LD (CD:LD ratio 1:4) to take orally or the reference therapy IR CD/LD containing 25mg CD and 100mg LD (CD:LD ratio 1:4) tablets to take orally. Subjects took multiples of the tablets to achieve the designated maintenance dose that had been established at the end of the dose conversion period or the dose adjustment period and the IR CD/LD tablets were split to achieve the desired dose. The Applicant used a double-dummy design because the test product was a capsule and the reference drug was a tablet. In this design, along with the treatment medication, each subject also received a matching placebo of the opposite drug.

**Assignment to Treatment**

At Visit 4, subjects were randomized, stratified by center, in a 1:1 ratio to either IPX203 (and matching IR CD/LD placebo) or IR CD/LD (and matching IPX203 placebo) The block size was 4.

**Blinding**

The 13-week double blind treatment maintenance period used a double-dummy design in which subjects received either IPX203 with a matching IR CD/LD placebo, or IR CD/LD with a matching IPX203 placebo. For the stable dosing subjects took the regimen established at the end of week 3 (Visit 2) for IR CD/LD and at the end of Week 3 (Visit 4) for IPX203.

*Reviewer's Comment:*

*The methods above used to minimize various forms of bias appear reasonable.*

**Dose Modification, Dose discontinuation**

Doses were not modifiable during the double-blind treatment period. During the dose conversion period, subjects were initially started on a regimen as described in "Dose Selection" above. Subsequently, during the dose conversion phase, Investigators could adjust the IPX203 regimen to minimize "off" time without causing troublesome dyskinesia or other dopaminergic side effects. They were given tips on how to adjust the dosing regimen during this period, such as increasing the first morning dose or suggesting a fasting first dose if the subject was "off" in the morning; or if the subject was "off" in the afternoon, to increase the preceding dose rather than reducing the dosing interval.

**Treatment Compliance**

Study staff and monitor performed drug accountability and reconciliation. The Applicant provided this information by subject in line listings. Each subject took an individualized dose and regimen that was determined during the dose adjustment and dose conversion periods and then maintained during the double-blind treatment period.

**Prior and Concomitant Therapy**

Subjects in each treatment group were continued on their documented non-CD/LD medications which were required to be stable for the 4 weeks preceding the study. Concomitant therapy with amantadine, MAO-B inhibitors, anticholinergics, and or dopamine agonists except apomorphine was allowed if doses had been stable for at least 4 weeks prior to Visit 1 and remained constant throughout the study. No medication adjustments were allowed following randomization and during the double-blind period of the study. Treatment with a dopamine antagonist antipsychotic agent for the purpose of psychosis or bipolar disorder within the preceding 2 years was not allowed and was an exclusion criterion. Use of antipsychotics for other reasons was potentially allowable after consultation with the medical monitor.

Neurosurgical treatment for PD was not allowed during the study and prompted discontinuation.

**Rescue Medications**

Rescue medications were not allowed at any point during the study. Use of a rescue medication prompted discontinuation from the study.

**Study Endpoints**

**The primary efficacy endpoint was:**

Mean change from baseline (randomization visit=Visit 4) in "good on" time in hours per day, averaged over three PD diary days, at the end of the double-blind treatment period (Visit 7/week 20/ET). At times the primary endpoint is also expressed as change from baseline to week 13 of the double-blind period. Good "on" time was defined as the sum of time "on without dyskinesia" and time "on with non-troublesome dyskinesia." It was derived from the 3-day PD diaries completed prior to Visits 4, 5, 6 and 7 or ET.

The primary and first key secondary endpoints (described below) were based on the PD diary. Subjects were required to complete PD diaries for 3 consecutive days before each study visit. In the PD diary, subjects record their state in 30-minute intervals over a 24-hour day, using the descriptors "Asleep," "Off," "On without dyskinesia," "On with non-troublesome dyskinesia," and "On with troublesome dyskinesia." Non-troublesome dyskinesias do not interfere with function or do not cause meaningful discomfort. Troublesome dyskinesias do interfere with function or cause meaningful discomfort.[4] When more than one state was checked, the worse result was used as the final reported outcome. A PD diary was valid if at least 1 full day (6am to 6am the following day) of diary data was available. For visits with no valid PD diary "good on" time was not derived and handled instead with the mixed model for repeated measures (MMRM) procedure.[5] The PD diary is a well-established accepted instrument that has been used to capture "on" time and "off" time in multiple PD-related trials.

**Key secondary endpoints were:**

At the end of the double-blind treatment period (Visit 7/week 20):

- Change from baseline in "off" time in hours per day, averaged of the PD diary days. This key secondary endpoint was calculated in a similar manner to the primary endpoint, summing time described as "off" and averaging it over the 3-day period, then subtracting the results at Visit 7/ET from that at baseline. "Off" time as calculated from PD diaries is an established and accepted endpoint that has been used in prior studies.

[4] From the Applicant's IPX203-B16-02 Clinical Study Report, p.50.
[5] From the Applicant's IPX203-B16-02 Clinical Study report, p.61.

- Proportion of patients with either “much improved” or “very much improved” on the Patient Global Impression of Change (PGI-C)

- Change from baseline in MDS-UPDRS Part III

- Change from baseline in the sum of MDS-UPDRS Parts II + III

**Statistical Analysis Plan**

Analysis populations

- Safety Population: all randomized patients who receive at least one dose of IPX203. Safety will be analyzed according to the treatment actually received.
- Modified Intent-to-Treat (mITT) Population: all randomized patients who receive at least one dose of FEN or placebo and who had a valid baseline PD diary and at least one valid post-randomization PD diary. Patients will be analyzed according to the treatment group to which they were randomized. The primary comparison of IPX203 variable dosing to IR CD/LD and the key secondary analyses will be performed on the mITT Population.

Details of the statistical analysis are described in the Statistical Review and Evaluation by Minjeong Park, PhD, referenced herein.

Primary efficacy analysis

The primary endpoint is the mean change from baseline in “good on” time in hours per day, averaged over three PD diary days, at the end of the double-blind treatment period (Visit 7/ week 20).

The primary efficacy endpoint was analyzed using a mixed model for repeated measures (MMRM). The model included baseline (Visit 4) “Good on” time as a covariate, treatment (IPX203 or IR CD/LD) and visit (5, 6, or 7/early termination (ET)) as fixed effects, pooled center as a random effect and a treatment-by-visit interaction. The model employed an unstructured within subject covariance matrix and a restricted maximum likelihood (ReML) estimation method. The degree-of-freedom of the denominator was estimated using the Kenward-Roger method. The primary analysis set was the mITT. If the model failed to converge with the unstructured covariance matrix, a simpler covariance matrix was to be employed in the order of 1) heterogeneous Toeplitz, 2) heterogeneous autoregressive of order 1, 3) heterogeneous compound symmetry, 4) Toeplitz, 5) autoregressive of order 1, 6) compound symmetry (CS). Missing visit data were handled via the MMRM model.

For the PD Diaries, missing data were imputed in one of two ways, depending on whether subjects had more than one day of data vs one day of data. For detailed rules applied depending on the degree of missing data please see Dr. Park’s review.

Key Secondary Endpoint Analyses:

1. **Change from baseline in "Off" time at the end of double-blind treatment period** (Visit 7/ET) was analyzed in a similar fashion to the primary endpoint.

2. **Proportion of subjects with either "much improved" or "very much improved" in Patient Global Impression of Change (PGI-C) scores** at the end of double-blind treatment period (Visit 7/ET) was analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by the pooled center to compare the proportion of subjects with either "much improved" or "very much improved" response at the end of the double-blind therapy between the two treatment groups.

3. **Change from baseline in the MDS-UPDRS Part III total score as the sum of the answer for all questions** at the end of double-blind treatment period (Visit 7/ET) was analyzed in the same manner as the primary endpoint.

4. **Change from baseline in the sum of MDS-UPDRS Part II and III as the sum of all answers** at the end of double-blind treatment period (Visit 7/ET) was analyzed in the same manner as MDS-UPDRS Part III.

If the MDS-UPDRS was missing for the particular visit, the missing data were handled via the MMRM model.

The primary endpoint and 4 key/important secondary endpoints were tested in a sequential hierarchical order at a significance level of 0.05, as follows:

1. The primary endpoint, the mean change from baseline in good "on" time (hours per day), was tested first at a 0.05 level of significance.
2. If statistical significance is demonstrated, then the first key secondary endpoint, the mean change from baseline in "Off" time (hours per day), was tested next at a 0.05 level of significance.
3. If statistical significance is demonstrated, then the second key secondary endpoint, the proportion of subjects with either "much improved" or "very much improved" on the PGI-C, was tested next at a 0.05 level of significance.
4. If statistical significance is demonstrated, then the third key secondary endpoint, the mean change from baseline in the MDS-UPDRS Part III, was tested at a 0.05 level of significance.
5. If statistical significance is demonstrated, then the fourth key secondary endpoint, the mean change from baseline in the sum of the MDS-UPDRS Parts II and III combined was tested next at a 0.05 level of significance.
6. If statistical significance is demonstrated, then the important secondary endpoint, being "on" upon awakening was tested next at a 0.05 level of significance.

Details of the Sensitivity Analyses are available in Dr. Park's review.

Subgroup Analyses:

- Age: < 65, ≥ 65 years old at study entry
- Sex: Males, Females
- Race: Caucasians, non-Caucasians
- Region: North America or Europe
- Ethnicity: Hispanic, Non-Hispanic or Unknown
- Concomitant medications: the following non-exclusive subgroups will be defined for subjects taking concomitant medications of the following categories:
    - o Amantadine
    - o selective MAOB inhibitors
    - o anticholinergic PD medications
    - o dopamine agonists
    - o others
- Weight: <75 kg or ≥75 kg
- Body mass index (BMI): <25 kg/$m^2$ or ≥25 kg/$m^2$
- PD duration at screening: <8 years or ≥8 years
- Age of PD onset: <65 years or ≥65 years
- "Good On" time at study entry: average <9h or ≥9h per day
- "Off" time at study entry: average <6h or ≥6h per day

**Protocol Amendments**

There were 8 protocol amendments, the latter four of which were international updates to the 4th amendment. The major amendments are summarized below:

| Amendment Number | Date | Major Changes |
|---|---|---|
| 1 | May 18, 2017 | • Subjects will continue to take non-CD/LD based PD medications throughout the study if documented in their pre-study regimen and if doses have been stable for 4 weeks prior to Visit 1.<br>• Rescue with additional or modified doses of concomitant PD medications or with use of IR CD/LD products other than the dispensed study medication are not permitted and will trigger discontinuation from the study.<br>• Inclusion Criteria: requires at least 100mg of LD for IR CD/LD for the first morning dose; and requires a total daily dose of at least 400mg LD and takes a maximum TDD of 2400mg; and has a dosing frequency of 4-9 times daily.<br>• Primary Endpoint: change from baseline in good "on" time in hours/day, averaged over the PD diary days at the end of the double-blind treatment period. Good "on" time is derived from the 3-day PD diaries and defined as the sum of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia.<br>• Secondary Endpoint: Change from baseline in the MDS-UPDRS-Part III at the end of double-blind treatment period (Visit 7 or early termination). |

| Amendment Number | Date | Major Changes |
|---|---|---|
| | | • Additional endpoints: 1) proportion of subjects with an improvement in good "on" time for at least 0.5, 1, 1.5, 2, 2.5 and 3 hours, and of reduction in "off" time of these amounts 2) Proportion of subjects who are "on" and "good on" on awakening 3) change from baseline in the average number of motor fluctuations per day averaged over the PD diaries.<br>• At Visit 1, 3-day PD diary must show subject is averaging at least 2.5 h/day of "off" time and at least 1.5 h/d of "off" time to continue in the study. If >1 day of the diary is not returned or missing, subject is discontinued.<br>• Outlined strategy for pooling centers with <5 subjects<br>• Outlined statistical strategy for missing data<br>• Identified subgroup analysands |
| 2 | October 23, 2017 | • Updated the dose conversion table<br>• Required closer contact between the Investigator and subject during dose conversion and recording changes<br>• Plans for missing data for subjects with more than one day of diary data |
| 3 | December 7, 2017 | • Clarified an IPX203 maximum daily dose of 600/2400mg CD/LD. |

### 6.1.2. Study Results

**Compliance with Good Clinical Practices**

The Applicant stated that Study B16-02 was conducted in in compliance with International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6: Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. The Applicant additionally stated that informed consent and assent, if possible, were obtained prior to carrying out any study procedures. The informed consent forms (ICF), protocol, and amendments for this trial were submitted to and approved by an IRB before the start of the study.

**Financial Disclosure**

In the financial disclosure summary, out of 519 total study investigators, the Applicant identified 19 investigators with disclosable financial interests outside of Study payments. The Applicant identified the total amount they had paid to these Investigators outside of Study payments by year from 2019-2022. Of these 19, 10 Investigators self-identified as having a disclosable financial interest consisting of consultations, honoraria, Speakers' Bureau engagements, an infomercial podcast; and one site investigator, the study's principal investigator, Dr. Robert Hauser, who had served on the Advisory Board in 2019.

Because of these discrepancies, the Division queried the Applicant for an explanation. The Applicant responded that they had drawn their accounting of the disclosable financial interests from their own accounting records, from the national Sunshine Act disclosures database and from the investigators' own disclosures. Where there were discrepancies, the Applicant queried

the investigators themselves with only partial responses resulting. Despite these deficiencies in self-disclosure from the investigators, the Applicant's own disclosures appeared comprehensive and their approach to the disclosable financial interest was satisfactory.

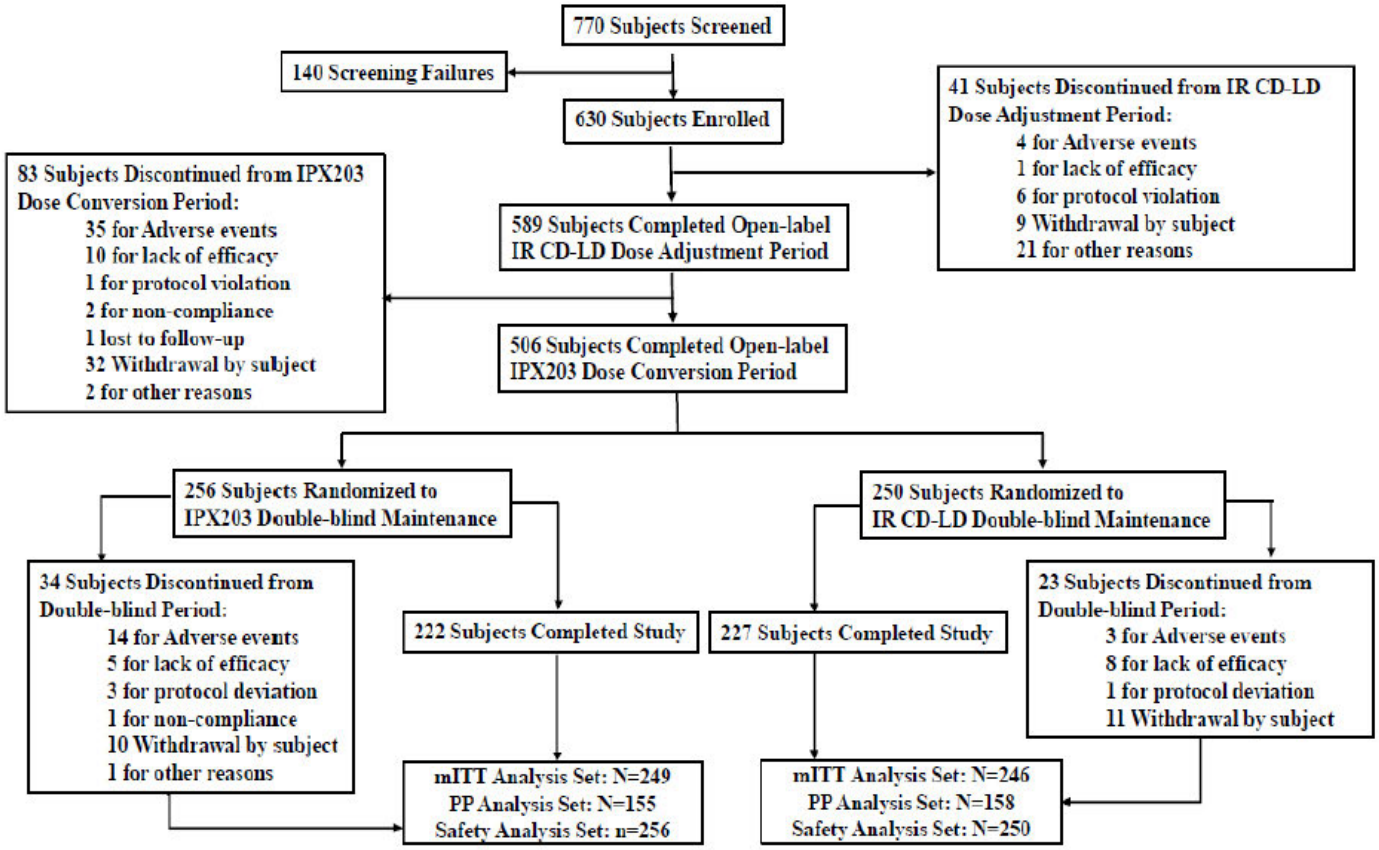
No investigators were full-time or part-time employees of Impax, and no investigator disclosed a proprietary or equity interest in the tested product. The study design does minimize potential bias because the treatment period was randomized in a block format, double blinded and the objective primary efficacy endpoint was based on subject-reported data from patient diaries.

No single trial site was the main contributor to the observed effects. Of the 19 study sites headed by an investigator with reportable financial disclosures, three (sites 100, 103 and 121, investigators LeWitt, Tosch, and Isaacson respectively) enrolled ≥10 subjects. The remainder enrolled ≤7 subjects. The FDA statistician reported that excluding any single site or group of low-enrolling sites from the efficacy analysis did not change the efficacy results.

**Subject Disposition**

Overall, 770 subjects were initially screened, 140 of whom failed screening. As seen in Figure 2 below, 630 subjects were enrolled in the Dose Adjustment Period, 41 of whom discontinued participation in the study. Of the 589 subjects who entered the Dose Conversion Period, 83 discontinued, and 506 subjects thus remained for randomization. These 506 subjects were randomized 1:1 with 256 assigned to IPX203, and 250 assigned to IR CD/LD. Of the 256 subjects in the IPX203 group, 222 completed the double-blind maintenance period. Of the 250 assigned to the IR CD/LD group, 227 completed the double-blind maintenance period.

**Figure 2: Study B16-02 Subject Disposition**




Abbreviations: IR CD/LD=immediate-release carbidopa-levodopa, mITT=modified intent-to-treat, PP=per-protocol.
Source: Applicant; Study B16-02 Clinical Study Report

**Table 2: Disposition for Exposed Subjects, Study B16-02**

| Disposition | Number (%) of Subjects Randomized | | |
|---|---|---|---|
| | IPX203 (N=256) | IR CD/LD (N=250) | Total (N=506) |
| Completed the double-blind period | 222 (86.7) | 227 (90.8) | 449 (88.7) |
| **Early discontinuation from double-blind period** | **34 (13.3)** | **23 (9.2)** | **57 (11.3)** |
| Adverse event | 14 (5.5) | 3 (1.2) | 17 (3.3) |
| Lost to follow-up | 0 | 0 | 0 |
| Lack of efficacy | 5 (2.0) | 8 (3.2) | 13 (2.6) |
| Non-compliance with study drug | 1 (0.4) | 0 | 1 (0.2) |
| Protocol deviation | 3 (1.2) | 1 (0.4) | 4 (0.8) |
| Withdrawal by subject | 10 (3.9) | 11 (4.4) | 21 (4.2) |
| Other | 1 (0.4) | 0 | 1 (0.2) |
| **Analysis sets** | | | |
| Safety analysis set | 256 (100) | 250 (100) | 506 (100) |
| ITT analysis set | 256 (100) | 250 (100) | 506 (100) |
| mITT analysis set | 249 (97.3) | 246 (98.4) | 495 (97.8) |
| Per-protocol analysis set | 155 (60.5) | 158 (63.2) | 313 (61.9) |
| Completers analysis set | 220 (85.9) | 226 (90.4) | 446 (88.1) |

Abbreviations: DBP=double-blind treatment period, IR CD/LD=immediate-release carbidopa-levodopa, ITT=intent-to-treat, mITT=modified intent-to-treat
Safety analysis set includes all subjects who were randomized and received at least one dose of study treatment.
mITT analysis set includes all subjects who were randomized and treated and had a valid baseline PD diary and at least one valid post-randomization PD diary.
*Source: Statistical Reviewer Analysis; adsl.xpt, ds.xpt*

Reviewer Comment:

*During the double-blind period, among subjects who entered the double blind (N=denominators), a slightly higher adverse event rate led to discontinuation in the IPX203 group (5.5%) compared to the IR CD/LD group (1.2%). However more subjects who withdrew because of lack of efficacy were taking IR CD/LD (3.2% IR CD/LD vs 2.0% IPX203).*

**Protocol Violations/Deviations**

There were 559 major protocol violations (Table 38); 241 of these occurred during the double-blind period. The types of deviations were diverse, and it is not apparent that any deviation or set of deviations affected the outcome.

Four subjects discontinued as a result of major protocol deviations related to dosing. One was during the dose adjustment period and three were during the double-blind maintenance period.

Of the three that occurred during the double-blind treatment period, Subject (b) (6) ran out of study medication and took Sinemet instead so was discontinued; Subject (b) (6) was

discontinued after the Site Investigator mistakenly changed the dose of IPX203 after randomization; and Subject (b) (6) was discontinued after a dosing error.

*Reviewer Comment:*

*Lack of compliance was more frequent in the IPX203 group during blinded treatment compared to the group randomized to IR CD/LD; however, the number is still small (16 deviations). The 16 deviations occurred in 6 subjects treated with IPX203 during the double-blind period. There were none in the IR CD/LD group.*

**Demographic Characteristics**

Demographics of the groups entered into the double-blind treatment period were similar. The mean age was 66.1 years in the IPX203 group and 66.6 years in the IR CD/LD group. A similar number of subjects was under 65 vs. 65 or over in each treatment group. A greater proportion of the female subject population (39% vs 29.3% was enrolled in the IPX203 vs IR CD/LD treatment groups, respectively, while a greater proportion of the male subject population (70.7% vs 62%) was enrolled in the IR CD/LD vs the IPX203 treatment group. The study population was over 96% White. Half the study population (50.3%) enrolled in the double-blind period was from the U.S. Among the U.S. subjects, 47% were in the IPX203 treatment group and 53.7% were in the IR CD/LD treatment group.

The IPX203 group had a slightly higher number of minimum hours of good "on" time without troublesome dyskinesia (the primary efficacy endpoint) at entry into the double-blind treatment period (1.7 hours vs 0.5 hours). However, the mean number of hours of good "on" time without troublesome dyskinesia was similar in both treatment groups. The disease characteristics were roughly evenly distributed between the IPX203 and the IR CD/LD groups.

**Table 3: Baseline Demographics, Study B16-02 (mITT Population)**

| Characteristic | IPX203 (N=249) | IR CD/LD (N=246) | Total (N=495) |
|---|---|---|---|
| **Age, years** | | | |
| n | 249 | 246 | 495 |
| Mean (SD) | 66.1 (9.00) | 66.6 (8.83) | 66.3 (8.91) |
| Median | 66.0 | 68.0 | 67.0 |
| IQR | 59.0, 72.0 | 61.0, 73.0 | 60.0, 72.0 |
| Min, Max | 44.0, 88.0 | 40.0, 89.0 | 40.0, 89.0 |
| **Age group, n (%)** | | | |
| < 65 years | 97 (39.0) | 90 (36.6) | 187 (37.8) |
| ≥ 65 years | 152 (61.0) | 156 (63.4) | 308 (62.2) |
| **Sex, n (%)** | | | |
| Male | 152 (61.0) | 174 (70.7) | 326 (65.9) |
| Female | 97 (39.0) | 72 (29.3) | 169 (34.1) |
| **Race, n (%)** | | | |
| White | 237 (95.2) | 239 (97.2) | 476 (96.2) |
| Black or African American | 2 (<1) | 3 (1.2) | 5 (1.0) |

| Characteristic | IPX203 (N=249) | IR CD/LD (N=246) | Total (N=495) |
|---|---|---|---|
| Asian | 5 (2.0) | 2 (<1) | 7 (1.4) |
| American Indian or Alaska Native | 3 (1.2) | 0 | 3 (<1) |
| Unknown or not reported | 2 (<1) | 2 (<1) | 4 (<1) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 32 (12.9) | 31 (12.6) | 63 (12.7) |
| Not Hispanic or Latino | 216 (86.7) | 211 (85.8) | 427 (86.3) |
| Not reported | 1 (<1) | 4 (1.6) | 5 (1.0) |
| **Region** | | | |
| Europe | 132 (53.0) | 114 (46.3) | 246 (49.7) |
| United States | 117 (47.0) | 132 (53.7) | 249 (50.3) |
| **Country** | | | |
| CZE | 16 (6.4) | 16 (6.5) | 32 (6.5) |
| DEU | 19 (7.6) | 19 (7.7) | 38 (7.7) |
| ESP | 32 (12.9) | 23 (9.3) | 55 (11.1) |
| FRA | 5 (2.0) | 5 (2.0) | 10 (2.0) |
| GBR | 7 (2.8) | 4 (1.6) | 11 (2.2) |
| ITA | 17 (6.8) | 13 (5.3) | 30 (6.1) |
| POL | 36 (14.5) | 34 (13.8) | 70 (14.1) |
| USA | 117 (47.0) | 132 (53.7) | 249 (50.3) |
| **Height, cm** | | | |
| n | 249 | 246 | 495 |
| Mean (SD) | 168.9 (10.16) | 171.7 (9.95) | 170.3 (10.14) |
| Median | 170.0 | 172.7 | 171.0 |
| IQR | 162.0, 176.0 | 164.0, 180.0 | 162.6, 177.8 |
| Min, Max | 124.5, 195.4 | 145.0, 193.0 | 124.5, 195.4 |
| **Weight, kg** | | | |
| n | 248 | 246 | 494 |
| Mean (SD) | 78.6 (17.69) | 80.9 (16.87) | 79.8 (17.31) |
| Median | 77.4 | 78.6 | 78.1 |
| IQR | 65.7, 89.2 | 70.0, 90.0 | 68.2, 89.8 |
| Min, Max | 41.8, 139.2 | 45.0, 140.1 | 41.8, 140.1 |
| **BMI, kg/m$^2$** | | | |
| n | 248 | 246 | 494 |
| Mean (SD) | 27.4 (5.06) | 27.3 (4.66) | 27.4 (4.86) |
| Median | 27.0 | 26.8 | 27.0 |
| IQR | 23.9, 30.4 | 24.2, 30.2 | 24.2, 30.3 |
| Min, Max | 16.3, 52.6 | 17.6, 45.1 | 16.3, 52.6 |

*Source: FDA analysis*

**Table 4: Baseline Disease Characteristics, Study B16-02 (mITT Population)**

| Characteristic | IPX203 (N=249) | IR CD/LD (N=246) | Total (N=495) |
|---|---|---|---|
| **Good "On" Time** | | | |
| N | 249 | 246 | 495 |
| Mean (SD) | 11.671 (2.943) | 11.724 (2.759) | 11.697 (2.850) |
| Median | 12.0 | 11.67 | 11.83 |

| Characteristic | IPX203 (N=249) | IR CD/LD (N=246) | Total (N=495) |
|---|---|---|---|
| Q1, Q3 | 10.17, 13.50 | 9.83, 13.67 | 10.08, 13.67 |
| Min., Max. | 0.50, 18.83 | 1.83, 18.0 | 0.50, 18.83 |
| **Screening MDS-UPDRS Part II Total Score, "ON" State** | | | |
| n | 248 | 244 | 492 |
| Mean (SD) | 13.06 (7.37) | 12.50 (7.22) | 12.78 (7.29) |
| Median | 12.0 | 12.0 | 12.0 |
| IQR | 8.0, 18.0 | 7.0, 17.0 | 8.0, 17.50 |
| Min, Max | 0.0, 38.0 | 0.0, 43.0 | 0.0, 43.0 |
| **Screening MDS-UPDRS Part III Total Score, "ON" State** | | | |
| n | 249 | 246 | 495 |
| Mean (SD) | 24.83 (16.09) | 24.88(15.61) | 24.86 (15.84) |
| Median | 21.0 | 22.0 | 22.0 |
| IQR | 14.0, 33.0 | 13.0, 32.0 | 13.0, 32.0 |
| Min, Max | 3.0, 96.0 | 3.0, 97.0 | 3.0, 97.0 |
| **Screening MDS-UPDRS Part II Total Score, "OFF" State** | | | |
| n | 249 | 246 | 495 |
| Mean (SD) | 15.14 (7.66) | 15.30 (7.60) | 15.22 (7.62) |
| Median | 14.0 | 14.0 | 14.0 |
| IQR | 9.0, 20.0 | 10.0, 20.0 | 10.0, 20.0 |
| Min, Max | 1.0, 38.0 | 1.0, 43.0 | 1.0, 43.0 |
| **Screening MDS-UPDRS Part III Total Score, "OFF" State** | | | |
| n | 249 | 246 | 495 |
| Mean (SD) | 45.57 (13.98) | 45.64 (14.17) | 45.60 (14.06) |
| Median | 44.0 | 44.0 | 44.0 |
| IQR | 36.0, 54.0 | 36.0, 54.0 | 36.0, 54.0 |
| Min, Max | 20.0, 99.0 | 21.0, 98.0 | 20.0, 99.0 |
| **Hoehn and Yahr Stage, "ON" State, n (%)** | | | |
| 0 | 0 | 0 | 0 |
| 1 | 26 (10.4) | 20 (8.1) | 46 (9.3) |
| 2 | 168 (67.5) | 172 (69.9) | 340 (68.7) |
| 3 | 49 (19.7) | 47 (19.1) | 96 (19.4) |
| 4 | 6 (2.4) | 7 (2.8) | 13 (2.6) |
| 5 | 0 | 0 | 0 |
| **Screening MoCA Score, n (%)** | | | |
| < 24 | 0 | 0 | 0 |
| 24 - < 26 | 54 (21.7) | 53 (21.5) | 107 (21.6) |
| 26 - < 28 | 69 (27.7) | 82 (33.3) | 151 (30.5) |
| 28 - < 30 | 102 (41.0) | 89 (36.2) | 191 (38.6) |
| 30 | 24 (9.6) | 22 (8.9) | 46 (9.3) |
| **Duration of PD** | | | |
| < 8 Years | 123 (49.4) | 122 (49.6) | 245 (49.5) |
| ≥ 8 Years | 126 (50.6) | 124 (50.4) | 250 (50.5) |
| **Age of Onset of PD, years** | | | |
| n | 249 | 246 | 495 |
| Mean (SD) | 57.7 (9.08) | 58.4 (9.60) | 58.1 (9.34) |
| Median | 58.0 | 58.5 | 58.0 |
| IQR | 51.0, 64.0 | 51.0, 65.0 | 51.0, 65.0 |
| Min, Max | 40.0, 83.0 | 34.0, 83.0 | 34.0, 83.0 |

*Source: FDA analysis*

*Reviewer Comment:*

*These demographics show a roughly 1.5 times greater prevalence of PD in males than in females, which is consistent with other epidemiologic studies on this subject. More than 95% of participants in the study were White, a distribution more pronounced than in the U.S. population alone, although consistent with the general observation that the prevalence of PD is higher among Caucasians than people of color. The proportion of subjects of Hispanic ethnicity exceeds that of PD patients in the U.S. population and likely resulted from recruiting in Spain. The mean duration of PD of roughly 8 years across groups is consistent with the typical time to emergence of troublesome motor fluctuations. There are no significant differences in demographics between the two groups in the double-blind period.*

**Efficacy Results – Primary Endpoint**

The primary efficacy endpoint was the mean change from baseline in good "on" time, measured in hours per day, averaged over the PD diary days, at the end of the double-blind treatment period (Visit 7 or ET (early termination)). Baseline was defined as the outcome measured at Visit 4, at the end of the IPX203 dose conversion period. Good "on" time consisted of the sum of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia, as subjects documented them in the 3-day PD diaries. Both "on" time without dyskinesia and "on" time with non-troublesome dyskinesia are commonly used measures of efficacy in Parkinson's disease treatment trials.

Both treatment groups showed a decline in good "on" time from baseline (Visit 4) and end of treatment (Visit 7); however, good "on" time decreased less in the IPX203 treatment group compared to the IR CD/LD group. The difference in hours between the least square mean change from baseline in good "on" time between the IPX203 and IR CD/LD treatment groups from beginning (Visit 4) to end (Visit 7 or ET) of the double-blind treatment period was 0.53 hours, or 31.8 minutes. This difference was statistically significant (p = 0.0194).

Per Dr. Park's review, the least square mean change (standard error) in good "on" time from baseline to Visit 7 was -0.385 (2.706) hours in the IPX203 treatment group and -0.968 (3.081) in the IR CD/LD group, a difference of 0.53 hours (95% CI [0.0859, 0.9727], p=0.0194), compared with the IR CD/LD group. Table 5 below summarizes these results:

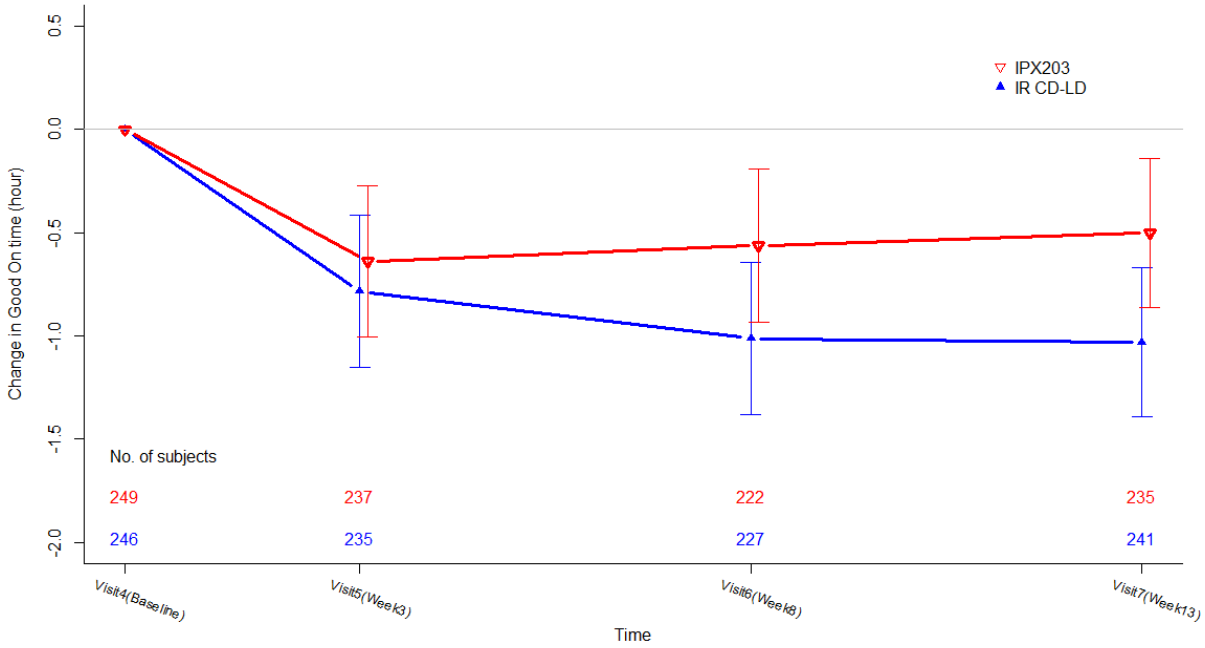
**Table 5: Primary Efficacy Endpoint: Change from Baseline to Visit 7/ET in "Good On" Time during DBP by Randomized Treatment Group (mITT Population)**

| | Randomized Treatment Group | | |
|---|---|---|---|
| **Statistics (hour)** | **IPX203 (N=249)** | **IR CD/LD (N=246)** | **Total (N=495)** |
| Baseline visit | | | |
| N | 249 | 246 | 495 |
| Mean (SD) | 11.671 (2.943) | 11.724 (2.759) | 11.697 (2.850) |
| Median (Q1, Q3) | 12.0 (10.17, 13.50) | 11.67 (9.83, 13.67) | 11.83 (10.08, 13.67) |
| Min., Max. | 0.50, 18.83 | 1.83, 18.0 | 0.50, 18.83 |
| Visit 7 (Week 13) | | | |
| N | 235 | 241 | 476 |
| Mean (SD) | 11.349 (3.065) | 10.773 (2.775) | 11.057 (2.933) |
| Median (Q1, Q3) | 11.50 (9.33, 13.50) | 10.83 (9.0, 12.67) | 11.17 (9.17, 13.0) |
| Min., Max. | 0, 17.67 | 1.50, 17.0 | 0.0, 17.67 |
| Change at Visit 7 (Week 13) from baseline | | | |
| N | 235 | 241 | 476 |
| Mean (SD) | -0.385 (2.706) | -0.968 (3.081) | -0.680 (2.914) |
| Median (Q1, Q3) | -0.33 (-1.83, 1.17) | -1.0 (-2.67, 0.83) | -0.71 (-2.17, 1.0) |
| Min., Max. | -9.67, 8.50 | -9.33, 8.0 | -9.67, 8.50 |
| LS Mean change (SE) at Week 12 from baseline | -0.5012 (0.1834) | -1.0305 (0.1828) | |
| LS Mean difference (95% CI) (IPX203 vs. IR CD/LD) | 0.5293 (0.0859, 0.9727) | | |
| p-value | 0.0194 | | |

Abbreviations: DBP=double-blind treatment period, ET=early termination, mITT=modified intent-to-treat, IR CD/LD=immediate-release carbidopa-levodopa, N=number, SD=standard deviation, Max=maximum, Min=minimum, Q1=quarter 1, Q3=quarter 3, LS=least squares, SE=standard error, CI=confidence interval.
The LS mean, SE, LS Mean Difference, 95% CIs and p-values have been obtained from the MMRM with treatment, visit as fixed effects, pooled center as a random effect, baseline assessment as a continuous fixed covariate, and a treatment-by-visit interaction
Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt

The difference between the treatment groups held throughout the treatment period, as seen in Figure 3 below.

**Figure 3: Change from Baseline to Visit7/ET in "Good On" Time during DBP by Randomized Treatment Group (mITT Population)**




Abbreviations: DBP=double-blind treatment period, ET=early termination, mITT=modified intent-to-treat, IR CD/LD=immediate-release carbidopa-levodopa, No.=number.
The LS means, 95% CIs and p-values have been obtained from the MMRM with treatment, visit as fixed effects, pooled center as a random effect, baseline assessment as a continuous fixed covariate, and a treatment-by-visit interaction.
Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt

*Reviewer Comment:*

*Compared with the IR CD/LD group, the IPX203 group demonstrated a statistically significant change from baseline in hours of good "on" time during the treatment period. Good "on" time, described as a combination of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia, is an accepted clinical endpoint that has been used in prior studies evaluating the efficacy of treatments for advanced PD. The relative gain (expressed as less of a decrease) of the IPX203-treated group in Study B16-02 was 31.8 minutes. This difference of 31.8 minutes was modestly clinically meaningful and was also supported by a modest statistically significant difference in the PGI-C in the IPX203 group compared to IR CD/LD.*

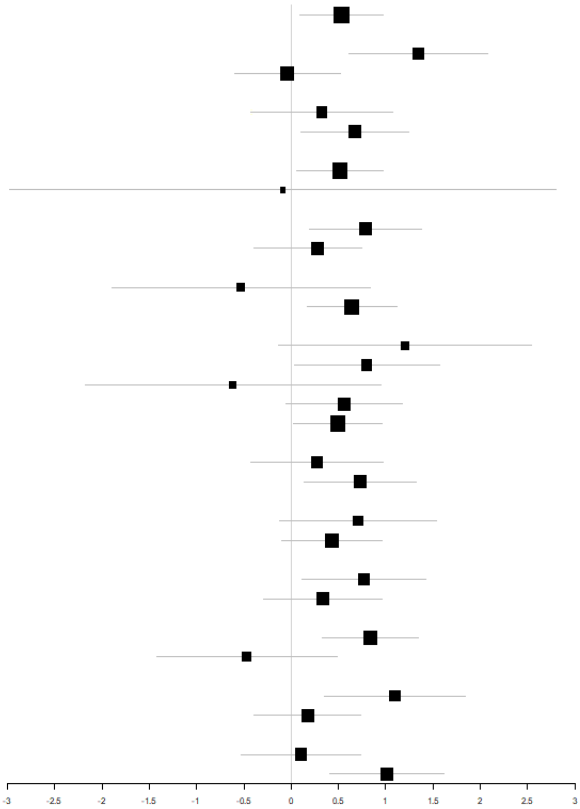
There were 105 recruiting sites in Study B16-02. Per the statistical reviewer, removing any individual site from the analysis did not alter the significance of the overall primary or secondary efficacy results.

MMRM applied to per protocol (PP) analysis set and MMRM and ANCOVA applied to the completer set, both produced no significantly different results.

Subgroup analyses were conducted for the mITT population using the MMRM to evaluate the effect of important subgroups. The forest plot below (Figure 4) summarizes these findings for the primary efficacy endpoint.

**Figure 4: Forest Plot of Subgroup Analysis for Primary Endpoint: Change from Baseline to Visit7/ET in "Good on" Time during DBP by Randomized Treatment Group (mITT Population)**

| | IR CD-LD n | IPX203 n | LS Mean Difference (95% CI) |
|---|---|---|---|
| Overall | 246 | 249 | 0.529 (0.086, 0.973) |
| Age | | | |
| <65 years | 90 | 97 | 1.348 (0.616, 2.079) |
| >=65 years | 156 | 152 | -0.041 (-0.598,0.517) |
| Gender | | | |
| Female | 72 | 97 | 0.326 (-0.426,1.078) |
| Male | 174 | 152 | 0.674 (0.103, 1.244) |
| Race | | | |
| Caucasian | 239 | 237 | 0.515 (0.061, 0.969) |
| Non-Caucasian | 7 | 12 | -0.089 (-2.980,2.802) |
| Region | | | |
| North America | 132 | 117 | 0.786 (0.193, 1.379) |
| Europe | 114 | 132 | 0.277 (-0.389,0.743) |
| Ethnicity | | | |
| Hispanic or Latino | 31 | 32 | -0.533 (-1.899,0.832) |
| Not Hispanic or Latino | 211 | 216 | 0.643 (0.167, 1.119) |
| Concomitant Medications | | | |
| Amantadine | 24 | 28 | 1.206 (-0.132,2.544) |
| Selective MAOB inhibitors | 76 | 88 | 0.799 (0.030, 1.568) |
| Anticholinergic PD medications | 9 | 13 | -0.617(-2.182,0.948) |
| Dopamine agonists | 116 | 142 | 0.556 (-0.06, 1.173) |
| Others | 227 | 231 | 0.494 (0.027, 0.960) |
| Weight | | | |
| <75 kg | 92 | 111 | 0.268 (-0.433,0.969) |
| >=75 kg | 154 | 137 | 0.728 (0.132, 1.325) |
| BMI | | | |
| <25 kg/m2 | 83 | 79 | 0.707 (-0.127,1.541) |
| >=25 kg/m2 | 163 | 169 | 0.430 (-0.10, 0.961) |
| PD duration | | | |
| <8 years | 122 | 123 | 0.769 (0.119, 1.419) |
| >=8 years | 124 | 126 | 0.332 (-0.297,0.962) |
| Age of PD onset | | | |
| <65 years | 180 | 191 | 0.835 (0.330, 1.341) |
| >=65 years | 66 | 58 | -0.468 (-1.426, 0.49) |
| Good On time at entry | | | |
| <9 h/day | 96 | 96 | 1.095 (0.350, 1.839) |
| >=9 h/day | 150 | 153 | 0.175 (-0.389, 0.74) |
| Off time at entry | | | |
| <6 h/day | 128 | 121 | 0.101 (-0.534,0.736) |
| >=6 h/day | 118 | 128 | 1.015 (0.413, 1.617) |




Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt

*Reviewer Comment:*

*For the primary endpoint, this subgroup analysis suggests that while there is an overall significant change in the primary outcome measure, the effect may be greatest in the subgroup of subjects <65 years of age which accounts for most of the observed change. In addition, subjects in the age of onset <65 group may experience the majority of the benefit in the primary outcome measure. However, the study and resulting analysis were not powered to detect these differences, therefore they cannot be stated as definitive conclusions.*

**Data Quality and Integrity**

The sponsor submitted all necessary analysis datasets and SAS programs. The statistical reviewer found the datasets acceptable. With these, the statistical reviewer verified the analysis datasets and the primary results from the clinical study report. OSI investigated two sites for this review. Drs. Klos and Fernandez were inspected in support of this NDA and covered Protocol IPX203-B16-02. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

1) Site 115: Kevin Klos, M.D., The Movement Disorder Clinic of Oklahoma, 7134 S. Yale Avenue, Suite 205, Tulsa, OK 74136; Inspection Dates: 1/3/2023 – 1/5/2023

   There was no evidence of underreporting of adverse events. No serious adverse events (SAEs) were reported for any subjects at this site.

2) Site 163: Manuel F. Fernandez, M.D., Medical Professional Clinical Research Center, Inc., 3850 SW 87 Ave, Suites 201 and 202, Miami, FL 33165; Inspection Dates: 2/9/2023 – 2/17/2023

   OSI found some irregularities here including one subject who was enrolled despite not meeting inclusion criteria, a protocol deviation that was not correctly remediated and not included in the protocol deviation line listings. Overall, however, OSI found that it was very unlikely the irregularities affected the efficacy analysis.

**Efficacy Results – Secondary and other relevant endpoints**

The pre-specified key secondary endpoints for Study B16-02 were:

1) Change from baseline in "off" time measured in hours, averaged over the PD diary days at the end of the double-blind treatment period (Visit 7 or ET)
2) PGI-C (Patient Global Impression of Change) Scores, being the proportion of subjects recording either "much improved" or "very much improved" at the end of the double-blind treatment period (Visit 7 or ET)
3) the MDS-UPDRS Part III Scores and
4) the sum of the MDS-UPDRS Parts II and III Scores.

The primary and the first key secondary endpoints that were measured from PD diaries were analyzed on the mITT set. For the other three key secondary endpoints, the Applicant were analyzed on the ITT set, as the PGI-C and MDS-UPDRS Parts II & III instrument ratings were independent of the diaries.

The following key secondary endpoint results were statistically significant:

(1) <u>"Off" Time: Change in hours from baseline (Visit 4) to end of treatment (Visit 7 /ET)</u>
The IPX203-treated group showed less increase in off time than the IR CD/LD-treated group over the same double-blind treatment period. The least square mean change at Visit 7 from baseline was -0.38 in the IPX203 treated group and -0.86 in

the IR CD/LD treated group, a difference of -0.48 hours = -28 minutes (p=0.025). This treatment effect held throughout the treatment period.

(2) PGI-C Scores at the end of the double-blind treatment period (Visit 7 or ET)
The proportion of subjects reporting either "much improved" or "very much improved" was 29.7% in the IPX203-treated group compared with 18.8% in the IR CD/LD-treated group, a difference of 10.9% (p=0.0015).

The change from baseline in the MDS-UPDRS Part III Score did not reach statistical significance. The LS mean change (SE) in the MDS-UPDRS Part III total score from baseline to Week 13 was 0.7648 (0.7087) for IPX203 and 0.8110 (0.7153) for IR CD/LD. The LS mean difference between two groups was -0.0461 (95% CIs [-1.7945, 1.7022], p = 0.9587). As the last key secondary endpoint (change from baseline in the sum of the MDS-UPDRS Parts II and III Scores) followed in the statistical hierarchy, it was not analyzed by Dr. Park. Per the CSR from Study B16-02, for the sum of MDS-UPDRS Parts II + III, the LS mean change in the total score from baseline to Week 13 was 1.7 for IPX203 and 1.8 for IR CD/LD. The LS mean difference between two groups was 1.11 ([-2.2, 2.1]).

*Reviewer Comment:*

*The primary endpoint (mean change from baseline in hours of good "on" time during the treatment period (-31.8 minutes)) and the first key secondary outcome measure (mean decrease in "off" time observed (-28 minutes)) were measured separately and counted as distinct clinical endpoints. However, they are related, as one would expect an increase in good "on" time to correlate with a decrease in "off" time (and possibly a decrease in "on" time with troublesome dyskinesia). These inverse results are consistent with each other, reinforcing the likelihood that the observed effects were not a result of chance. An approximate half hour of regained good "on" time without troublesome dyskinesia /decreased "off" time is modestly clinically meaningful.*

*Measurement of "off" time as recorded in patient diaries is an accepted measure of clinical efficacy. Similar measures were used in prior pivotal trials for Parkinson's disease, including as the primary outcome measure for ADVANCE-PD, the pivotal Phase 3 trial for Rytary, in which the primary efficacy outcome was "Percentage of 'Off' Time During Waking Hours at End of Study" and a key secondary outcome was "'Off' time hours measured by using the Parkinson's disease diary.' In present Study B16-02 the mean change in off time is 28 minutes. In prior studies by the present study's principal investigator that sought to establish a threshold for clinical meaningfulness, the proposed a measure of clinical meaningfulness (the Minimal Clinically Important Difference, MCID) for PD studies and observed that "In surveying the literature to date, studies suggest that*

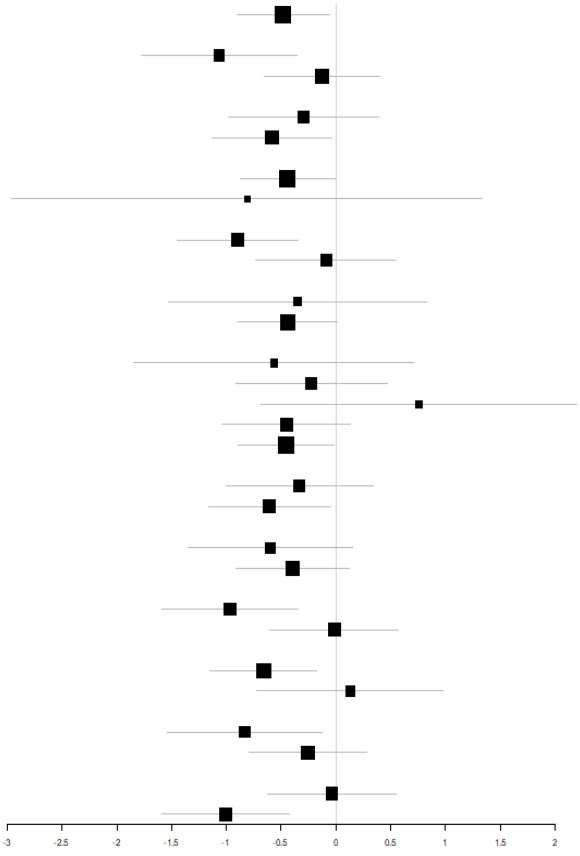
*the lower limit of MCID for total UPDRS (I + II + III) is −3.8 and for change on OFF time is −1.0 hour."*[6,7]

*The PGI-C is also an accepted clinical efficacy measure. It is used here not as a stand-alone measure of efficacy but rather as a reinforcement to the primary efficacy endpoint, which the statistically significant result supports.*

Subgroup Analyses of the two secondary endpoints with statistically significant efficacy results showed similar trends to the subgroup analyses for the primary efficacy endpoint:

**Figure 5: Forest Plot of Subgroup Analysis for Key Secondary Endpoint: Change from Baseline to Visit7/ET in "Off" Time during DBP by Randomized Treatment Group (mITT Population)**

| | IR CD-LD n | IPX203 n | LS Mean Difference (95% CI) |
|---|---|---|---|
| Overall | 246 | 249 | -0.481 (-0.902, -0.060) |
| Age | | | |
| <65 years | 90 | 97 | -1.067 (-1.782,-0.351) |
| >=65 years | 156 | 152 | -0.125 (-0.654,0.404) |
| Gender | | | |
| Female | 72 | 97 | -0.298 (-0.984,0.389) |
| Male | 174 | 152 | -0.586 (-1.135,-0.037) |
| Race | | | |
| Caucasian | 239 | 237 | -0.445 (-0.878,-0.012) |
| Non-Caucasian | 7 | 12 | -0.810 (-2.96, 1.339) |
| Region | | | |
| North America | 132 | 117 | -0.896 (-1.449,-0.343) |
| Europe | 114 | 132 | -0.091 (-0.733, 0.551) |
| Ethnicity | | | |
| Hispanic or Latino | 31 | 32 | -0.351 (-1.533, 0.831) |
| Not Hispanic or Latino | 211 | 216 | -0.444 (-0.903, 0.015) |
| Concomitant Medications | | | |
| Amantadine | 24 | 28 | -0.566 (-1.845, 0.713) |
| Selective MAOB inhibitors | 76 | 88 | -0.226 (-0.917, 0.465) |
| Anticholinergic PD medications | 9 | 13 | 0.754 (-0.687, 2.197) |
| Dopamine agonists | 116 | 142 | -0.453(-1.038, 0.133) |
| Others | 227 | 231 | -0.456(-0.897,-0.016) |
| Weight | | | |
| <75 kg | 92 | 111 | -0.333 (-1.005, 0.339) |
| >=75 kg | 154 | 137 | -0.607 (-1.165,-0.049) |
| BMI | | | |
| <25 kg/m2 | 83 | 79 | -0.599 (-1.354, 0.155) |
| >=25 kg/m2 | 163 | 169 | -0.393 (-0.908, 0.122) |
| PD duration | | | |
| <8 years | 122 | 123 | -0.968 (-1.59, -0.345) |
| >=8 years | 124 | 126 | -0.015 (-0.602, 0.572) |
| Age of PD onset | | | |
| <65 years | 180 | 191 | -0.660 (-1.147,-0.173) |
| >=65 years | 66 | 58 | 0.129 (-0.722, 0.98) |
| Good On time at entry | | | |
| <9 h/day | 96 | 96 | -0.833 (-1.535,-0.131) |
| >=9 h/day | 150 | 153 | -0.258 (-0.794, 0.279) |
| Off time at entry | | | |
| <6 h/day | 128 | 121 | -0.037 (-0.621, 0.548) |
| >=6 h/day | 118 | 128 | -1.009 (-1.594,-0.424) |

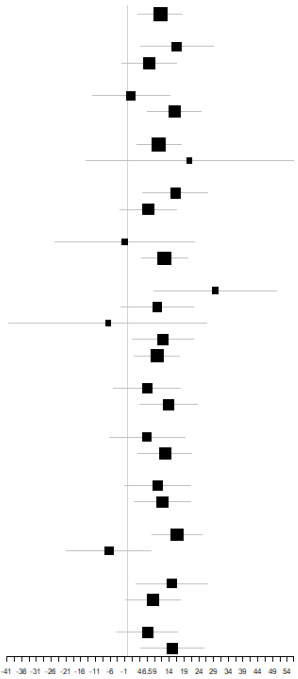



Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt

[6] Hauser RA, Auinger P, On Behalf of the Parkinson Study Group Determination of minimal clinically important change in early and advanced Parkinson's disease. Movement Disorders. 2011;26(5):813–818.
[7] Hauser RA, Gordon MF, Mizuno Y, Poewe W, Barone P, Schapira AH, Rascol O, Debieuvre C, Fräßdorf M. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis. 2014;2014:467131. doi: 10.1155/2014/467131. Epub 2014 Apr 1.

**Figure 6: Forest Plot of Subgroup Analysis for Key Secondary Endpoint: PGI-C Scores by Randomized Treatment Group (ITT Population)**

| | IR CD-LD n(%) of much/ very much improved | IPX203 n(%) of much/ very much improved | Percent Difference (95% CI) |
|---|---|---|---|
| Overall | 47 (18.8) | 76 (29.7) | 10.9 (3.5, 18.3) |
| Age | | | |
| <65 years | 17 (18.5) | 35 (35.0) | 16.5 (4.3, 28.8) |
| >=65 years | 30 (19.0) | 41 (26.3) | 7.3 (-1.9, 16.5) |
| Gender | | | |
| Female | 18 (24.7) | 25 (25.8) | 1.1 (-12.1, 14.3) |
| Male | 29 (16.4) | 51 (32.1) | 15.7 (6.6, 24.8) |
| Race | | | |
| Caucasian | 46 (19.0) | 72 (29.5) | 10.5 (2.9, 18.1) |
| Non-Caucasian | 1 (12.5) | 4 (33.3) | 20.8 (-14.3, 56.0) |
| Region | | | |
| North America | 29 (21.6) | 46 (37.7) | 16.1 (5.0, 27.1) |
| Europe | 18 (15.5) | 30 (22.4) | 6.9 (-2.8, 16.5) |
| Ethnicity | | | |
| Hispanic or Latino | 11 (35.5) | 11 (34.4) | -1.1 (-24.7, 22.4) |
| Not Hispanic or Latino | 36 (16.7) | 65 (29.1) | 12.4 (4.6, 20.2) |
| Concomitant Medications | | | |
| Amantadine | 2 (8.3) | 11 (37.9) | 29.6 (8.8, 50.4) |
| Selective MAOB inhibitors | 13 (16.7) | 24 (26.7) | 10.0 (-2.3, 22.3) |
| Anticholinergic PD medications | 2 (22.2) | 2 (15.4) | -6.8 (-40.3, 26.7) |
| Dopamine agonists | 22 (18.5) | 44 (30.3) | 11.9 (1.6, 22.1) |
| Others | 43 (18.7) | 68 (28.6) | 9.9 (2.2, 17.5) |
| Weight | | | |
| <75 kg | 18 (19.1) | 29 (25.7) | 6.5 (-4.8, 17.8) |
| >=75 kg | 29 (18.6) | 46 (32.4) | 13.8 (4.0, 23.6) |
| BMI | | | |
| <25 kg/m2 | 17 (19.8) | 21 (26.2) | 6.5 (-6.3, 19.3) |
| >=25 kg/m2 | 30 (18.3) | 54 (30.9) | 12.6 (3.5, 21.6) |
| PD duration | | | |
| <8 years | 30 (24.2) | 43 (34.4) | 10.2 (-1.0, 21.4) |
| >=8 years | 17 (13.5) | 33 (25.2) | 11.7 (2.2, 21.2) |
| Age of PD onset | | | |
| <65 years | 30 (16.3) | 64 (33.0) | 16.7 (8.2, 25.2) |
| >=65 years | 17 (25.8) | 12 (19.3) | -6.4 (-20.8, 8.0) |
| Good On time at entry | | | |
| <9 h/day | 18 (18.6) | 32 (33.3) | 14.8 (2.6, 27.0) |
| >=9 h/day | 29 (18.9) | 44 (27.5) | 8.5 (-0.7, 17.8) |
| Off time at entry | | | |
| <6 h/day | 24 (18.7) | 32 (25.4) | 6.6 (-3.5, 16.8) |
| >=6 h/day | 23 (18.8) | 44 (33.8) | 15.0 (4.3, 25.7) |




Source: Statistical Reviewer Analysis; adpddep.xpt, adsl.xpt

*Reviewer Comment:*

*Similar to the primary endpoint, these secondary endpoint subgroup analyses suggest that while there is an overall significant change in these secondary outcome measures, the effects may be greatest in the age <65 group, and the age of onset <65 group compared to those aged ≥ 65 or with age of onset ≥ 65. These younger, and younger age at onset groups that are driving the majority of the significant results seen here may experience the majority of benefit from IPX203. However, the study and resulting analysis were not powered to detect these differences, therefore these cannot be stated as definitive conclusions.*

All the other subgroup analysis results were consistent with the overall efficacy analysis results.

**Dose/Dose Response**

This study was not designed to assess a dose response.

**Durability of Response**

This study was not designed to assess durability of response.

**Persistence of Effect**

This study was not designed to assess persistence of effect.

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

Not Applicable. Study B16-02 is the only randomized, double-blind, controlled clinical trial submitted with the NDA.

### 7.1.1. Primary Endpoints

Not Applicable.

### 7.1.2. Secondary and Other Endpoints

Not Applicable.

### 7.1.3. Subpopulations

See section 6.1.2 above for a discussion of subgroup analyses in Study B16-02.

### 7.1.4. Dose and Dose Response

Study B16-02 was a flexible dose study; dose response was not assessed.

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

During the double-blind treatment period of Study B16-02, in both the IPX203 and IR CD/LD treatment groups, there was a sharp decline in the primary endpoint, change in good "on" time from baseline to Visit 7/ET that occurred between the outset of the randomization period (Visit) and Study Visit 5, 3 weeks later. The IPX203 group showed less of a decline than the IR CD/LD group and this difference gradually slightly widened through the end of the 13-week double-blind period (Visit 7/ET).

## 7.2. Additional Efficacy Considerations

The Applicant has proposed labeling for a broader indication than that which was studied, including post-encephalitic parkinsonism and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication, which is the indication for both Sinemet and Rytary Given the lack of an adequate scientific bridge to the listed drugs, it is unclear if the Applicant can rely on the listed drugs to support the proposed indication given that the efficacy study was completed only in patients with advanced PD with motor fluctuations. However, it still may be possible to use the bridge to IR CD/LD for the levodopa component alone; this may be a

reasonable approach, given that the efficacy is expected to come from levodopa. However, because of the safety concerns resulting in a Complete Response, this determination will be a matter of review upon resubmission.

#### 7.2.1. Considerations on Benefit in the Post-market Setting

Not applicable at this time.

#### 7.2.2. Other Relevant Benefits

None.

### 7.3. Integrated Assessment of Effectiveness

The change from baseline to the end of the double-blind treatment period for good "on" time (primary endpoint), decreased "off" time (key secondary endpoint) and in PGI-C at the end of the double-blind treatment period (key secondary endpoint) in Study B16-02 showed a statistically significant change favoring IPX203 compared to IR CD/LD in subjects with moderate to advanced PD with motor fluctuations.

The results of this single, large, multicenter, adequate and well-controlled trial demonstrate an effect on a distinct and prespecified, clinically meaningful endpoint (relatively less decrease from baseline in good "on" time without troublesome dyskinesia and decrease from baseline in "off" time) and is complemented by a statistically significant difference in a subjective, patient-reported endpoint (the PGI-C), establishing internal consistency across results.

Additionally, the mechanism of action of carbidopa/levodopa is well-understood and well-established. These factors meet the standard of a single adequate and well-controlled clinical investigation together with confirmatory evidence in the form of compelling mechanistic evidence, in the setting of a well-understood disease pathophysiology; well-documented natural history of disease; and support by scientific knowledge about the effectiveness of other drugs in the same pharmacologic class. The Applicant has met the regulatory requirement for demonstrating substantial evidence of effectiveness of IPX203 for the treatment of advanced PD.

## 8. Review of Safety

### 8.1. Safety Review Approach

The Applicant conducted a development program for the indication of treatment of Parkinson's disease, post-encephalitic parkinsonism and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication, based on a randomized, double-blind, active-controlled trial of IPX203 vs. IR CD/LD and a PK comparison of IPX203 to IR CD/LD and ER CD/LD. The primary safety data were generated from the controlled safety database, which

includes the data from Study B16-02, which is described in Section 6.

**Uncontrolled Safety Data:**
All subjects who completed Study B16-02 had the option of continuing into an open-label extension study, Study B16-03. All subjects who chose to enroll in Study B16-03 (both those who had received IPX203 and those who had received IR CD/LD in the double-blind period of the controlled study) were reinstated on their final dose regimen of IPX203 established in the dose conversion phase of Study B16-02. Investigators were then permitted to adjust and optimize the dose and regimen of IPX203, and all changes were recorded. The open label study consisted of a Baseline visit 1, followed by three visits (Visits 2-4) spaced at 3-month intervals.

**Pooling Data across Studies**:
Because the patient populations and IPX203 doses were comparable in Studies B16-02 and B16-03, the Applicant proposed to pool safety analyses from both studies. The Division accepted this approach for the exposure analysis, as all subjects in both the controlled and uncontrolled trials had received at least one dose of the study drug. However, these studies differed sufficiently in design to prevent pooling for analyses of adverse events, vital signs, laboratory findings, and ECGs; one is controlled and blinded, whereas the other is uncontrolled and open-label. The Division therefore analyzed the two studies individually for the remainder of the safety analyses.

Analyses in this section are based on the controlled safety datasets from the IR CD/LD dose adjustment phase, IPX203 conversion phase, and double-blind phase of the randomized controlled blinded trial, with additional analyses from the open-label uncontrolled trial. Certain additional analyses pooled data from both studies, specifically the analysis of adverse events from any time period.

**Analyses of Adverse Event Data**
The adae.xpt datafile was examined for accuracy of translation from verbatim to preferred term through manual review of all unique pairs of verbatim and preferred terms. Some AEs were coded under slightly different terms, although the underlying events were very similar and/or related. Therefore, several AE terms were recoded to avoid underestimating prevalence of a specific adverse event. Some terms were also recoded for ease of review, although none rose to the level of a new safety concern. The following table shows the original AE code on the left after the subject identifier, and revised codes on the right. Terms that only resulted in the addition of one or two cases after recoding are not included in the table.

**Table 6: Treatment Emergent Adverse Event Coding Errors, Study B16-02**

| Unique Subject Identifier | Reported Term for the Adverse Event | Dictionary-Derived Term | Reviewer comment or Recode |
|---|---|---|---|
| IPX203-B16-02-(b) (6) | abdominal pain due to GERD | abdominal pain | Need to report GERD. |
| IPX203-B16-02-(b) (6) | bilateral radicular ls neuropathy | radiation neuropathy | Radiculopathy |

| Unique Subject Identifier | Reported Term for the Adverse Event | Dictionary-Derived Term | Reviewer comment or Recode |
|---|---|---|---|
| IPX203-B16-02-(b) (6) | increasing dyskinesia | dystonia | Dyskinesia |
| IPX203-B16-02-(b) (6) | inner unrest | restlessness | Akathisia |
| IPX203-B16-02-(b) (6) | intermittent internal shaky feeling- not tremor | nervousness | Shakiness |
| IPX203-B16-02-(b) (6) | intermittent lightheaded when standing | dizziness | Orthostatic Dizziness |
| IPX203-B16-02-(b) (6) | involuntary clenching of teeth- muscle contractions involuntary | muscle contractions involuntary | Trismus |
| IPX203-B16-02-(b) (6) | lightheadedness on standing, unknown cause | dizziness | Orthostatic Dizziness |
| IPX203-B16-02-(b) (6) | loss of balance - as induced by dystonia. no falls. | balance disorder | Dystonia |
| IPX203-B16-02-(b) (6) | mental cloudiness | depressed level of consciousness | Mental Impairment |
| IPX203-B16-02-(b) (6) | myoclonic leg jerks | muscle twitching | Myoclonus |
| IPX203-B16-02-(b) (6) | overweight. the patient gained 3 kg in weight during the last visits. the patient's inactivity may have contributed to this. | overweight | Hyperphagia |
| IPX203-B16-02-(b) (6) | pessimistic thoughts | thinking abnormal | Depression |
| IPX203-B16-02-(b) (6) | wife covid pos, patient negative in the rapid test | viral test negative | Not an adverse event |

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

All of the safety data in the primary safety analyses were generated in Studies B16-02 and B16-03. The data from these studies provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs.

The primary NDA safety database from Study B16-02 includes a total of 589 subjects who were exposed to at least one dose of IPX203. The uncontrolled safety dataset from Study B16-03 comprises 419 subjects, all of whom had been included in the 589-person sample from Study B16-02 and completed the IPX203 conversion period. Of these, 220 had additionally received IPX203 during the double-blind treatment period of Study B16-02.

Table 7 below illustrates the total number of subjects in Study B16-02 exposed to any dose of IPX203 and the differences in period of exposure by study group. Of the initial 770 subjects who completed screening for Study B16-02, 630 enrolled and entered the IR CD/LD dose adjustment period. Of these, 589 completed that period and entered the IPX203 Conversion period. A total of 506 subjects completed the conversion period; these entered the randomization period and were treated during the double-blind (DB) period with 495 subjects included in the mITT

population.

In the mITT population, 249 subjects received IPX203 while 246 received IR CD/LD. Of these, 446 subjects completed the double-blind treatment period; 220 received IPX203 and 226 received IR CD/LD. Of these 446 completers, 419 subsequently enrolled in the open-label trial, in which all received IPX203. Among the subjects in the uncontrolled OLE study (Table 8), 352 completed the study, 179 of whom had received IPX203 during the controlled study's double-blind phase.

**Table 7: Analysis Populations, Study B16-02**

| | Dose Adjustment Period | Conversion Period | Double-Blind Period | | |
|---|---|---|---|---|---|
| | IR CD/LD | IPX203 | IPX203 | IR CD/LD | All |
| **Enrolled Population** | 630 | 589 | 256 | 250 | 506 |
| **Randomized Population** | 506 | 506 | 256 | 250 | 506 |
| **Treated in DB Period** | 506 | 506 | 256 | 250 | 506 |
| **Intent-To-Treat Population** | 506 | 506 | 256 | 250 | 506 |
| **Modified Intent-to-Treat Population** | 495 | 495 | 249 | 246 | 495 |
| **Completers Population** | 446 | 446 | 220 | 226 | 446 |
| **Per-Protocol Population** | 313 | 313 | 155 | 158 | 313 |

Source: FDA Analysis

**Table 8: Analysis Populations, Study B16-03**

| | Dose Adjustment Period | Conversion Period | Double-Blind Period | | |
|---|---|---|---|---|---|
| | IR CD/LD | IPX203 | IPX203 | IR CD/LD | All |
| **Enrolled Population** | 419 | 419 | 206 | 213 | 419 |
| **Completers Population** | 352 | 352 | 179 | 173 | 352 |

Source: FDA Analysis

The pooled exposure population thus consists of multiple populations who received IPX203 for variable periods of time, depending on whether they were randomized to IPX203 in the double-blind period, whether they progressed to the open-label study, or whether they withdrew or were dropped from the studies at any point after beginning the IPX203 conversion period.

In addition to differences in exposure period, the trial design of Study B16-02 involved flexible dosing in the IPX203 conversion period. Once the treating clinician found the optimal dose of IPX203, the dose was to remain constant during the double-blind treatment period. This same dose established in the Study B16-02 conversion period later became the fixed dose used for the duration of the open-label trial. Because dosing was flexible, duration of exposure by dose was assessed in dose groups.

As seen in Table 9 below, the Applicant originally submitted the exposure data in the pooled safety population as a function of average total daily dose, which produced a higher number of subjects (43) taking near-maximal doses (> 2000mg/day) exposed for a period of at least 12 months. This number approached but did not meet the Agency's exposure criteria of 100

subjects exposed for a minimum of 1 year with at least half of the subjects taking the maximum dose requested (here 2400mg/day). Of note, it is not possible to administer (b) (4) (the proposed maximum dose) using the dosage strength the Applicant proposes.

**Table 9: Total Daily Dose and Exposure (mean average total daily dose) (Pooled Safety Population)**

| Characteristic | ≥ 1 day | ≥ 3 months | ≥ 6 months | ≥ 9 months | ≥ 12 months |
|---|---|---|---|---|---|
| Number of Subjects | 584 | 429 | 385 | 363 | 179 |
| IPX203 mean average total daily dose (mg) | | | | | |
| N | 584 | 429 | 385 | 363 | 179 |
| Mean (SD) | 1521 (588.2) | 1492 (600.8) | 1500 (597.3) | 1493 (594.8) | 1503 (615.9) |
| Median (Min, Max) | 1535 (398.5, 3987) | 1427 (433.2, 3987) | 1462 (433.2, 3987) | 1425 (433.2, 3987) | 1456 (499.1, 3987) |
| IPX203 average total daily dose category, n (%) | | | | | |
| < 400 | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 400 - < 800 | 62 (10.6) | 51 (11.9) | 45 (11.7) | 41 (11.3) | 22 (12.3) |
| 800 - < 1200 | 123 (21.1) | 100 (23.3) | 86 (22.3) | 84 (23.1) | 39 (21.8) |
| 1200 - < 1600 | 121 (20.7) | 88 (20.5) | 82 (21.3) | 81 (22.3) | 36 (20.1) |
| 1600 - < 2000 | 132 (22.6) | 90 (21.0) | 83 (21.6) | 74 (20.4) | 39 (21.8) |
| 2000 - < 2400 | 112 (19.2) | 75 (17.5) | 66 (17.1) | 62 (17.1) | 32 (17.9) |
| 2400 - < 2800 | 28 (4.8) | 21 (4.9) | 19 (4.9) | 17 (4.7) | 9 (5.0) |
| 2800 - < 3200 | 2 (0.3) | 1 (0.2) | 1 (0.3) | 1 (0.3) | 0 (0.0) |
| > 3200 | 3 (0.5) | 3 (0.7) | 3 (0.8) | 3 (0.8) | 2 (1.1) |

Source: FDA clinical analyst, confirming Applicant's initial exposure analysis

Upon request, the Applicant then submitted the datasets with the modal daily dose included. Modal daily dose for any given subject is defined as the most frequently observed total daily dose for that subject and is the preferred method for calculating exposure in a flexible dose study such as Studies B16-02 and B16-03. Mean daily dose is an average that may not necessarily reflect what daily dose individual subjects actually took; in contrast, modal daily dose more accurately captures most subjects' actual exposures.

Table 10 characterizes exposure to IPX203 as a function of modal daily dose pooled across both the controlled and the open-label study. This analysis shows that there was an insufficient number of subjects (67) who received IPX203 for 1 year at ANY dose.

**Table 10: Exposure by Modal Daily Dose and Duration (Pooled Safety Population)**

| | ≥ 180 Days | ≥ 360 Days |
|---|---|---|
| **Modal Daily Dose Binned (200 mg)** | **Sum** | **Sum** |
| 200 to 399 | 0 | 0 |
| 400 to 599 | 25 | 10 |
| 600 to 799 | 10 | 5 |
| 800 to 999 | 46 | 8 |
| 1000 to 1199 | 21 | 2 |
| 1200 to 1399 | 47 | 9 |
| 1400 to 1599 | 23 | 1 |

| | ≥ 180 Days | ≥ 360 Days |
|---|---|---|
| **Modal Daily Dose Binned (200 mg)** | **Sum** | **Sum** |
| 1600 to 1799 | 44 | 15 |
| 1800 to 1999 | 12 | 3 |
| 2000 to 2199 | 27 | 6 |
| 2200 to 2399 | 27 | 8 |
| 2400 to 2599 | 9 | 0 |
| 2600 to 2799 | 1 | 0 |
| 2800 to 2999 | 5 | 0 |
| 3200 to 3399 | 2 | 0 |
| 5000 to 5199 | 0 | 0 |
| All | 299 | 67 |

Source: FDA Analysis

Further, a finer analysis of the modal daily doses (Table 11) shows that only 14 subjects took at least 2000 mg for 1 year. No subjects were exposed to IPX203 for 12 months or greater at doses of 2400mg or greater.

**Table 11: Exposure to IPX203 ≥ 2000mg Modal Daily Dose by Duration (Pooled Safety Population)**

| | ≥ 180 Days | ≥ 360 Days |
|---|---|---|
| **Modal Daily Dose Binned (100 mg)** | **Sum** | **Sum** |
| 2000 to 2099 | 2 | 0 |
| 2100 to 2199 | 25 | 6 |
| 2200 to 2299 | 14 | 3 |
| 2300 to 2399 | 13 | 5 |
| 2400 to 2499 | 0 | 0 |
| 2500 to 2599 | 9 | 0 |
| 2600 to 2699 | 1 | 0 |
| 2800 to 2899 | 3 | 0 |
| 2900 to 2999 | 2 | 0 |
| 3300 to 3399 | 2 | 0 |
| 5000 to 5099 | 0 | 0 |
| All | 71 | 14 |

Source: FDA Analysis

*Reviewer comment:*

*Based on these analyses, IPX203 lacks sufficient exposure data at the full range of doses proposed in the labeling. In light of this formulation's lack of a bridge to IR CD/LD (Sinemet) or CD/LD-ER (Rytary), the chronic exposure data in this NDA submission are not sufficient to support the safety of chronic dosing of IPX203.*

### 8.2.2. Relevant characteristics of the safety population:

Baseline demographics and disease characteristics for subjects in the double-blind safety population were balanced between the IPX203 and IR CD/LD groups (Table 12). Just over 60%

of subjects were 65 or older and just under 40% were under age 65. Most patients were male, about 65% at each stage. About half of the total subjects recruited and enrolled were in the United States. The overwhelming majority (~96%) were White. The mean duration of PD was 8 years.

At the time of entry into Study B16-02, 71.7% of subjects were Hoehn and Yahr Stage 2 and 17.3% were Hoehn and Yahr Stage 3. Stage 2 implies bilateral disease; Stage 3 implies postural imbalance. The Hoehn and Yahr criteria do not describe motor fluctuations, which was the target population; this was assessed indirectly with the measurement of mean daily "off" time and mean daily "good on" time (defined as on time without troublesome dyskinesia). These proportions were preserved across the phases of Study B16-02 [and at entry into Study B16-03].

**Table 12: Baseline Demographic and Disease Characteristics, Study B16-02 (Controlled Safety Population)**

| | Dose Adjustment Period IR CD/LD | Conversion Period IPX203 | Double-Blind Period | |
|---|---|---|---|---|
| | | | IPX203 | IR CD/LD |
| **Age** | | | | |
| N | 630 (100%) | 589 (93.5%) | 256 (40.6%) | 250 (39.7%) |
| Mean | 66.5 | 66.3 | 66.1 | 66.5 |
| Min | 40 | 40 | 44 | 40 |
| Max | 89 | 89 | 88 | 89 |
| Median | 67 | 67 | 66.5 | 68 |
| **Pooled Age Group 1** | | | | |
| < 65 years | 236 (37.5%) | 226 (38.4%) | 100 (39.1%) | 92 (36.8%) |
| ≥ 65 years | 394 (62.5%) | 363 (61.6%) | 156 (60.9%) | 158 (63.2%) |
| **Sex** | | | | |
| F | 234 (37.1%) | 217 (36.8%) | 97 (37.9%) | 73 (29.2%) |
| M | 396 (62.9%) | 372 (63.2%) | 159 (62.1%) | 177 (70.8%) |
| **Race** | | | | |
| American Indian or Alaska Native | 3 | 3 | 3 | 0 |
| Asian | 10 | 10 | 5 | 3 |
| Black or African American | 6 | 6 | 2 | 3 |
| Unknown | 5 | 4 | 2 | 2 |
| White | 606 (96.2%) | 566 (96.1%) | 244 (95.3%) | 242 (96.8%) |
| **Ethnicity** | | | | |
| Hispanic or Latino | 77 | 74 | 32 | 31 |
| Not Hispanic or Latino | 544 | 507 | 223 | 215 |
| Not Reported | 9 | 8 | 1 | 4 |
| **Country** | | | | |
| CZE | 45 | 42 | 17 | 16 |
| DEU | 48 | 44 | 19 | 19 |
| ESP | 71 | 61 | 33 | 23 |
| FRA | 13 | 12 | 5 | 5 |
| GBR | 12 | 11 | 7 | 4 |
| ITA | 36 | 35 | 17 | 15 |
| POL | 78 | 75 | 36 | 34 |

| | Dose Adjustment Period IR CD/LD | Conversion Period IPX203 | Double-Blind Period | |
|---|---|---|---|---|
| | | | IPX203 | IR CD/LD |
| USA | 327 (52%) | 309 (52.5%) | 122 (47.6%) | 134 (53.6%) |
| **Baseline Weight (kg)** | | | | |
| N | 628 | 587 | 255 | 250 |
| Mean | 78.9 | 79 | 78.7 | 80.7 |
| Min | 41.8 | 41.8 | 41.8 | 45 |
| Max | 165.5 | 165.5 | 139.2 | 140.1 |
| Median | 77.6 | 77.9 | 77.4 | 78.6 |
| **Baseline Height (cm)** | | | | |
| N | 629 | 588 | 256 | 250 |
| Mean | 169.6 | 169.6 | 169.1 | 171.7 |
| Min | 124.5 | 124.5 | 124.5 | 145 |
| Max | 195.4 | 195.4 | 195.4 | 193 |
| Median | 170.2 | 170.2 | 170 | 172.7 |
| **Baseline BMI (kg/m2)** | | | | |
| N | 628 | 587 | 255 | 250 |
| Mean | 27.3 | 27.3 | 27.4 | 27.3 |
| Min | 16.3 | 16.3 | 16.3 | 17.6 |
| Max | 52.6 | 52.6 | 52.6 | 45.1 |
| Median | 26.7 | 26.7 | 27 | 26.8 |
| **Baseline BMI Category** | | | | |
| < 25 kg/m2 | 213 | 199 | 80 | 86 |
| ≥ 25 kg/m2 | 415 | 388 | 175 | 164 |
| **Duration of PD (Years)** | | | | |
| N | 630 | 589 | 256 | 250 |
| Mean | 8.5 | 8.4 | 8.4 | 8.2 |
| Min | 0 | 0 | 0 | 0 |
| Max | 30 | 24 | 23 | 24 |
| Median | 8 | 8 | 8 | 8 |
| **Duration of PD (Category)** | | | | |
| < 8 years | 303 | 289 | 125 | 124 |
| ≥8 years | 327 | 300 | 131 | 126 |
| **Good On Time at Study Entry (avg. h/day)** | | | | |
| N | 630 | 589 | 256 | 250 |
| Mean | 9.6 | 9.5 | 9.5 | 9.6 |
| Min | 0.5 | 0.5 | 1.7 | 0.5 |
| Max | 15.8 | 15.8 | 14.8 | 15.8 |
| Median | 9.7 | 9.7 | 9.7 | 9.7 |
| **Good On Time at Study Entry Category** | | | | |
| < 9 h | 239 | 228 | 96 | 97 |
| ≥ 9 h | 391 | 361 | 160 | 153 |
| **Off Time at Study Entry (avg. h/day)** | | | | |
| N | 630 | 589 | 256 | 250 |
| Mean | 6.1 | 6.2 | 6.1 | 6.1 |
| Min | 1.7 | 1.7 | 2.2 | 1.7 |
| Max | 16.7 | 16.7 | 13.7 | 13.2 |
| Median | 6 | 6 | 6 | 5.8 |
| **Off Time at Study Entry Category** | | | | |

| | Dose Adjustment Period IR CD/LD | Conversion Period IPX203 | Double-Blind Period IPX203 | Double-Blind Period IR CD/LD |
|---|---|---|---|---|
| < 6 h | 310 | 287 | 126 | 128 |
| ≥ 6 h | 320 | 302 | 130 | 122 |
| **Baseline Hoehn-Yahr Stage (n (%))** | | | | |
| 0 | 1 (0.2) | 0 | 0 | 0 |
| 1 | 28 (6.7) | 53 (9.0) | 27 (10.5) | 21 (8.4) |
| 2 | 299 (71.7) | 409 (69.4) | 173 (67.6) | 173 (69.2) |
| 3 | 72 (17.3) | 113 (19.2) | 50 (19.5) | 49 (19.6) |
| 4 | 16 (3.8) | 14 (2.4) | 6 (2.3) | 7 (2.8) |
| 5 | 1 (0.2) | 0 | 0 | 0 |
| All | 417 (100.0) | 589 (100.0) | 256 (100.0) | 250 (100.0) |

Source: FDA Analysis

The demographics of Study B16-03 were similar to those of Study B16-02 (Table 13). The baseline values for subjects enrolled in both studies were identical.

**Table 13: Demographics and Disease Characteristics, Study B16-03 (Open-Label Safety Population)**

| | IPX203 N=419 |
|---|---|
| **Age** | |
| N | 419 |
| Mean | 66.89 |
| Std Dev | 8.86 |
| Min | 41 |
| Max | 90 |
| Median | 68 |
| **Age Group** | **n (%)** |
| 39 < Age ≤64 | 152 (36.3) |
| 64<Age ≤74 | 191 (45.6) |
| Age >74 | 76 (18.1) |
| All | 419 (100.0) |
| **Sex** | **n (%)** |
| Female | 140 (33.4) |
| Male | 279 (66.6) |
| All | 419 (100.0) |
| **Race** | **n (%)** |
| Asian | 6 (1.4) |
| Black or African American | 4 (1.0) |
| Unknown | 3 (0.7) |
| White | 406 (96.9) |
| All | 419 (100.0) |
| **Ethnicity** | **n (%)** |
| Hispanic or Latino | 46 (11.0) |
| Not Hispanic or Latino | 369 (88.1) |
| Not Reported | 4 (1.0) |
| All | 419 (100.0) |

| | IPX203 N=419 |
|---|---|
| **Country** | **n (%)** |
| CZE | 28 (6.7) |
| DEU | 30 (7.2) |
| ESP | 3 (0.7) |
| ESP | 39 (9.3) |
| FRA | 3 (0.7) |
| GBR | 10 (2.4) |
| ITA | 27 (6.4) |
| POL | 66 (15.8) |
| USA | 209 (49.9) |
| **Baseline BMI (kg/m2)** | |
| N | 417 |
| Mean | 27.5 |
| Min | 16.6 |
| Max | 53.2 |
| Median | 27.0 |
| **Duration of PD (years)** | |
| N | 419 |
| Mean | 8.8 |
| Min | 1.0 |
| Max | 25.0 |
| Median | 8.0 |
| **Baseline Hoehn-Yahr Stage** | **n (%)** |
| 0 | 1 (0.2) |
| 1 | 28 (6.7) |
| 2 | 299 (71.7) |
| 3 | 72 (17.3) |
| 4 | 16 (3.8) |
| 5 | 1 (0.2) |
| All | 417 (100.0) |

Source: FDA Analysis

*Reviewer Comment:*

*Notably, there was significant dropout at each successive stage of the trials. Because the phases unfolded sequentially, the substrates for each successive phase are filtrates of the prior phase, for example, subjects who encountered difficulty during the levodopa optimization would be largely excluded from the IPX203 conversion phase and those who had problems during the IPX203 optimization stage would be excluded from the subsequent randomization. The numbers of dropouts are consistent with other trials for this condition. However, the diminishing cohort in this design raised the question of whether the population ultimately randomized, and later continued into the open-label study, was sufficiently similar to that initially enrolled. Table 12 indicates that these groups were similar in the controlled trial. Exceptions were in the distribution of males vs. females and in the duration of PD. With respect to distribution by sex, males comprised 63% of subjects in the IR CD/LD dose adjustment and IPX203 conversion periods, 62% in the IPX203 group in the blinded phase, but 70% of subjects in the IR CD/LD*

*group in the blinded period. In the duration of PD in years, the maximum duration of PD in any subject enrolled was 30 years; this subject discontinued participation in the dose adjustment period bringing the maximum duration to 23-24 years in subsequent periods (not affecting mean and median). Demographic and clinical parameters were otherwise preserved across study phases. These differences did not affect the safety analyses.*

### 8.2.3. Adequacy of the safety database

Based on the disease characteristics in Table 12, the study population adequately represented the target population of people with moderate to advanced PD with motor fluctuations. The sex distribution is consistent the male predominance seen in PD. However, notwithstanding the well-reported predominance of white vs non-white patients in PD, the studies enrolled only 5 Black subjects, 7 Asian subjects, and 3 Native American or Alaskan Native (NAAN) subjects. The course of PD is not known to differ substantially by sex or race, nor is response to treatment. It is not known what factors are responsible for the increased prevalence of PD seen in White vs non-White populations; the answer is likely multifactorial, and partly genetic. A more racially diverse study population is preferable and given the lack of data provided, the risk of IPX203 to these minority populations cannot be specified. Nonetheless, the exposure data provided here seem adequately generalizable to the to-be-marketed U.S. patient population based on the current state of knowledge about Parkinson's disease.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

Issues identified that required revision included a) the request for exposure data by modal daily dose described in Section 8.2.1 above and b) in the laboratory data, where the values were gathered from multiple laboratory sites with variable reference ranges and were not harmonized at the time of submission. This limited the interpretation of the laboratory studies analysis in calculating the means, partly because of discrepant units of measurement.

Routine clinical safety evaluations were scheduled (and generally occurred) at the following timepoints:

- Study B16-02: Study visits occurred at screening and at weeks 0, 3, 5, 7, 10, 15 and 20. Visit 1/Week 0 was during the IR dose adjustment, Visits 2-4/Weeks 3-7 were during the 4 weeks IPX203 dose conversion and Visits 5-7/Weeks 10-20 were during the double-blind treatment period. Vital signs, C-SSRS and MDS-UPDRS were collected at every study visit and the ECG at the screening and at the beginning and end of the treatment period (or end of study visit). Additional safety evaluations were collected according to the Event Schedule shown below. There was also a follow up visit one week after Visit 7 (or the End of Study Visit).
- Study IPX B16-03: Study Visits occurred at enrollment and then at three-month intervals, thereafter, following the Safety data collection scheme below.

**Table 14: Event Schedule, Study B16-02**

| Assessment | Screening | 3 Weeks of IR CD/LD Dose Adjustment | 4 Weeks of IPX203 Dose Conversion | | | 13 Weeks of Double-Blind Therapy | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4 Randomization** | **Visit 5** | **Visit 6** | **Visit 7 / Study Exit / Early Termination[a]** |
| **Study Week[b]** | **–4** | **0** | **3** | **5** | **7** | **10** | **15** | **20** |
| Informed consent and HIPAA authorization[c] | X | | | | | | | |
| Contact IWRS | X | X | X | X | X | X | X | X |
| Randomization | | | | | X | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Medical history | X | | | | | | | |
| Physical examination | X | | | | | | | X |
| Vital signs[d] | X | X | X | X | X | X | X | X |
| Height and weight | X | | | | | X[e] | | Xe |
| C-SSRS | X | X | X | X | X | X | X | X |
| Clinical laboratory tests | X | | | | | X | | X |
| Urine pregnancy test | X | | | | | | | |
| Urine screen for drug abuse | X | | | | | | | |
| Alcohol breath test | X | | | | | | | |
| ECG | X | | | | | X | | X |
| MoCA[f] | X | | | | | | | |
| MDS-UPDRS Parts I-IV | X[g] | X | X | | X | X | X | X |
| PGI-C | | | | | | X | X | X |
| CGI-C | | | | | | X | X | X |
| PGI-S | | X | | | X | | | X |
| CGI-S | | X | | | X | | | X |
| PDQ-39 | | X | | | X | | X | X |
| GCSI | | X | | | | | | X |
| NMSS | | X | | | X | | X | X |
| PDSS-2 | | X | | | X | | X | X |
| PAS | | X | | | X | | X | X |
| PD Diary training; perform concordance testing at Screening only[h] | X | X | X | X | X | X | X | |
| Dispense PD Diaries[i] | X | X | | X | X | X | X | |
| Review PD Diaries[j] | | X | X | | X | X | X | X |
| Reminder phone calls[k],l | X[k] | X[l] | X[l] | X[l] | X[l] | X | X | X |

| Assessment | Screening | 3 Weeks of IR CD/LD Dose Adjustment | 4 Weeks of IPX203 Dose Conversion | | | 13 Weeks of Double-Blind Therapy | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4 Randomization** | **Visit 5** | **Visit 6** | **Visit 7 / Study Exit / Early Termination[a]** |
| **Study Week[b]** | **–4** | **0** | **3** | **5** | **7** | **10** | **15** | **20** |
| Dispense study medication | | X | X | X | X | X | X | |
| Collect empty medication bottles and any unused study drug/Perform study drug accountability | | | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X |

Source: Table 5, Study B16-02, CSR

Abbreviations: CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; GCSI = Gastroparesis Cardinal Symptom Index; HIPAA = Health Insurance Portability and Accountability Act; IR CD/LD = immediate-release carbidopa-levodopa; IWRS = interactive web response system; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NMSS = Non-Motor Symptom Assessment Scale; PAS = Parkinson Anxiety Scale; PD = Parkinson's disease; PDQ-39 = 39-Item Parkinson's Disease Questionnaire; PDSS-2 = Parkinson's Disease Sleep Scale-2; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impressions of Severity.

a. Study exit procedures were conducted at the end of Visit 7 or during an early termination visit.

b. The interval between Screening and Visit 1 (Day 1) was not to exceed 4 weeks. Study visits had to occur within ± 3 days of their specified timing.

c. Subjects enrolled at sites in the United States had to sign HIPAA authorization prior to the conduct of any study-specific procedures.

d. Record vital signs (blood pressure, heart rate, respiratory rate, and temperature [Screening and Study Exit only]) after subject had been resting supine for at least 5 minutes, then record orthostatic blood pressure and heart rate after subject had been standing for approximately 2 minutes. At Visits 1 and 4, orthostatic vital signs (blood pressure and heart rate) were performed in triplicate, each set separated by at least 15 minutes from the previous set.

e. Weight only. f. MoCA in the "On" state.

g. At Screening MDS-UPDRS Parts I through IV was done in both the "On" and "Off" state.

h. Training at Screening and then as needed at subsequent visits. Concordance testing was performed at Screening.

i. Dispensed PD Diaries at Screening and Visits 1, 3, 4, 5, and 6. Called subjects 4 days prior to Visits 1, 2 and 4-7 to remind them to complete PD Diaries. Subjects recorded diary information for 3 consecutive days immediately prior to each of the visits (Days -3, -2, and -1). Subjects were called the day prior to each visit to remind them to bring the PD Diaries, empty medication bottles, and any unused study drug to the office.

j. Reviewed PD Diaries at Visits 1, 2, and 4-7.

k. Post-Screening reminder phone call: notified individuals who successfully completed Screening procedures following review of all study entry criteria and clinical laboratory results that they could continue in the study. The interval between Screening and Visit 1 was not to exceed 4 weeks.

l. Reminder phone calls for Visits 1 through 4: In addition to the calls discussed above, regular phone calls were made (approximately every 1 to 3 days) to subjects throughout the IR CD/LD dose-adjustment and IPX203 dose-conversion periods to evaluate each subject's adjustment to the study medication regimen.

### 8.3.2. Categorization of Adverse Events

The Applicant used standard procedures to collect and analyze adverse event (AE) data. Adverse events were recorded at all subject visits, and subjects were to be monitored for adverse events through 28 days after the last dose of test drug. Investigators were asked to decide on causality and to provide their opinion on intensity (mild, moderate, severe) of each AE. AE relationship to the study drug was graded as not related, unlikely related, possibly related, or related. For summaries by relationship to the study drug, the Applicant grouped the AEs that had been assessed as "unlikely related" or "not related" as "unrelated." The Applicant grouped those AEs assessed as "possibly related" and "related" and also those where the relationship to study drug were unknown or missing, as "related." If a subject reported more than one AE within the same treatment group, system organ class (SOC) and dictionary-derived term, and any were related, the AE was summarized as related.

The standard definition of serious adverse event (SAE) was used in the development program. Treatment emergent adverse events (TEAEs) were defined as any AE that, based on start date information, occurred after the first intake of study treatment. Multiple occurrences of adverse events were counted once, per specific Medical Dictionary for Regulatory Activities (MedDRA) preferred term. MedDRA (version 19.0) was used for coding of adverse events for all the clinical studies.

As noted in Section 8.1 above, the adae.xpt datafile was reviewed for accuracy of translation from verbatim to preferred term through manual review.

The Applicant did not designate any adverse events of special interest (AESI). However, this reviewer did pay specific attention to certain adverse events known to be more germane to Parkinson's disease or generally associated with carbidopa and levodopa, namely: dyskinesia; orthostatic hypotension and hypotension-related events; nausea, vomiting and gastrointestinal distress; gait and balance disturbances; cardiac arrythmia; impulse control disorders; and psychiatric disorders including depression, depressive symptoms, and anxiety.

### 8.3.3. Routine Clinical Tests

Assessments of vital signs and laboratory monitoring were performed at screening and at multiple timepoints throughout both trials. Laboratory monitoring included assessments of the following:

- Chemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, creatine kinase, glucose,), phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total protein, and uric acid.
- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin

concentration, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.
- Urinalysis

Laboratory tests were performed at Screening and at visits 5 and 7/Early Termination in Study B16-02 and at all visits in Study B16-03. There was no indication that laboratory data were obtained in the fasting state. The Applicant evaluated laboratory values based on the Common Terminology Criteria for Adverse Events grading scheme (version 4.03). Vital signs were obtained at all visits.

## 8.4. Safety Results

### 8.4.1. Deaths

There was one death in the controlled trial. Subject ID (b) (6) died in a motor vehicle accident during the screening phase and did not receive any treatment.

In the uncontrolled trial there were five deaths. The Applicant coded them all as TEAEs, and all but one as Not Related. There was one drowning that was adjudicated as Related by the Applicant. As this was the open-label trial, all these subjects who died would have been on IPX203 at the time the adverse events developed. Of these, two had had treatment with IPX203 during Study B16-02:

1) Subject (b) (6) developed a subarachnoid hemorrhage on day 215 and died on day 240, without any change in the dose of IPX203.
2) Subject (b) (6) drowned on day 135 and died on day 142. IPX203 was withdrawn during this interval.

The other three subjects who died had had prior treatment with IR CD/LD:

3) Subject (b) (6) had a medical history of COPD and was diagnosed with lung cancer on Study Day 135, then died of a pulmonary embolism on Study Day 141. IPX203 had been withdrawn.
4) Subject (b) (6) had an intestinal volvulus on Study Day 155 and died the following day. His IPX203 dose was not changed.
5) Subject (b) (6) developed sepsis and psychosis on Study Day 56. He was treated with sedatives and antipsychotics without change to the dose of IPX203, and the psychosis improved the following day. The patient remained infected, developed an acute abdominal problem on Study Day 59 and died on Study Day 63.

**Table 15: Treatment Emergent Adverse Events with Fatal Outcome, Study B16-03 (Open-Label Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| Nervous system disorders | Subarachnoid hemorrhage | 1 (0.2) |
| Infections and infestations | Sepsis | 1 (0.2) |
| Gastrointestinal disorders | Abdominal distension | 1 (0.2) |
| | Volvulus | 1 (0.2) |
| General disorders and administration site conditions | Drowning | 1 (0.2) |
| Respiratory, thoracic and mediastinal disorders | Chronic obstructive pulmonary disease | 1 (0.2) |
| | Pulmonary embolism | 1 (0.2) |
| Cardiac disorders | Cardiogenic shock | 1 (0.2) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Lung neoplasm malignant | 1 (0.2) |

*Reviewer's comment:*

*Of the five deaths observed, two were gastrointestinal. The other causes of SAEs resulting in death were diverse. The subject who drowned had been walking on the beach, went to wash his feet, and was found drowned; he became comatose after attempted resuscitation and later died, with the cause of death recorded as drowning.*

*The overall fatality rate was 1.2%. Studies of Parkinson's disease that follow cohorts of subjects from the time of diagnosis have described an overall mortality ratio (9 studies; 1,801 patients; median follow-up duration, 9 years) of 1.52 (95% CI, 1.25-1.78).[8] The deaths in the open label trial are therefore plausibly unrelated to the study drug, as this is an older population with moderate to advanced disease that has a comparable expected mortality rate to those seen in comparable cohorts with PD outside this trial.*

### 8.4.2. Serious Adverse Events

**Controlled Trial**

A total of 45 serious TEAEs occurred in 31 patients during the dose adjustment, IPX203 conversion and double-blind periods in Study B16-02. About two-thirds of these events occurred during the IR CD/LD dose adjustment period (12 SAEs in 7 subjects [1.1%]) and IPX203 conversion period (19 SAEs in 14 subjects [2%]). In the double-blind period, twelve subjects (2.4%) experienced 14 serious adverse events, 8 (3.1%) in the IPX203 group and 4 (1.6%) in the IR CD/LD group. Thus, the incidences of SAEs were generally low, but they were higher in the IPX203 group than the IR CD/LD group during the double-blinded period.

[8] Macleod, A.D., Taylor, K.S.M. and Counsell, C.E. (2014), Mortality in Parkinson's disease: A systematic review and meta-analysis. Mov Disord., 29: 1615-1622. https://doi.org/10.1002/mds.25898

As seen in Table 16, with one exception, no single serious TEAE in Study B16-02 occurred in more than one subject during the DBP. The only TESAE that occurred in more than one subject was transient ischemic attack during the conversion period.

**Table 16: Treatment Emergent Serious Adverse Events, Study B16-02 (Full Safety Population)**

| Primary System Organ Class | Dictionary-Derived Term | Dose Adjustment | Dose Conversion | Blinded Treatment | |
|---|---|---|---|---|---|
| | | IR CD/LD (N=630) | IPX203 (N=589) | IPX203 (N=256) | IR CD/LD (N=250) |
| **Any SAE** | | **7 (1.1)** | **12 (2.0)** | **8 (3.1)** | **4 (1.6)** |
| **Nervous system disorders** | Transient ischemic attack | 0 | 2 (0.3) | 0 | 0 |
| | Cognitive disorder | 1 (0.2) | 0 | 0 | 0 |
| | Dyskinesia | 1 (0.2) | 0 | 0 | 0 |
| | Epilepsy | 0 | 0 | 1 (0.4) | 0 |
| | Neuralgia | 1 (0.2) | 0 | 0 | 0 |
| | On and off phenomenon | 1 (0.2) | 0 | 0 | 0 |
| | Syncope | 0 | 0 | 1 (0.4) | 0 |
| | Vertebral artery aneurysm | 0 | 0 | 1 (0.4) | 0 |
| **Infections and infestations** | Urinary tract infection | 0 | 1 (0.2) | 0 | 1 (0.4) |
| | Cystitis | 0 | 1 (0.2) | 0 | 0 |
| | Epididymitis | 1 (0.2) | 0 | 0 | 0 |
| | Influenza | 0 | 1 (0.2) | 0 | 0 |
| | Pneumonia | 0 | 1 (0.2) | 0 | 0 |
| | Pyelonephritis | 0 | 0 | 1 (0.4) | 0 |
| | Sepsis | 0 | 1 (0.2) | 0 | 0 |
| **Injury, poisoning and procedural complications** | Contusion | 0 | 1 (0.2) | 0 | 0 |
| | Hip fracture | 0 | 1 (0.2) | 0 | 0 |
| | Radiation neuropathy | 1 (0.2) | 0 | 0 | 0 |
| | Skin laceration | 0 | 1 (0.2) | 0 | 0 |
| | Subdural hematoma | 0 | 1 (0.2) | 0 | 0 |
| **Renal and urinary disorders** | Acute kidney injury | 1 (0.2) | 0 | 0 | 0 |
| | Nephrolithiasis | 0 | 1 (0.2) | 0 | 0 |
| | Urinary retention | 0 | 1 (0.2) | 0 | 0 |
| | Urinary tract obstruction | 1 (0.2) | 0 | 0 | 0 |
| **Cardiac disorders** | Atrioventricular block complete | 0 | 0 | 0 | 1 (0.4) |
| | Bradycardia | 0 | 0 | 1 (0.4) | 0 |
| | Cardiac failure | 0 | 0 | 0 | 1 (0.4) |
| **General disorders and administration site conditions** | Asthenia | 0 | 0 | 1 (0.4) | 0 |
| | Chest pain | 0 | 1 (0.2) | 0 | 0 |
| | Fatigue | 0 | 0 | 1 (0.4) | 0 |
| | Duodenitis | 1 (0.2) | 0 | 0 | 0 |

| Primary System Organ Class | Dictionary-Derived Term | Dose Adjustment | Dose Conversion | Blinded Treatment | |
|---|---|---|---|---|---|
| | | IR CD/LD (N=630) | IPX203 (N=589) | IPX203 (N=256) | IR CD/LD (N=250) |
| **Gastrointestinal disorders** | Inguinal hernia | 1 (0.2) | 0 | 0 | 0 |
| **Metabolism and nutrition disorders** | Hypokalemia | 0 | 1 (0.2) | 0 | 0 |
| | Hyponatremia | 1 (0.2) | 0 | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | Back pain | 0 | 0 | 0 | 1 (0.4) |
| | Osteoarthritis | 1 (0.2) | 0 | 0 | 0 |
| **Blood and lymphatic system disorders** | Anemia | 0 | 1 (0.2) | 0 | 0 |
| **Investigations** | Ejection fraction decreased | 0 | 0 | 1 (0.4) | 0 |
| **Neoplasms** | Bladder transitional cell carcinoma | 0 | 1 (0.2) | 0 | 0 |
| **Psychiatric disorders** | Hallucinations, mixed | 0 | 0 | 1 (0.4) | 0 |
| **Reproductive system and breast disorders** | Benign prostatic hyperplasia | 0 | 0 | 0 | 1 (0.4) |
| **Respiratory, thoracic and mediastinal disorders** | Chronic obstructive pulmonary disease | 0 | 1 (0.2) | 0 | 0 |
| **Surgical and medical procedures** | Inguinal hernia repair | 0 | 1 (0.2) | 0 | 0 |

Source: FDA analysis

*Reviewer's comment:*

*Significant numbers of subjects dropped out at each of these stages, with the result that the actual double blind treatment stage resulted in just 12 subjects (2.4%) experiencing 14 serious adverse events, 8 (3.1%) in the IPX203 group and 4 (1.6%) in the IR CD/LD group. It seems likely that the subjects most likely to experience SAEs during the double-blinded period had already been eliminated during the dose adjustment and dose conversion periods, so the serious adverse event rate generated by the double-blind period may be a conservative estimate.*

*The SAE rates in the preceding open-label dose adjustment and dose conversion periods were also low, and not vastly different between the open-label IR CD/LD and IPX203 periods, meaning that even if these subjects had been included in the double-blind period, they were unlikely to have substantially affected the result.*

**Uncontrolled Safety Data**

As seen in Table 17 below, 73 serious TEAEs occurred in 43 patients in the uncontrolled safety population, or 10.3% of the enrolled population in the open-label study. Again, however, when looked at by Body system or Organ Class, each specific event reported affected less than 1% of the study population.

In general, psychiatric, nervous system, infectious, and psychiatric serious TEAEs occurred most frequently (3.1%, 2.1%, and 1.9%, respectively) followed by injuries (1.7%). Seizure, confusional state, and COVID-19 each occurred in 3 subjects in the uncontrolled safety population. All other serious TEAEs occurred in 1 or 2 subjects each.

**Table 17: Treatment Emergent Serious Adverse Events, Study B16-03 (Open Label Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| **Any Serious TEAE** | | **43 (10.3)** |
| **Nervous system disorders** | Syncope | 2 (0.5) |
| | Polyneuropathy | 1 (0.2) |
| | Seizure | 3 (0.7) |
| | Freezing phenomenon | 1 (0.2) |
| | Cauda equina syndrome | 1 (0.2) |
| | Cerebrovascular accident | 1 (0.2) |
| | Epilepsy | 1 (0.2) |
| | Parkinson's disease | 1 (0.2) |
| | Peripheral sensory neuropathy | 1 (0.2) |
| | Subarachnoid hemorrhage | 1 (0.2) |
| **Psychiatric disorders** | Depression | 1 (0.2) |
| | Confusional state | 3 (0.7) |
| | Delirium | 1 (0.2) |
| | Psychotic disorder | 2 (0.5) |
| | Hypersexuality | 1 (0.2) |
| | Mental status changes | 1 (0.2) |
| **Infections and infestations** | COVID-19 | 3 (0.7) |
| | Pneumonia | 2 (0.5) |
| | COVID-19 pneumonia | 1 (0.2) |
| | Encephalitis | 1 (0.2) |
| | Gastroenteritis viral | 1 (0.2) |
| | Gastrointestinal infection | 1 (0.2) |
| | Herpes zoster | 1 (0.2) |
| | Post procedural infection | 1 (0.2) |
| | Sepsis | 1 (0.2) |
| **Gastrointestinal disorders** | Vomiting | 1 (0.2) |
| | Abdominal distension | 1 (0.2) |
| | Colitis | 1 (0.2) |
| | Volvulus | 2 (0.5) |
| | Fall | 1 (0.2) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| **Injury, poisoning and procedural complications** | Concussion | 1 (0.2) |
| | Femur fracture | 2 (0.5) |
| | Joint dislocation | 1 (0.2) |
| | Overdose | 1 (0.2) |
| | Head injury | 1 (0.2) |
| | Spinal cord injury cervical | 1 (0.2) |
| **Musculoskeletal and connective tissue disorders** | Lumbar spinal stenosis | 1 (0.2) |
| | Scoliosis | 1 (0.2) |
| **General disorders and administration site conditions** | Pyrexia | 1 (0.2) |
| | Chest pain | 1 (0.2) |
| | Asthenia | 1 (0.2) |
| | Drowning | 1 (0.2) |
| | Non-cardiac chest pain | 1 (0.2) |
| **Renal and urinary disorders** | Nephrolithiasis | 1 (0.2) |
| | Neurogenic bladder | 1 (0.2) |
| **Respiratory, thoracic and mediastinal disorders** | Chronic obstructive pulmonary disease | 2 (0.5) |
| | Pulmonary embolism | 2 (0.5) |
| | Aspiration | 1 (0.2) |
| | Hypoxia | 1 (0.2) |
| **Cardiac disorders** | Atrial fibrillation | 2 (0.5) |
| | Acute myocardial infarction | 1 (0.2) |
| | Cardiac failure | 1 (0.2) |
| | Cardiogenic shock | 1 (0.2) |
| **Metabolism and nutritional disorders** | Dehydration | 1 (0.2) |
| | Hypokalemia | 1 (0.2) |
| **Blood and lymphatic system disorders** | Anemia | 1 (0.2) |
| **Ear and labyrinth disorders** | Vertigo | 1 (0.2) |
| **Neoplasms** | Lung neoplasm malignant | 1 (0.2) |
| **Immune system disorders** | Hypersensitivity | 1 (0.2) |

(Source: FDA analysis)

*Reviewer's comment*

*It is not apparent why the rates of serious TEAEs were higher in the open-label study (10.3%) than in the group treated with IPX203 in the double-blind treatment phase of Study B16-02 (3.1%), particularly as the open-label study consisted of a winnowed subset of subjects from that study. Possibly this was a result of the open-label study's longer duration capturing more of these events. This trial was uncontrolled; therefore, it is difficult to say whether this rate of adverse events exceeds that expected in an older, sicker population with PD. The more salient comparison is between the IPX203 and IR CD/LD groups in the double-blind period, in which the IPX203 group experienced a frequency of SAEs that while overall low, was three times that of the IR CD/LD active control group.*

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

**Controlled Trial**

As Table 18 and Table 19 below show, 4 subjects (0.6%) discontinued early because of adverse events during the IR CD/LD Dose Adjustment stage and another 35 (5.9%) discontinued during the IPX203 Conversion Period of Study B16-02. During the Study's double-blind stage, 17 subjects withdrew because of adverse events; of these, 14 subjects (5.5%) were taking IPX203 vs 3 (1.2%) who were taking IR CD/LD. Thus, during the double-blind period, a greater percentage of subjects who were taking IPX203 withdrew because of adverse events. The data used to calculate the discontinuation rate due to AEs was derived from the ADaM datasets for each study, as well as listings from the CSR for each study and confirmed on review of the patients' disposition CRFs.

**Table 18: Subject Disposition, Study B16-02 (Full Safety Population)**

| | | IPX203 (N) |
|---|---|---|
| Screened Population | | 770 |
| Enrolled Population | | 630 |
| Entered Dose Adjustment Period | | 630 |
| Entered IPX203 Conversion Period | | 589 |
| Randomized Population | | 506 |
| Completers Population | | 446 |
| **Period of Discontinuation** | **Reason For Discontinuation** | |
| Screening | Screen Failure | 140 |
| Dose Adjustment | Adverse Event | 4 |
| | Lack of Efficacy | 1 |
| | Other | 21 |
| | Protocol Deviation | 6 |
| | Withdrawal By Subject | 9 |
| IPX203 Conversion | Adverse Event | 35 |
| | Lack of Efficacy | 10 |
| | Lost to Follow-Up | 1 |
| | Non-Compliance With Study Drug | 2 |
| | Other | 2 |
| | Protocol Deviation | 1 |
| | Withdrawal by Subject | 32 |
| Blinded Treatment | Adverse Event | 17 |
| | Lack Of Efficacy | 13 |
| | Non-Compliance With Study Drug | 1 |
| | Other | 1 |
| | Protocol Deviation | 4 |
| | Withdrawal by Subject | 21 |
| **Period of Discontinuation** | **Subject Death** | |
| Screening | | 1 |
| **Period of Discontinuation** | **Discontinuation Related to COVID-19** | |
| Dose Adjustment | | 5 |
| Blinded Treatment | | 1 |

Source: FDA analysis

**Table 19: Subject Disposition for Double Blind Period by Treatment Group, Study B16-02 (Controlled Safety Population)**

| | Actual Treatment for Double Blind Period | | |
|---|---|---|---|
| | **IPX203** | **IR CD/LD** | **All** |
| **Randomized Population** | 256 | 250 | 506 |
| **Safety Population** | 256 | 250 | 506 |
| **Reason for Discontinuation from Study** | | | |
| Adverse event | 14 | 3 | 17 |
| Lack of efficacy | 5 | 8 | 13 |
| Non-compliance with study drug | 1 | 0 | 1 |
| Other | 1 | 0 | 1 |
| Protocol deviation | 3 | 1 | 4 |
| Withdrawal by subject | 10 | 11 | 21 |
| All | 34 | 23 | 57 |
| **Completers Population** | 220 | 226 | 446 |

Source: FDA analysis

Specific TEAEs leading to discontinuation during Study B16-02 are summarized in Table 20 below. TEAEs leading to discontinuation during the IR CD/LD dose adjustment stage were few, 4 subjects reported only 10 events, each of which occurred only once.

In the IPX203 dose conversion stage, 35 subjects reported 74 events. The most frequent reasons for discontinuation were dyskinesia and dizziness (7 subjects each, or 1.2% each), and nausea (5 subjects, 0.8% each), followed by sleep issues of insomnia and abnormal dreams (4 events or 0.7% each + 2 events or 0.3% each = 6 events and 1.0%). Other events including ones of particular interest such as problems with gait and balance, impulse control disorders, orthostatic hypotension and mood disorders occurred at rates below 1%.

In the double-blind period, 17 subjects reported 26 adverse events leading to discontinuation; of these, 3 were in the IR CD/LD group and 14 were in the IPX203 group. The AEs that did happen occurred in one or at most two subjects at a time. Although the number of reports in the IPX203 group was higher, there was not a major difference between the two groups given the low numbers of events overall.

*Reviewer Comment:*

*The relative absence of adverse events leading to discontinuations in both groups during the double-blind period vs the dose adjustment and conversion periods may have been because the subjects most likely to experience adverse events prompting discontinuation had already experienced them and been discontinued during the preceding IR CD/LD dose adjustment and IPX203 dose conversion stages. There was a notable difference between groups during the double-blind period in the discontinuation due to adverse events. This occurred even after almost 6% of subjects exited early during the dose conversion period. These findings suggest*

*that IPX203 may not be as well-tolerated as IR CD/LD.*

**Table 20: Treatment Emergent Adverse Events Leading to Discontinuation Study B16-02 (Full Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | Dose Adjustment | Dose Conversion | Double Blind | |
|---|---|---|---|---|---|
| | | IR CD/LD N=630 n (%) | IPX203 N=589 n (%) | IR CD/LD N=250 n (%) | IPX203 N=256 n (%) |
| **Any TEAE leading to discontinuation** | | **4 (0.6)** | **35 (5.9)** | **3 (1.2)** | **14 (5.5)** |
| **Nervous system disorders** | Dyskinesia | 1 (0.2) | 7 (1.2) | 0 | 2 (0.8) |
| | Dizziness | 1 (0.2) | 7 (1.2) | 0 | 0 |
| | Parkinson's disease | 0 | 3 (0.5) | 2 (0.8) | 1 (0.4) |
| | On and off phenomenon | 1 (0.2) | 1 (0.2) | 0 | 2 (0.8) |
| | Balance disorder | 0 | 2 (0.3) | 0 | 0 |
| | Freezing phenomenon | 0 | 2 (0.3) | 0 | 0 |
| | Anosognosia | 0 | 0 | 0 | 1 (0.4) |
| | Cognitive disorder | 1 (0.2) | 0 | 0 | 0 |
| | Dysesthesia | 0 | 0 | 0 | 1 (0.4) |
| | Dysarthria | 0 | 1 (0.2) | 0 | 0 |
| | Dystonia | 0 | 0 | 0 | 1 (0.4) |
| | Epilepsy | 0 | 0 | 0 | 1 (0.3) |
| | Judgement impaired | 0 | 0 | 0 | 1 (0.3) |
| | Memory impairment | 0 | 1 (0.2) | 0 | 0 |
| | Movement disorder | 0 | 1 (0.2) | 0 | 0 |
| | Neuralgia | 1 (0.2) | 0 | 0 | 0 |
| | Transient ischemic attack | 0 | 1 (0.2) | 0 | 0 |
| | Tremor | 0 | 1 (0.2) | 0 | 0 |
| **Psychiatric disorders** | Insomnia | 0 | 4 (0.7) | 0 | 0 |
| | Depression | 0 | 3 (0.5) | 0 | 0 |
| | Abnormal dreams | 0 | 2 (0.3) | 0 | 0 |
| | Anxiety | 0 | 1 (0.2) | 0 | 1 (0.3) |
| | Hallucination | 0 | 2 (0.3) | 0 | 0 |
| | Agitation | 0 | 0 | 0 | 1 (0.3) |
| | Confusional state | 0 | 1 (0.2) | 0 | 0 |
| | Hallucinations, mixed | 0 | 0 | 0 | 1 (0.3) |
| | Impulse-control disorder | 0 | 1 (0.2) | 0 | 0 |
| | Irritability | 0 | 1 (0.2) | 0 | 0 |
| | Mania | 0 | 1 (0.2) | 0 | 0 |
| | Mood altered | 0 | 1 (0.2) | 0 | 0 |
| | Mood swings | 0 | 1 (0.2) | 0 | 0 |
| | Nervousness | 0 | 1 (0.2) | 0 | 0 |
| | Nightmare | 1 (0.2) | 0 | 0 | 0 |
| **Gastrointestinal disorders** | Nausea | 0 | 5 (0.8) | 0 | 2 (0.5) |
| | Vomiting | 0 | 3 (0.5) | 0 | 0 |
| | Dry mouth | 0 | 2 (0.3) | 0 | 0 |
| | Chapped lips | 0 | 1 (0.2) | 0 | 0 |
| | Duodenitis | 1 (0.2) | 0 | 0 | 0 |
| | Dyspepsia | 1 (0.2) | 0 | 0 | 0 |
| | Dysphagia | 0 | 1 (0.2) | 0 | 0 |

| Body System or Organ Class | Dictionary-Derived Term | Dose Adjustment | Dose Conversion | Double Blind | |
|---|---|---|---|---|---|
| | | IR CD/LD N=630 n (%) | IPX203 N=589 n (%) | IR CD/LD N=250 n (%) | IPX203 N=256 n (%) |
| **General disorders and administration site conditions** | Asthenia | 0 | 1 (0.2) | 1 (0.4) | 1 (0.2) |
| | Balance disorder | 0 | 0 | 1 (0.4) | 0 |
| | Fatigue | 0 | 0 | 0 | 2 (0.5) |
| | Feeling abnormal | 0 | 0 | 0 | 2 (0.4) |
| | Gait disturbance | 1 (0.2) | 0 | 0 | 1 (0.2) |
| **Vascular disorders** | Hypertension | 0 | 1 (0.2) | 0 | 0 |
| | Hypertensive urgency | 0 | 1 (0.2) | 0 | 0 |
| | Hypotension | 0 | 1 (0.2) | 0 | 0 |
| | Orthostatic hypotension | 0 | 1 (0.2) | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | Back pain | 0 | 1 (0.2) | 0 | 0 |
| | Musculoskeletal stiffness | 0 | 1 (0.2) | 0 | 0 |
| | Neck pain | 0 | 1 (0.2) | 0 | 0 |
| **Infections and infestations** | Corona virus infection | 0 | 1 (0.2) | 0 | 0 |
| | Urinary tract infection | 0 | 1 (0.2) | 0 | 0 |
| **Investigations** | Blood pressure increased | 0 | 2 (0.3) | 0 | 0 |
| **Ear and labyrinth disorders** | Vertigo | 0 | 0 | 0 | 1 (0.2) |
| **Injury, poisoning and procedural complications** | Radiation neuropathy | 1 (0.2) | 0 | 0 | 0 |
| **Metabolism and nutrition disorders** | Decreased appetite | 0 | 1 (0.2) | 0 | 0 |
| **Neoplasms** | Bladder transitional cell carcinoma | 0 | 1 (0.2) | 0 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea | 0 | 1 (0.2) | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | Hyperhidrosis | 0 | 1 (0.2) | 0 | 0 |

The controlled trial was affected by the concurrent COVID-19 pandemic. Five subjects discontinued in the initial IR CD/LD dose adjustment stage because of COVID-19. One additional subject, who had been randomized to IPX203, withdrew during the double-blind treatment stage for COVID-19 reasons. None of these subjects actually had COVID-19 at the time of discontinuation; rather their discontinuations were for structural reasons such as difficulty traveling to the study site resulting from travel restrictions; problems completing study visits resulting from study site closure; and fear of contracting the virus.

*Reviewer Comment:*

*Of the subjects who dropped out after the IR CD/LD optimization stage, a number were*

*disqualified from continuing in the study because the IR CD/LD optimization had worked "too well," and the subjects no longer had the requisite amount of "off" time. Other subjects dropped out during the IPX203 conversion who felt that the optimized IR CD/LD dose had worked better for them and therefore they chose to return to it. Therefore, the subjects who were randomized may be a relatively refractory population, for whom optimized IR CD/LD had failed to adequately control their symptoms of PD. This finding suggests that IPX203 is a reasonable treatment option for patients in whom IR CD/LD optimization has been insufficient to treat their advanced PD symptoms.*

**Uncontrolled Trial**

Table 21 below summarizes the discontinuation data for the open-label trial. There were 20 subjects who discontinued because of adverse events and 5 who died; the deaths are discussed in Section 8.4.1 above.

**Table 21: Discontinued Subjects, Study B16-03 (Open Label Safety Population)**

| Reason for Discontinuation from Study | N |
|---|---|
| Adverse Event | 20 |
| Death | 5 |
| Lack of Efficacy | 14 |
| Lost to Follow-Up | 2 |
| Non-Compliance With Study Drug | 2 |
| Other | 1 |
| Withdrawal By Subject | 22 |
| All | 66 |

Table 22 below describes the reported TEAEs leading to discontinuation during the open-label trial. There was no signal of particular types of adverse events leading to discontinuation and the overall frequency of any specific type and of events overall was acceptably low.

**Table 22: Treatment Emergent Adverse Events Leading to Discontinuation, Study B16-03 (Open Label Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| **Any TEAE leading to discontinuation** | | **20 (4.8)** |
| Nervous system disorders | On and off phenomenon | 2 (0.5) |
| | Brachial plexopathy | 1 (0.2) |
| | Dizziness | 1 (0.2) |
| | Dyskinesia | 1 (0.2) |
| | Epilepsy | 1 (0.2) |
| | Hyperkinesia | 1 (0.2) |
| | Hypoesthesia | 1 (0.2) |
| | Paresthesia | 1 (0.2) |
| | Peripheral sensorimotor neuropathy | 1 (0.2) |
| | Peripheral sensory neuropathy | 1 (0.2) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| | Seizure | 1 (0.2) |
| | Subarachnoid hemorrhage | 1 (0.2) |
| | Tremor | 1 (0.2) |
| Psychiatric disorders | Anxiety | 1 (0.2) |
| | Confusional state | 1 (0.2) |
| | Delirium | 1 (0.2) |
| | Depressed mood | 1 (0.2) |
| | Hypersexuality | 1 (0.2) |
| | Insomnia | 1 (0.2) |
| | Psychotic disorder | 1 (0.2) |
| Infections and infestations | COVID-19 | 2 (0.5) |
| | Encephalitis | 1 (0.2) |
| | Gastrointestinal infection | 1 (0.2) |
| | Sepsis | 1 (0.2) |
| Injury, poisoning and procedural complications | Facial bones fracture | 1 (0.2) |
| | Fall | 1 (0.2) |
| | Head injury | 1 (0.2) |
| | Overdose | 1 (0.2) |
| | Spinal cord injury cervical | 1 (0.2) |
| Gastrointestinal disorders | Nausea | 2 (0.5) |
| | Abdominal distension | 1 (0.2) |
| | Vomiting | 1 (0.2) |
| General disorders | Drowning | 1 (0.2) |
| | Pyrexia | 1 (0.2) |
| Respiratory, thoracic and mediastinal disorders | Chronic obstructive pulmonary disease | 1 (0.2) |
| | Pulmonary embolism | 1 (0.2) |
| Cardiac disorders | Cardiogenic shock | 1 (0.2) |
| Ear and labyrinth disorders | Vertigo | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | Muscle spasms | 1 (0.2) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Lung neoplasm malignant | 1 (0.2) |
| Renal and urinary disorders | Nephrolithiasis | 1 (0.2) |

### 8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Controlled population during Study B16-02

During the double-blind period, subjects reported more TEAEs in the IPX203 group (49%) than in the IR CD/LD group (28%) (Table 23). Specifically, there was more dyskinesia in the IPX203 group (2%) than in the IR CD/LD group (0.4%). During the blinded period, the IPX203 subjects reported more nausea (4.3%) compared to IR CD/LD (0.8%). They reported more dizziness (2.3% vs 0.8%); more anxiety (2.7% vs 0%); and more constipation and vomiting.

Uncontrolled Population during Study B16-02

A total of 229 subjects (38.9%) experienced any TEAE during the IPX203 conversion period, which was when subjects were initially exposed to IPX203. The most commonly reported TEAEs during the IPX203 conversion period were dyskinesia (6.8%), nausea (4.9%), dry mouth (4.9%), dizziness (2.9%) and anxiety (1.5%).

**Table 23: Treatment Emergent Adverse Events ≥ 2% in Total IPX203, Study B16-02 (Full Safety Population)**

| Primary System Organ Class | Dictionary-Derived Term | IR CD/LD Dose Adjustment N=630 n (%) | IPX203 Dose Conversion N=589 n (%) | Double Blind | | Total | |
|---|---|---|---|---|---|---|---|
| | | | | IPX203 N=256 n (%) | IR CD/LD N=250 n (%) | IPX203 N=589 n (%) | IR CD/LD N=630 n (%) |
| **Any AE** | | **118 (18.7)** | **229 (38.9)** | **107 (41.8)** | **78 (31.2)** | **289 (49.1)** | **178 (28.3)** |
| Nervous system disorders | Dyskinesia | 11 (1.7) | 40 (6.8) | 5 (2.0) | 1 (0.4) | 45 (7.6) | 12 (1.9) |
| | Dizziness | 3 (0.5) | 17 (2.9) | 6 (2.3) | 2 (0.8) | 23 (3.9) | 5 (0.8) |
| | Headache | 8 (1.3) | 9 (1.5) | 3 (1.2) | 0 (0.0) | 12 (2.0) | 8 (1.3) |
| Gastrointestinal disorders | Nausea | 7 (1.1) | 29 (4.9) | 11(4.3) | 2 (0.8) | 40 (6.8) | 9 (1.4) |
| | Dry mouth | 2 (0.3) | 25 (4.2) | 3 (1.2) | 2 (0.8) | 28 (4.8) | 4 (0.6) |
| | Constipation | 7 (1.1) | 12 (2.0) | 4 (1.6) | 1 (0.4) | 16 (2.7) | 8 (1.3) |
| | Vomiting | 3 (0.5) | 13 (2.2) | 3 (1.2) | 0 (0.0) | 16 (2.7) | 3 (0.5) |
| Psychiatric disorders | Insomnia | 6 (1.0) | 13 (2.2) | 2 (0.8) | 1 (0.4) | 15 (2.5) | 7 (1.1) |
| | Anxiety | 1 (0.2) | 9 (1.5) | 7 (2.7) | 0 (0.0) | 16 (2.7) | 1 (0.2) |
| Injury, poisoning and procedural complications | Fall | 6 (1.0) | 13 (2.2) | 5 (2.0) | 9 (3.6) | 18 (3.1) | 15 (2.4) |

Source: FDA analysis

*Reviewer Comment:*

*In the controlled study, the percentage of subjects with TEAEs taking IPX203 were higher than in subjects taking IR CD/LD. The overall trend in all stages of this trial is for a higher rate of TEAEs with IPX203 than with IR CD/LD. Nausea was notably more frequent in the IPX203 group. Dyskinesia, dry mouth, and to a lesser extent, dizziness were also more frequently reported overall among subjects taking IPX203. While these are all well-known side effects of carbidopa/levodopa, they occurred more commonly in subjects taking IPX203 than in subjects taking IR CD/LD. The overall lower frequency of nausea, dyskinesia and dizziness and other adverse events in the double-blind vs the open-label portions of this trial may be partly attributable to subjects having discontinued for these reasons before entering the double-blind period.*

Uncontrolled population (Study B16-03)

A total of 221 subjects (53%) experienced any TEAE during Study B16-03. Nervous System disorders accounted for the most frequently reported adverse events, with 85 subjects (20.3%) reporting TEAEs in this body system (Table 38, Appendix). The next most frequently reported

TEAEs in subjects were psychiatric (12.2%), infection/infestation (13.1%) and musculoskeletal (9.1%).

With respect to specific TEAEs (Table 24), the most frequently reported TEAEs in the uncontrolled population were dyskinesia, falls, and urinary tract infections, each of which occurred in 21 (5%) subjects each (Table 24). Fifteen (3.6%) subjects reported back pain, 11 (2.6%) subjects reported constipation and 8 (1.9%) reported nausea while 6 (1.4%) reported vomiting. Eight (1.9%) subjects reported hallucinations, 7 (1.7%) reported depression, and 6 subjects (1.4%) each reported insomnia, hypertension, or orthostatic hypotension. This study took place during the COVID-19 pandemic and 10 subjects (2.4%) reported COVID-19 infection.

**Table 24: Treatment Emergent Adverse Events in >1% of Subjects Study B16-03 (Open Label Safety Population)**

| Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|
| **Any TEAE** | **221 (52.7)** |
| Dyskinesia | 21 (5.0) |
| Fall | 21 (5.0) |
| Urinary tract infection | 21 (5.0) |
| Back pain | 15 (3.6) |
| Constipation | 11 (2.6) |
| COVID-19 | 10 (2.4) |
| Hallucination | 8 (1.9) |
| Nausea | 8 (1.9) |
| Depression | 7 (1.7) |
| Syncope | 7 (1.7) |
| Dizziness | 6 (1.4) |
| Hypertension | 6 (1.4) |
| Insomnia | 6 (1.4) |
| On and off phenomenon | 6 (1.4) |
| Orthostatic hypotension | 6 (1.4) |
| Vomiting | 6 (1.4) |
| Anemia | 5 (1.2) |
| Confusional state | 5 (1.2) |
| Edema peripheral | 5 (1.2) |
| Musculoskeletal pain | 5 (1.2) |
| Nephrolithiasis | 5 (1.2) |
| Rash | 5 (1.2) |
| Restless legs syndrome | 5 (1.2) |
| Sciatica | 5 (1.2) |
| Weight decreased | 5 (1.2) |

Source: FDA analysis

*Reviewer's Comments:*

*Although this is a relatively older population with moderate to advanced stages of a chronic,*

*progressive neurological disease, and the time period of the open-label study was longer thereby capturing more adverse events, the overall trend in Study B16-03 is for a higher rate of TEAEs with IPX203 than with IR CD/LD. This trend is most pronounced for dyskinesia. 5% of subjects reported falls in the uncontrolled trial. Urinary tract infection was more common than in the double-blind of the controlled trial; it is plausible that the longer uncontrolled trial simply captured more of these events during the trial period, but these data are not enough to conclude whether the drug increased the risk. The other salient TEAEs in the uncontrolled trial were constipation, nausea and vomiting. For the remainder of TEAEs reported and summarized above, the overall number of subjects reporting remained low.*

**Treatment Emergent Adverse Events in the Phase 1 and 2 Studies**
In the Phase 1 study B16-06, one subject experienced a TEAE of vomiting that led to discontinuation from the study. Another subject in Study B16-06 experienced a TEAE of elevated cholesterol. Neither of these TEAEs were considered serious and both resolved. No other TEAEs were reported. In the Phase 1 study B16-05, one healthy volunteer experienced a TEAE of dizziness, which was mild.

In the Phase 2 studies in subjects with advanced PD (Studies B14-02 and B16-01), 18 of 54 subjects experienced TEAEs (Table 25). The most commonly reported TEAEs in these studies were dyskinesia in 6 subjects, dizziness in 5 subjects, nausea in 4 subjects, and hypertension in 3 subjects, including one SAE described below. The rest of the AEs occurred in one subject each.

**Table 25: Treatment Emergent Adverse Events in the Phase 2 Studies**

| Dictionary-Derived Term | IPX203 |
|---|---|
| | n (%) |
| Dyskinesia | 6 (11.1) |
| Dizziness | 5 (9.3) |
| Nausea | 4 (7.4) |
| Hypertension | 3 (5.6) |
| Abdominal pain | 1 (1.9) |
| Balance disorder | 1 (1.9) |
| Bronchitis | 1 (1.9) |
| Confusional state | 1 (1.9) |
| Diarrhea | 1 (1.9) |
| Dry mouth | 1 (1.9) |
| Dystonia | 1 (1.9) |
| Hypersomnia | 1 (1.9) |
| Hypotension | 1 (1.9) |
| Insomnia | 1 (1.9) |
| Musculoskeletal stiffness | 1 (1.9) |
| Nephrolithiasis | 1 (1.9) |
| Occipital neuralgia | 1 (1.9) |
| Orthostatic hypertension | 1 (1.9) |
| Orthostatic hypotension | 1 (1.9) |

| Dictionary-Derived Term | IPX203 |
|---|---|
| | n (%) |
| Tinea pedis | 1 (1.9) |
| Tremor | 1 (1.9) |
| Upper respiratory tract infection | 1 (1.9) |
| Urinary tract infection | 1 (1.9) |
| Vomiting | 1 (1.9) |

Source: FDA analysis

One serious TEAE was reported in the Phase 2 studies: a 78-year-old male subject with advanced PD and hypertension developed elevated blood pressure on study day 3. The subject was hospitalized, but his blood pressure returned to baseline, and he was discharged. No change was made to the study drug and the subject continued participation in the study. No deaths were reported. No AEs led to discontinuation.

### 8.4.5. Laboratory Findings

The Applicant used two different reference laboratories to complete the clinical laboratory testing. The two laboratory vendors listed in the study report were (b) (4) . The Study B16-02 laboratory datasets (ADaM-ADLB) listed different ranges of normal as illustrated in the table below (Table 26). Additionally, a harmonized set of laboratory values and reference ranges was not included in the ADLB dataset; thus, the measures of central tendencies should be interpreted with caution. The analysis of shifts from the normal range appears to have included the reference range for each subject and may be interpreted with greater confidence. Although this problem also affected the hematology tests, it appears to have affected fewer parameters.

**Table 26: Examples of Inconsistent Use of Laboratory Reference Ranges for Chemistry and Hematology Analytes, Study B16-02**

| Unique Subject Identifier | Parameter | Analysis Value | Analysis Normal Range Lower Limit | Analysis Normal Range Upper Limit |
|---|---|---|---|---|
| IPX203-B16-02 (b) (6) | Creatinine | 105 | 62 | 106 |
| IPX203-B16-02 | Creatinine | 107 | 62 | 106 |
| IPX203-B16-02 | Creatinine | 80 | 44 | 80 |
| IPX203-B16-02 | Creatinine | 67 | 44 | 80 |
| IPX203-B16-02 | Creatinine | 94 | 62 | 106 |
| IPX203-B16-02 | Creatinine | 53 | 44 | 80 |
| IPX203-B16-02 | Creatinine | 86 | 62 | 106 |
| IPX203-B16-02 | Creatinine | 78 | 62 | 106 |
| IPX203-B16-02 | Creatinine | 71 | 62 | 106 |
| IPX203-B16-02 | Creatinine | 70 | 44 | 80 |
| IPX203-B16-02 | Hematocrit | 0.44 | 0.4 | 0.52 |
| IPX203-B16-02 | Hematocrit | 0.43 | 0.4 | 0.52 |
| IPX203-B16-02 | Hematocrit | 0.39 | 0.36 | 0.46 |
| IPX203-B16-02 | Hematocrit | 0.42 | 0.4 | 0.52 |
| IPX203-B16-02 | Hematocrit | 0.44 | 0.36 | 0.46 |

| | (b) (6) | | | | |
|---|---|---|---|---|---|
| IPX203-B16-02 | | Hematocrit | 0.44 | 0.36 | 0.46 |
| IPX203-B16-02 | | Hematocrit | 0.45 | 0.36 | 0.46 |

Source: FDA analysis

**Laboratory Analysis of Study B16-02 (Controlled Study)**

The measures of central tendencies for serum chemistry analytes are listed in Table 40 in the Appendix. The table columns refer to the treatment assignment in the double-blind period. The "not assigned" column refers to subjects who were treated in the IR CD/LD dose adjustment period and/or the IPX203 dose conversion period but were not randomized in the double-blind period. The mean, median, and extreme values are presented for each serum chemistry analyte by study visit. There were no meaningful differences in the mean or median values for any chemistry analyte in either treatment arm at any study visit.

Table 41 shows the number of subjects who had a categorical shift in serum chemistry value based on the lower and upper limits of the clinical laboratory reference range from the baseline visit to the final study visit (Visit 7) or end of treatment (ET) before the final visit in the double-blind period. The number of subjects who shifted from normal or low at baseline to high at Visit 7/ET was not meaningfully different for subjects randomized to IPX203 or IR CD/LD.

**Outlier analysis key serum chemistry analytes Study B16-02 (Safety Analysis Set)**

B16-02 Creatinine

In the safety population, 18 (3.1%) subjects treated with IPX203 with a normal creatinine at baseline shifted to high in any phase of the trial. Fourteen (2.2%) subjects treated with IR CD/LD shifted from normal at baseline to high. None of these subjects has a creatinine value that exceeded 1.75 X ULN.

B16-02 Creatine Kinase

In the safety population, 32 (5.4%) subjects treated with IPX203, and 30 (4.7%) subjects treated with IR CD/LD shifted from a normal creatine kinase level at baseline to high during the study. The highest ratio for the increase from baseline to any study visit was 4.3 X ULN in a subject treated with IPX203 and 3.7 X ULN in a subject treated with IR CD/LD.

B16-02 Blood Urea Nitrogen (BUN)

Twenty-three (3.9%) subjects in the safety population treated with IPX203 experienced a shift in Blood Urea Nitrogen (BUN) from normal at baseline to high during the trial compared with 16 (2.5%) subjects treated with IR CD/LD. The highest shift in either group was 1.6 X ULN in a subject in the IPX203 Conversion Phase of the trial.

*Reviewer Comment:*

*The subjects who shifted from normal at baseline to high for indicators of renal function (BUN and creatinine) and muscle (creatine kinase) during the study were not clinically meaningful.*

*Outliers for bilirubin and hepatic transaminases for Study B16-02 are discussed in the review of potential Hy's Law cases below.*

**Hematology Laboratory Values**

Table 42 in the Appendix shows the results for the measures of central tendencies for hematology parameters in subjects randomized to IPX203 or IR CD/LD in the double-blind period and subjects who were treated in the open label IR CD/LD dose adjustment period and/or the IPX203 conversion period (Not Assigned). There were no meaningful differences in the mean or median values for hematology parameters. The subject with the minimum value for platelets who was randomized to IPX203 was potentially clinically meaningful but the minimum value for platelets was approximately the same at baseline through Visit 7/ET (40,000 to 32,000). The subject with the maximum value for platelets in the group randomized to IPX203 had a modestly elevated count at baseline (494,000) to a maximum of 612,000 at Visit 5. Although the extreme values were above the upper limit of the normal range or below the lower limit, they were abnormal at baseline and did not appear to change meaningfully during the study.

**Outlier analysis of key hematologic parameters in Study B16-02**

Table 43 in the Appendix shows the number of subjects who had a categorical shift in hematology value based on the lower and upper limits of the clinical laboratory reference range from the baseline visit to the final study visit (Visit 7) or end of treatment (ET) before the final visit in the double-blind period. The number of subjects who shifted from normal or low at baseline to high at Visit 7/ET was not meaningfully different for subjects randomized to IPX203 or IR CD/LD.

<u>White Blood Cell (WBC) count</u>

Eleven (1.9%) subjects experienced a shift in WBC count from normal to low during treatment with IPX203, including one subject who shifted from normal to low during the follow up period after completing the double-blind period of the trial. Seven (1.1%) subjects experienced a shift in WBC count from normal to low during treatment with IR CD/LD during the trial. The lowest reported WBC count in either treatment group was 3.4 X $10^9$/L.

<u>Neutrophils</u>

One subject treated with IPX203 in the double-blind period shifted from high to low (1.5 X $10^9$/L). Another subject treated with IR CD/LD during the double-blind period shifted from normal to low (1.4 X $10^9$/L).

<u>Hemoglobin</u>

Thirty-two (5.4%) subjects treated with IPX203 during the double-blind period compared with 26 (4.1%) treated with IR CD/LD shifted from normal to low. The changes were not clinically meaningful.

Platelets

Eleven subjects (1.9%) treated with IPX203, and 13 subjects (2.1%) treated with IR CD/LD during the trial shifted from a normal platelet count at baseline to a low platelet count during the study. All subjects had platelet counts over 100 X $10^9$ with two notable exceptions. The first subject is a 73-year-old white female randomized to IR CD/LD during the double-blind part of the trial. The subject's platelet count was 262 X $10^9$ and 254 X $10^9$ at baseline and on day 146 (Visit 5), respectively, and fell to 38 X $10^9$ at Visit 7 (end of the study). The subject had no medical history or adverse events to suggest an underlying cause for a drop in platelet count and other blood counts remained within the normal range. The subject completed Study B16-02 and enrolled in open label Study B16-03. The subject's platelet count, 2 months after the low value of 38 X $10^9$ returned to the normal range (193 X $10^9$) and remained normal through completion of Study B16-03. A second subject, an 82-year-old White female also had a normal platelet count at baseline and on Visit 5. The subject completed the dose adjustment and IPX203 conversion periods before she withdrew from study participation after experiencing an SAE of "epilepsy."

Nine IPX203 treated subjects and 4 IR CD/LD treated subjects shifted from a normal platelet count at the baseline visit to a high platelet count during the study. None of the high platelet counts were clinically meaningful with the highest platelet count in either group of 465 X $10^9$.

**Laboratory Analysis of Study B16-03 (Uncontrolled Study)**

Changes in chemistry analytes during the open label study B16-03

The same issue of not harmonizing the reference high and low values for all the chemistry analytes in the ADaM (ADLB) dataset before calculating the descriptive statistics also affected Study B16-03. The ability to interpret the results of changes in the mean, median and extreme values in study B16-03 is limited. There are no meaningful changes in the number of subjects who experienced a shift to the abnormal range in chemistry analytes from baseline to Visit 4/ET in open label study B16-03.

Changes in hematology analytes during the open label study B16-03

There were no meaningful differences in the mean or median values for hematology parameters by study visit. Similarly, there were no meaningful shifts in hematology parameters from baseline to the end of treatment.

**Analysis of Potential Hy's Law Cases**

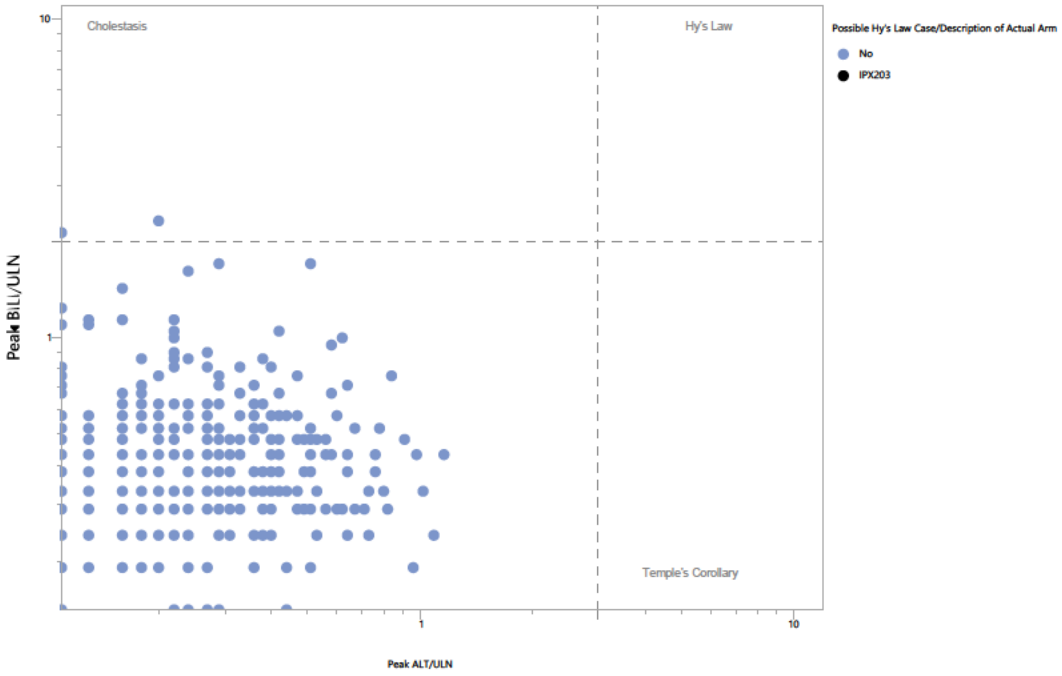
There were no potential Hy's Law cases found in Study B16-03, based on ALT or AST ≥3 X ULN and BILI ≥ 2 X ULN (Figure 7). There were no meaningful shifts in serum AST, ALT, ALP, or bilirubin (Table 27).

**Table 27: Shift in Hepatic Transaminases and Bilirubin, Study B16-03 (Open Label Safety Population)**

| | Description of Actual Arm | |
|---|---|---|
| | IPX203 | |
| | N | % |
| **ALT Counts and Percent** | | |
| Less than 3x ULN | 409 | 100.0% |
| All | 409 | 100.0% |
| **AST Counts and Percent** | | |
| Less than 3x ULN | 409 | 100.0% |
| All | 409 | 100.0% |
| **BILI Counts and Percent** | | |
| Less than 2x ULN | 407 | 99.5% |
| Between 2x and 5x ULN | 2 | 0.5% |
| All | 409 | 100.0% |
| **ALP Counts and Percent** | | |
| Less than 2x ULN | 409 | 100.0% |
| All | 409 | 100.0% |

Source: FDA Analysis

**Figure 7: Hy's Law Analysis**




Subjects with Elevated Bilirubin

A 60-year-old white male who was previously treated with IPX203 in study B16-02 and

completed the study. While participating in open-label study B16-03, he experienced a mild increase in bilirubin which was reported as an adverse event. The subject's bilirubin was 18 umol/L (reference ULN=21 umol/L) at baseline. At Visit 1, the subject's bilirubin was elevated to 45 umol/L. Study treatment was continued at the same dose and by Visit 3 the level modestly decreased and by Visit 4, the end of treatment, the subject's bilirubin decreased to 29 umol/L. There were no other laboratory abnormalities listed for this subject.

A 74-year-old male with a normal bilirubin at baseline and a mildly elevated ALP of 169 U/L (Reference range ULN= 129 U/L). The subject was previously treated with IPX203 in double blind study B16-02. At Visit 2 in study B16-03, the subject's bilirubin was elevated to 45 umol/L (Reference ULN=21 umol/L). The subject's ALP remained 169 throughout open label study participation. Sometime after Visit 3 the subject withdrew from the study for "lack of efficacy." The subject's bilirubin was 29 umol/L at the end of treatment visit on study day 219 after treatment with open label IPX203 for 219 days.

*Reviewer's comment:*

*It is not possible to draw any meaningful conclusions from these two instances, particularly since there were no Hy's Law cases.*

### 8.4.6. Vital Signs

There were no meaningful differences in the mean or median vital signs by treatment arm or by study visit (Table 48). There was an overall trend towards a lower blood pressure in subjects randomized to IPX203 in the categorical classification of vital signs (Table 49). A few more subjects randomized to IPX203 had a lower standing systolic (<90 mm Hg) and diastolic (<60 mm Hg) including at the baseline visit. The same was true at Visit 7/ET, however, at other visits there were no meaningful between group differences in the number of subjects with low standing systolic or diastolic blood pressure. See Section 8.5.2 below for a specific discussion of hypotension.

Vital Signs Open-Label Study B16- 03

There were no meaningful changes in the mean or median values from baseline (Table 50) or shifts (Table 51) in heart rate or blood pressure in the supine or standing position by study visit.

### 8.4.7. Electrocardiograms (ECGs)

There were no meaningful differences in the mean or median ECG parameter from baseline to the end of treatment. There were no meaningful differences in the number of subjects with QTcF (Corrected QT-Fridericia) greater than 450 msec. See Table 52 and Table 53 in the Appendix for specifics.

Study B16-02 QTcF Outliers

There were no meaningful differences among subjects treated with IPX203 or IR CD/LD who experienced QTcF prolongation, as seen in Table 28 and Table 29 below.

**Table 28: Subjects with a Change in QTcF, Study B16-03 (Full Safety Population)**

| Description of Planned Arm | Parameter | < 30 msec | 30 - < 60 msec | >= 60 msec |
|---|---|---|---|---|
| IPX203 | QTcF Interval, Aggregate | 439 | 22 | 12 |
| IR CD/LD | QTcF Interval, Aggregate | 438 | 20 | 11 |
| Not Assigned | QTcF Interval, Aggregate | 84 | 3 | 1 |

Source: FDA analysis

**Table 29: Subjects with a Change in QTcF >60 msec and QTcF Duration >500 msec, Study B16-02 (Full Safety Population)**

| | Planned Treatment | |
|---|---|---|
| **Change from Baseline Category** | **IPX203** | **IR CD/LD** |
| >= 60 msec | 7 | 6 |
| **Analysis Value Category** | | |
| > 450 – 500 msec | 4 | 4 |
| > 500 msec | 3 | 2 |

Source: FDA analysis

Study B16-02 QTcF Outliers

In controlled study B16-02, 7 subjects randomized to IPX203 had a normal QTcF at baseline which increased by ≥ 60 msec during the study. The overall QTcF duration was 450 to 500 msec in 34 subjects and >500 msec in 3 subjects. Six subjects randomized to IR CD/LD had an increase in QTcF of > 60 msec. Four subjects had a QTcF duration of 450 to 500 msec and 3 with a QTcF duration of >500 msec. There were no adverse event reports of ventricular arrhythmia or torsades de pointes in Study B16-02.

In open label study B16-03, 15 subjects had a QTcF greater than 450 to 500 msec at baseline, and 17 subjects with a QTcF between 450 and 500 msec at Visit 4/ET. Six subjects with a change from baseline in QTcF ≥ 60 msec and a QTcF duration of 450 to 500 msec at any time during the study. One subject had a QTCF of > 500 msec at any time during the study. This subject also had a reported change in QTcF of >60 msec at Visit 2. There were no adverse events of ventricular arrhythmia or torsade de pointes in study B16-03.

### 8.4.8. Immunogenicity

Immunogenicity testing was not performed.

## 8.5.Analysis of Submission-Specific Safety Issues

### 8.5.1. Central Nervous System TEAEs

Please refer to Section 8.4.4 for a review of TEAEs affecting the central nervous system.

Dyskinesia:

The most prominent CNS TEAE in this review was the increased rate of dyskinesia in subjects taking IPX203 in the dose conversion period of Study B16-02 (6.8%) after the dyskinesia rate had been lower in the preceding IR CD/LD dose adjustment period (1.7%); in the double-blind period of the same study (2% vs 0.4%); and in Study B16-03 (5%). In total during Study B16-02, 7.6% of subjects taking IPX203 reported dyskinesia at any time, while 1.9% of subjects taking IR CD/LD reported dyskinesia at any time.

*Reviewer's Comment:*

*Regarding the reports of dyskinesia in subjects taking IPX203, Study B16-03 was an open-label study of IPX203 with no comparator and the levodopa component of IPX203 is already well-known to cause dyskinesia routinely. The increased percentage of subjects reporting dyskinesia when converting from IR-CD/LD to IPX203 and when the two groups in the double-blind period are compared, suggests IPX203 may cause greater frequency of dyskinesia as compared to IR-CD/LD.*

Hallucinations/Illusions:

Hallucinations (visual, auditory, tactile, or mixed) and illusions can be features of advanced Parkinson's disease; dopamine replacement therapy can also precipitate or exacerbate hallucinations and/or illusions. These effects are often dose and exposure-dependent, so it is not unexpected that with the higher exposures of levodopa in IPX203, more subjects developed these symptoms. In Study B16-02, 18 subjects reported 19 events associated with hallucinations and illusions. As seen in Table 30 below, during the blinded period, a greater percentage of subjects treated with IPX203 (2.7%) reported all types of hallucinations and illusions than did those taking IR CD/LD (0.2%).

**Table 30: Treatment Emergent Adverse Events Related to Hallucinations, Study B16-02 (Full Safety Population)**

| | IPX203 | | | IR CD/LD | | |
|---|---|---|---|---|---|---|
| | Epoch | | | Epoch | | |
| **Dictionary-Derived Term** | **Blinded Treatment N=256** | **IPX203 Conversion N=589** | **All N=589** | **Blinded Treatment N=250** | **Dose Adjustment N=630** | **All N=630** |
| Hallucination | 2 (0.8) | 6 (1.0) | 8 (1.4) | 0 | 1 (0.4) | 1 (0.2) |
| Hallucination, auditory | 1 (0.4) | 0 | 1 (0.4) | 0 | 0 | 0 |

| | IPX203 | | | IR CD/LD | | |
|---|---|---|---|---|---|---|
| | Epoch | | | Epoch | | |
| **Dictionary-Derived Term** | **Blinded Treatment N=256** | **IPX203 Conversion N=589** | **All N=589** | **Blinded Treatment N=250** | **Dose Adjustment N=630** | **All N=630** |
| Hallucination, visual | 3 (1.2) | 3 (0.5) | 6 (1.0) | 1 (0.2) | 0 | 1 (0.2) |
| Hallucinations, mixed | 0 | 0 | 1 (0.4)* | 0 | 0 | 0 |
| Illusion | 1 (0.4) | 0 | 1 (0.4) | 0 | 0 | 0 |
| All | 7 (2.7) | 9 (1.5) | 17 (2.7)* | 1 (0.2) | 1 (0.4) | 2 (0.3) |

*Note: One subject experienced two TEAEs related to hallucinations: Illusions reported in the IPX203 Blinded Treatment period and a second time for "Hallucinations mixed" reported in the IPX203 Follow up period.
Source: FDA analysis

Somnolence:

Somnolence, specifically daytime sleepiness, is a known side effect of dopamine replacement therapy. In Study B16-02, 28 people had 29 events associated with somnolence (Table 31). During the double-blind period, a slightly greater percentage of subjects in the IPX203 group (3.5%) than in the IR CD/LD group (2%) reported symptoms associated with somnolence. The percentage of subjects reporting each of these events was under 2%.

**Table 31: Treatment Emergent Adverse Events Related to Somnolence, Study B16-02 (Full Safety Population)**

| | IPX203 | | | IR CD/LD | | |
|---|---|---|---|---|---|---|
| | Epoch | | | Epoch | | |
| **Dictionary-Derived Term** | **Blinded Treatment N=256 n (%)** | **IPX203 Conversion N=589 n (%)** | **All N=589 n (%)** | **Blinded Treatment N=250 n (%)** | **Dose Adjustment N=630 n (%)** | **All N=630 n (%)** |
| Fatigue | 4 (1.6) | 5 (0.9) | 9 (1.5) | 3 (1.2) | 1 (0.2) | 4 (0.6) |
| Hypersomnia | 1 (.4) | 1 (0.2) | 2 (0.3) | 0 | 2 (0.4) | 2 (0.4) |
| Somnolence | 4 (1.6) | 5 (0.9) | 9 (1.5) | 2 (0.8) | 1 (0.2) | 3 (0.5) |
| All | 9 (3.5) | 11 (1.9) | 20 (3.4)* | 5 (2.0) | 4 (0.6) | 9 (1.4)* |

*Note: One subject reported somnolence in the IR CD/LD Dose Adjustment period and in the IPX203 Conversion period.
Source: FDA analysis

Impulse Control Disorders:

Two subjects in the IPX2-3 group reported events related to impulse control disorders (ICD), while one subject in the IR CD/LD treated group reported two separate ICD-related events (Table 32). These numbers are too small to draw conclusions, except to observe that there was no marked increase in ICD-related events in subjects taking IPX203 during the controlled study.

**Table 32: Treatment Emergent Adverse Events Related to Impulse Control Disorders, Study B16-02 (Full Safety Population)**

| | Epoch | | |
|---|---|---|---|
| | Blinded Treatment | | IPX203 Conversion |
| Dictionary-Derived Term | IPX203 N=256 n (%) | IR CD/LD* N=250 n (%) | IPX203 N=589 n (%) |
| Binge eating | 0 | 1 (0.4) | 0 |
| Impulse-control disorder | 0 | 0 | 1 (1.7) |
| Libido increased | 0 | 1 (0.4) | 0 |
| Obsessive-compulsive disorder | 1 (0.4) | 0 | 0 |

*Note: One subject had 2 separate events in the IR CD/LD treated group in blinded treatment. Two subjects reported a single impulse control event on IPX203
Source: FDA analysis

*Reviewer comment:*

*More subjects taking IPX203 also reported hallucinations/illusions and somnolence, but these contrasts were less pronounced. As a caveat to this, the open-label study permitted adjustment of IPX203 doses and of other PD medications, and even permitted deep brain stimulation, limiting interpretation of targeting adverse events that can be attributed to IPX203 in this trial.*

### 8.5.2. Hypotension

Orthostatic hypotension and symptomatic hypotension are frequently reported non-motor signs of Parkinson's disease, particularly in the disease's moderate to advanced stages. Levodopa administration itself is associated with negative inotrope effects of decreased mean arterial pressure, cardiac stroke volume, and cardiac contractility.[9] Because of concern for a possible exacerbation of underlying autonomic dysregulation with increased levodopa exposure we specifically examined events coded with terms that could be proxies for hypotension and postural hypotension including dizziness, postural dizziness, presyncope, syncope, hypotension and orthostatic hypotension. This analysis demonstrated greater incidence of all these events (except presyncope, which was reported/coded only once, in a subject taking IR CD/LD) in the subjects taking IPX203 in any period (Table 33). Overall, 4% of all subjects (n=23) taking IPX203 reported dizziness contrasting with 0.8% of subjects (n=5) who took IR CD/LD. For all other hypotensive symptoms, they were all more frequent in subjects taking IPX203, but at low incidences overall (<2%). See Section 8.4.6 for a discussion of specific vital signs findings.

[9] Noack C, Schroeder C, Heusser K, Lipp A. Cardiovascular effects of levodopa in Parkinson's disease. Parkinsonism Relat Disord. 2014 Aug;20(8):815-8. doi: 10.1016/j.parkreldis.2014.04.007. Epub 2014 Apr 30. PMID: 24819390.

**Table 33: Treatment Emergent Adverse Events Associated with Hypotension, Study B16-02 (Full Safety Population)**

| | Actual Treatment | | | | | |
|---|---|---|---|---|---|---|
| | IPX203 | | | IR CD/LD | | |
| Dictionary-Derived Term | Conversion N=589 n (%) | Blinded Treatment N=256 n (%) | All N=589 n (%) | Dose Adjustment N=630 n (%) | Blinded Treatment N=250 n (%) | All N=630 n (%) |
| Dizziness | 17 (2.9) | 6 (2.3) | 23 (4.0) | 3 (0.5) | 2 (0.8) | 5 (0.8) |
| Orthostatic hypotension | 8 (1.4) | 2 (0.8) | 10 (1.7) | 5 (0.8) | 1 (0.4) | 6 (1.0) |
| Syncope | 3 (0.5) | 1 (0.4) | 4 (0.7) | 1 (0.2) | 0 | 1 (0.2) |
| Hypotension | 3 (0.5) | 1 (0.4) | 4 (0.7) | 0 | 0 | 0 |
| Dizziness postural | 0 | 1 (0.4) | 1 (0.2) | 0 | 0 | 0 |
| Presyncope | 0 | 0 | 0 | 0 | 1 (0.4) | 1 (0.2) |
| Any | 28 (4.8) | 10 (3.9) | 37 (6.3) | 9 (1.4) | 4 (1.6) | 13 (2.1) |

Source: FDA Analysis

### 8.5.3. Suicidality

Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS was administered at the Screening visit, and at each of the 7 Study Visits in Study B16-02 and at every visit in Study B16-03. There were no recorded suicides. One subject in the IPX203-treated group during the double-blind period of Study B16-02 had suicidal behavior that emerged at day 70. During the double-blind period at Visit 7/ET a slightly greater percentage of subjects in the IPX203-treated group (n=3, 1.2%) reported suicidal ideation (SI) than in the IR CD/LD-treated group (n=0, 0%). These numbers had been even at Visit 4 (n=1, 0.4% in both groups).

The PD population overall has a high rate of SI with some studies finding nearly one in five PD patients has SI.[10]

### 8.5.4. Gastroparesis

Gastroparesis is a frequent non-motor complication of Parkinson's disease. The Gastroparesis Cardinal Symptom Index (GCSI) was used to assess gastrointestinal symptoms. Mean total GCSI scores were similar across treatment groups from baseline to the last assessment.

## 8.6. Safety Analyses by Demographic Subgroups

In Study B16-02 in all age groups, the most frequent adverse event was dyskinesia; this was substantially higher in the IPX203 group than in the IR CD/LD group at every age (Table 34). Nausea, dry mouth, and vomiting were more reported more frequently in the IPX203 group than the IR CD/LD group, at every age. The incidence of dizziness was greater in subjects taking

[10] Rezvani Z, Barr E, Gruber A, et. Parkinson's disease, Suicidal ideation and associated risk factors (P1.101). Neurology Apr 2017, 88 (16 Supplement) P1.101;

IPX203 under age 75 than in subjects taking IR CD/LD, but there was no difference between groups in subjects ≥ 75 years of age.

**Table 34: Frequent Treatment Emergent Adverse Events by Age Category, Study B16-02 (Full Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | Age <65 yrs | | Age 65 to <75 yrs | | Age ≥ 75 yrs | |
|---|---|---|---|---|---|---|---|
| | | IR CD/LD N=236 n (%) | IPX203 N=226 n (%) | IR CD/LD N=282 n (%) | IPX203 N=262 n (%) | IR CD/LD N=112 n (%) | IPX203 N=100 n (%) |
| Nervous system disorders | Dyskinesia | 4 (1.7) | 17 (7.5) | 7 (2.5) | 20 (7.6) | 1 (0.9) | 8 (8.0) |
| | Dizziness | 2 (0.8) | 14 (6.2) | 1 (0.4) | 8 (3.0) | 2 (1.8) | 1 (1.0) |
| | Headache | 2 (0.8) | 4 (1.8) | 5 (1.8) | 7 (2.7) | 1 (0.9) | 1 (1.0) |
| | Somnolence | 2 (0.8) | 6 (2.7) | 1 (0.4) | 2 (0.8) | 0 | 1 (1.0) |
| | Balance disorder | 0 | 4 (1.8) | 1 (0.4) | 3 (1.1) | 0 | 1 (1.0) |
| | Parkinson's disease | 0 | 3 (1.3) | 1 (0.4) | 2 (0.8) | 2 (1.8) | 0 |
| | Tremor | 2 (0.8) | 2 (0.9) | 2 (0.7) | 1 (0.4) | 0 | 1 (1.0) |
| | Dystonia | 2 (0.8) | 3 (1.3) | 0 | 2 (0.8) | 0 | 0 |
| | Freezing phenomenon | 1 (0.4) | 2 (0.9) | 0 | 0 | 1 (0.9) | 3 (3.0) |
| | On and off phenomenon | 0 | 3 (1.3) | 2 (0.7) | 0 | 0 | 1 (1.0) |
| | Syncope | 0 | 0 | 1 (0.4) | 4 (1.5) | 0 | 0 |
| | Cognitive disorder | 0 | 0 | 3 (1.1) | 0 | 0 | 1 (1.0) |
| | Hypersomnia | 0 | 0 | 2 (0.7) | 0 | 0 | 2 (2.0) |
| | Hypoesthesia | 0 | 1 (0.4) | 0 | 3 (1.1) | 0 | 0 |
| | Restless legs syndrome | 3 (1.3) | 0 | 0 | 1 (0.4) | 0 | 0 |
| | Sciatica | 3 (1.3) | 0 | 0 | 1 (0.4) | 0 | 0 |
| Gastrointestinal disorders | Nausea | 5 (2.1) | 15 (6.6) | 3 (1.1) | 18 (6.8) | 1 (0.9) | 7 (7.0) |
| | Dry mouth | 1 (0.4) | 15 (6.6) | 3 (1.1) | 11 (4.2) | 0 | 2 (2.0) |
| | Constipation | 2 (0.8) | 7 (3.1) | 3 (1.1) | 4 (1.5) | 3 (2.7) | 5 (5.0) |
| | Vomiting | 2 (0.8) | 6 (2.7) | 1 (0.4) | 6 (2.3) | 0 | 4 (4.0) |
| | Diarrhea | 0 | 2 (0.9) | 2 (0.7) | 2 (0.8) | 2 (1.8) | 1 (1.0) |
| | Dyspepsia | 0 | 1 (0.4) | 0 | 2 (0.8) | 2 (1.8) | 1 (1.0) |
| Psychiatric disorders | Insomnia | 2 (0.8) | 5 (2.2) | 5 (1.8) | 5 (1.9) | 0 | 5 (5.0) |
| | Anxiety | 0 | 8 (3.5) | 1 (0.4) | 6 (2.3) | 0 | 2 (2.0) |
| | Depression | 0 | 1 (0.4) | 1 (0.4) | 6 (2.3) | 1 (0.9) | 4 (4.0) |
| | Hallucination | 0 | 2 (0.9) | 1 (0.4) | 4 (1.5) | 0 | 2 (2.0) |
| | Hallucination, visual | 1 (0.4) | 1 (0.4) | 0 | 4 (1.5) | 0 | 2 (2.0) |
| | Sleep disorder | 0 | 0 | 2 (0.7) | 5 (1.9) | 1 (0.9) | 0 |
| | Abnormal dreams | 0 | 1 (0.4) | 1 (0.4) | 4 (1.5) | 0 | 0 |
| | Confusional state | 0 | 1 (0.4) | 1 (0.4) | 2 (0.8) | 0 | 2 (2.0) |
| | Restlessness | 1 (0.4) | 1 (0.4) | 0 | 3 (1.1) | 0 | 0 |
| Infections and infestations | Urinary tract infection | 0 | 4 (1.8) | 6 (2.1) | 4 (1.5) | 3 (2.7) | 3 (3.0) |
| | Nasopharyngitis | 3 (1.3) | 6 (2.7) | 2 (0.7) | 0 | 0 | 3 (3.0) |
| | Upper respiratory tract infection | 1 (0.4) | 3 (1.3) | 3 (1.1) | 1 (0.4) | 1 (0.9) | 0 |
| | Fall | 3 (1.3) | 8 (3.5) | 7 (2.5) | 5 (1.9) | 5 (4.5) | 5 (5.0) |

| Body System or Organ Class | Dictionary-Derived Term | Age <65 yrs | | Age 65 to <75 yrs | | Age ≥ 75 yrs | |
|---|---|---|---|---|---|---|---|
| | | IR CD/LD N=236 n (%) | IPX203 N=226 n (%) | IR CD/LD N=282 n (%) | IPX203 N=262 n (%) | IR CD/LD N=112 n (%) | IPX203 N=100 n (%) |
| Injury, poisoning and procedural complications | Skin laceration | 0 | 1 (0.4) | 1 (0.4) | 0 | 3 (2.7) | 0 |
| Musculoskeletal and connective tissue disorders | Back pain | 4 (1.7) | 7 (3.1) | 6 (2.1) | 1 (0.4) | 0 | 0 |
| | Muscle spasms | 1 (0.4) | 4 (1.8) | 0 | 1 (0.4) | 0 | 1 (1.0) |
| | Pain in extremity | 0 | 3 (1.3) | 1 (0.4) | 2 (0.8) | 0 | 1 (1.0) |
| | Arthralgia | 0 | 2 (0.9) | 0 | 3 (1.1) | 0 | 0 |
| General disorders and administration site conditions | Fatigue | 2 (0.8) | 3 (1.3) | 1 (0.4) | 4 (1.5) | 1 (0.9) | 2 (2.0) |
| | Feeling abnormal | 0 | 1 (0.4) | 0 | 5 (1.9) | 0 | 0 |
| Vascular disorders | Hypertension | 3 (1.3) | 1 (0.4) | 6 (2.1) | 5 (1.9) | 1 (0.9) | 0 |
| | Orthostatic hypotension | 1 (0.4) | 3 (1.3) | 4 (1.4) | 6 (2.3) | 1 (0.9) | 1 (1.0) |
| Investigations | Blood pressure increased | 0 | 1 (0.4) | 1 (0.4) | 4 (1.5) | 0 | 3 (3.0) |
| Eye disorders | Vision blurred | 0 | 3 (1.3) | 0 | 1 (0.4) | 1 (0.9) | 0 |

Source: FDA Analysis

In Study B16-03, there were more reports of dyskinesia, insomnia, constipation, back pain, and muscle spasms in subjects under 65 years old (Table 35). Those aged 65 years or greater reported more falls and UTIs, consistent with this age group. The remainder of TEAEs were reported more frequently in the older age group or not significantly different.

**Table 35: Treatment Emergent Adverse Events by Age Group ≥ 2% Study B16-03 (Open-Label Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | IPX203 Age < 65 N= 152 n (%) | IPX203 Age ≥65 N=267 n (%) |
|---|---|---|---|
| Nervous system disorders | Dyskinesia | 10 (6.6) | 11 (4.1) |
| | Syncope | 1 (0.7) | 6 (2.2) |
| | Dizziness | 1 (0.7) | 5 (1.9) |
| | On and off phenomenon | 3 (2.0) | 3 (1.1) |
| Psychiatric disorders | Hallucination | 0 | 8 (3.0) |
| | Depression | 1 (0.7) | 6 (2.2) |
| | Insomnia | 4 (2.6) | 2 (0.7) |
| | Confusional state | 0 | 5 (1.9) |
| Infections and infestations | Urinary tract infection | 3 (2.0) | 18 (6.7) |
| | COVID-19 | 5 (3.3) | 5 (1.9) |
| Gastrointestinal disorders | Constipation | 6 (3.9) | 5 (1.9) |
| | Nausea | 2 (1.3) | 6 (2.2) |
| | Vomiting | 1 (0.7) | 5 (1.9) |
| Injury, poisoning and procedural complications | Fall | 4 (2.6) | 17 (6.4) |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | Back pain | 7 (4.6) | 8 (3.0) |
| | Muscle spasms | 3 (2.0) | 1 (0.4) |
| Investigations | Blood creatine phosphokinase increased | 3 (2.0) | |
| General disorders and administration site conditions | Pyrexia | 3 (2.0) | 1 (0.4) |
| | Pain | 3 (2.0) | |
| Renal and urinary disorders | Nephrolithiasis | 0 | 5 (1.9) |
| Vascular disorders | Hypertension | 1 (0.7) | 5 (1.9) |
| | Orthostatic hypotension | 1 (0.7) | 5 (1.9) |
| Skin and subcutaneous tissue disorders | Rash | 0 | 5 (1.9) |
| Blood and lymphatic system disorders | Anemia | 0 | 5 (1.9) |

Source: FDA Analysis

TEAEs by Sex:

In the controlled trial, there were no substantive differences by sex for IR CD/LD, except for slightly more falls in females (10=4.3% vs 5=1.3%), and more UTIs.

As seen in Table 36, for IPX203, a greater percentage of females reported dyskinesia (10.1% females vs 6.2% males), nausea (13.4% vs 2.7%), vomiting (6.5% vs 0.5%), anxiety (4.1% vs 1.6%) and depression (3.2% vs 1.1%). Six female subjects (2.8%) taking IPX203 during any study period reported hypertension compared to none among male subjects taking IPX203. The remainder of reports were not substantially different by sex.

**Table 36: All Treatment Emergent Adverse Events by Sex ≥ 1% in Any Period, Study B16-02 (Full Safety Population)**

| Primary System Organ Class | Dictionary-Derived Term | IPX203 Male N=372 n (%) | IPX203 Female N=217 n (%) | IR CD/LD Male N=396 n (%) | IR CD/LD Female N=234 n (%) |
|---|---|---|---|---|---|
| Nervous system disorders | Dyskinesia | 23 (6.2) | 22 (10.1) | 9 (2.3) | 3 (1.3) |
| | Dizziness | 13 (3.5) | 10 (4.6) | 5 (1.3) | 0 (0.0) |
| | Headache | 6 (1.6) | 6 (2.8) | 3 (0.8) | 5 (2.1) |
| | Somnolence | 7 (1.9) | 2 (0.9) | 3 (0.8) | 0 (0.0) |
| | Balance disorder | 4 (1.1) | 4 (1.8) | 0 (0.0) | 1 (0.4) |
| | Parkinson's disease | 4 (1.1) | 1 (0.5) | 2 (0.5) | 1 (0.4) |
| | Dystonia | 1 (0.3) | 4 (1.8) | 1 (0.3) | 1 (0.4) |
| | Freezing phenomenon | 2 (0.5) | 3 (1.4) | 1 (0.3) | 1 (0.4) |
| Gastrointestinal disorders | Nausea | 10 (2.7) | 29 (13.4) | 5 (1.3) | 4 (1.7) |
| | Dry mouth | 17 (4.6) | 10 (4.6) | 3 (0.8) | 1 (0.4) |
| | Constipation | 10 (2.7) | 5 (2.3) | 7 (1.8) | 1 (0.4) |
| | Vomiting | 2 (0.5) | 14 (6.5) | 1 (0.3) | 2 (0.9) |
| | Diarrhea | 2 (0.5) | 3 (1.4) | 0 (0.0) | 4 (1.7) |
| | Dyspepsia | 1 (0.3) | 3 (1.4) | 1 (0.3) | 1 (0.4) |
| Psychiatric disorders | Insomnia | 11 (3.0) | 4 (1.8) | 3 (0.8) | 4 (1.7) |
| | Anxiety | 6 (1.6) | 9 (4.1) | 1 (0.3) | 0 (0.0) |

| Primary System Organ Class | Dictionary-Derived Term | IPX203 Male N=372 n (%) | IPX203 Female N=217 n (%) | IR CD/LD Male N=396 n (%) | IR CD/LD Female N=234 n (%) |
|---|---|---|---|---|---|
| | Depression | 4 (1.1) | 7 (3.2) | 2 (0.5) | 0 (0.0) |
| | Hallucination | 6 (1.6) | 2 (0.9) | 0 (0.0) | 1 (0.4) |
| | Hallucination, visual | 6 (1.6) | 1 (0.5) | 1 (0.3) | 0 (0.0) |
| | Abnormal dreams | 4 (1.1) | 1 (0.5) | 1 (0.3) | 0 (0.0) |
| | Confusional state | 5 (1.3) | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Infections and infestations | Urinary tract infection | 5 (1.3) | 5 (2.3) | 3 (0.8) | 6 (2.6) |
| | Nasopharyngitis | 7 (1.9) | 1 (0.5) | 3 (0.8) | 2 (0.9) |
| | Upper respiratory tract infection | 4 (1.1) | 0 (0.0) | 5 (1.3) | 0 (0.0) |
| | Influenza | 4 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Injury, poisoning and procedural complications | Fall | 10 (2.7) | 7 (3.2) | 5 (1.3) | 10 (4.3) |
| | Contusion | 0 (0.0) | 2 (0.9) | 0 (0.0) | 3 (1.3) |
| | Skin laceration | 0 (0.0) | 1 (0.5) | 0 (0.0) | 4 (1.7) |
| Musculoskeletal and connective tissue disorders | Back pain | 6 (1.6) | 2 (0.9) | 5 (1.3) | 5 (2.1) |
| | Muscle spasms | 4 (1.1) | 2 (0.9) | 1 (0.3) | 0 (0.0) |
| | Pain in extremity | 5 (1.3) | 1 (0.5) | 1 (0.3) | 0 (0.0) |
| | Arthralgia | 5 (1.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| General disorders and administration site conditions | Fatigue | 5 (1.3) | 4 (1.8) | 2 (0.5) | 2 (0.9) |
| | Feeling abnormal | 1 (0.3) | 4 (1.8) | 0 (0.0) | 0 (0.0) |
| Vascular disorders | Hypertension | 0 (0.0) | 6 (2.8) | 5 (1.3) | 5 (2.1) |
| | Orthostatic hypotension | 7 (1.9) | 3 (1.4) | 5 (1.3) | 1 (0.4) |
| | Blood pressure increased | 5 (1.3) | 3 (1.4) | 0 (0.0) | 1 (0.4) |
| Renal and urinary disorders | Nephrolithiasis | 4 (1.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Respiratory, thoracic and mediastinal disorders | Dyspnea | 1 (0.3) | 3 (1.4) | 1 (0.3) | 0 (0.0) |
| Metabolism and nutrition disorders | Decreased appetite | 1 (0.3) | 5 (2.3) | 2 (0.5) | 0 (0.0) |

Source: FDA Analysis

*Reviewer Comment:*

*In females, IPX203 was comparatively less well-tolerated than IR CD/LD, with the female*

*subjects in the double-blind period reporting more adverse events associated with dyskinesia, nausea, vomiting, anxiety and depression. The study was not designed in a way to determine whether this discrepancy was dose-related.*

In the uncontrolled study males and females reported dyskinesia equally. As seen in Table 37 below, more females reported on/off phenomena, UTIs, nausea, vomiting, and GERD. A slightly greater percentage of female subjects taking IPX203 also reported more rashes, anemia, and vertigo, compared to males. The remainder of reporting differences were not significantly divergent between males and females (≤1% difference).

**Table 37: Treatment Emergent Adverse Events by Sex ≥ 1%, Study B16-03 (Open-Label Safety Population)**

| Body System or Organ Class | Dictionary-Derived Term | IPX203 Females N=140 n (%) | IPX203 Males N=279 n (%) |
|---|---|---|---|
| Nervous system disorders | Dyskinesia | 7 (5.0) | 14 (5.0) |
| | On and off phenomenon | 4 (2.9) | 2 (0.7) |
| | Restless legs syndrome | 3 (2.1) | 2 (0.7) |
| | Sciatica | 3 (2.1) | 2 (0.7) |
| | Carpal tunnel syndrome | 3 (2.1) | 1 (0.4) |
| | Headache | 3 (2.1) | 1 (0.4) |
| Psychiatric disorders | Hallucination | 3 (2.1) | 5 (1.8) |
| Infections and infestations | Urinary tract infection | 10 (7.1) | 11 (3.9) |
| Gastrointestinal disorders | Constipation | 4 (2.9) | 7 (2.5) |
| | Nausea | 6 (4.3) | 2 (0.7) |
| | Vomiting | 5 (3.6) | 1 (0.4) |
| | Gastroesophageal reflux disease | 3 (2.1) | 1 (0.4) |
| Injury, poisoning and procedural complications | Fall | 8 (5.7) | 13 (4.7) |
| Musculoskeletal and connective tissue disorders | Back pain | 4 (2.9) | 11 (3.9) |
| Vascular disorders | Hypertension | 3 (2.1) | 3 (1.1) |
| Skin and subcutaneous tissue disorders | Rash | 3 (2.1) | 2 (0.7) |
| Blood and lymphatic system disorders | Anemia | 3 (2.1) | 2 (0.7) |
| Ear and labyrinth disorders | Vertigo | 3 (2.1) | 1 (0.4) |

Source: FDA Analysis

## 8.7. Additional Safety Explorations

### 8.7.1. Human Carcinogenicity or Tumor Development

Not applicable.

### 8.7.2. Human Reproduction and Pregnancy

The applicant conducted no studies in pregnant women with IPX203 to assess risks. No pregnancies were reported during the development program. Levodopa is known to cross the human placental barrier. Carbidopa/levodopa has been shown to be developmentally toxic (including teratogenic effects) in animals, at clinically relevant doses

### 8.7.3. Pediatrics and Assessment of Effects on Growth

The Applicant received a pediatric waiver and conducted no pediatric studies.

### 8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses were reported during the development program. No AEs consistent with withdrawal phenomena were reported during the dose adjustment or double-blind period of the controlled study.

Carbidopa/levodopa is generally not considered a drug of abuse, insofar as it is not a drug of abuse for people unaffected by Parkinson's disease. There are reports of acute overdose in the medical literature, but they are infrequent.

More frequently reported is the also-uncommon phenomenon of Dopamine Dysregulation Syndrome (DDS), in which people taking various formulations of dopamine replacement therapy for symptoms of Parkinson's disease take greater than prescribed doses of the prescribed medication, obsessively, either chasing a level of symptomatic perfection and symptom eradication that is generally not achievable with the condition, or out of an intolerance for "off" symptoms. This phenomenon has also been observed in people with PD taking dopamine agonists and with injectable apomorphine. The frequency of DDS has been estimated at 3-4% in tertiary centers.[11] It may occur more frequently with shorter-acting forms of levodopa.

The development program for IPX203 showed no increased incidence of DDS among TEAEs in the controlled or uncontrolled study, and the expectation based on the current data presented for IPX203 is that the frequency of this syndrome would be resemble that for other existing extended-release forms of levodopa.

## 8.8. Safety in the Postmarket Setting

### 8.8.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. IPX203 is not currently marketed.

[11] Advanced Therapies for the Management of Dopamine Dysregulation Syndrome in Parkinson's Disease Sanskriti Sasikumar MD, Roberto Matta, Renato P. Munhoz MD, PhD, Mateusz Zurowski MD, Yu-Yan Poon RN, Mojgan Hodaie MD, MSc, Suneil K. Kalia MD, PhD, Andres M. Lozano MD, PhD, Alfonso Fasano MD, PhD . Movement Disorders. Volume 8, Issue 3, April 2021 pp 400-405. First published 25 January 2021 https://doi.org/10.1002/mdc3.13154.

### 8.8.2. Expectations on Safety in the Postmarket Setting

In general, I expect that the patterns of adverse reactions in the post-market setting will be similar to those seen during the controlled and uncontrolled clinical studies. The data regarding a possibly increased frequency of falls and of urinary tract infections in subjects taking IPX203 in these trials were ambiguous; a longer duration of treatment in a larger population may clarify whether there is a relationship.

### 8.8.3. Additional Safety Issues from Other Disciplines

Not applicable.

## 8.9. Integrated Assessment of Safety

The Applicant proposes a maximum daily dose of (b) (4) of carbidopa/levodopa in an extended-release capsule formulation. To support the safety of IPX203, the Applicant provided safety data primarily from two Phase 3 clinical trials: one double-dummy, active-controlled study lasting 20 weeks incorporating a 13-week double-blind period, and one longer-term open-label safety study lasting 9 months. The subjects in these trials were adults diagnosed with Parkinson's disease after age 40 and who had moderate to advanced Parkinson's disease with motor fluctuations, with a mean duration of disease of 8 years. 731 unique subjects were exposed to IPX203 across all studies in the development program.

The primary FDA safety analyses were performed on the following datasets:

- Controlled safety population: Study B16-02, including TEAEs from the dose adjustment, dose conversion, and double-blind periods.
- Uncontrolled safety population: Study B16-03, through its 9-month completion date. The Applicant submitted no new clinical trials data in the 120-day safety report. There was nothing in the literature review that they submitted with this update that indicated new safety information.

During the review, it was noted that the safety database was inadequate for review because the datasets in the initial submission included the exposure data by total daily dose and mean daily dose only. The Phase 3 safety database was adequate for review once the Applicant adjusted and resubmitted the data to include exposure data by modal daily dose. In general, the Agency requires 100 subjects be exposed for a minimum of at least one year with at least half (or a substantial proportion of) the subjects taking the maximum dose proposed in the labeling (here (b) (4) per day).

Although initially considered adequate for review, it was eventually determined that the available data did not meet the requirements for exposure duration at the maximum doses proposed for marketing. Specifically, the exposure dataset included in the initial NDA submission reported exposures using the mean total daily dose for the pooled safety population. Based on the mean total daily dose, the Applicant reported 179 subjects with at

least 1-year exposure to IPX203 at any dose and 43 subjects who had taken doses ≥2000mg/day for a period of at least 12 months. However, the mean daily dose is an average that may not necessarily reflect what daily dose individual subjects actually took, particularly in a flexible dose study such as Study B16-02 and Study B16-03. When exposure was calculated using the modal total daily dose, only 67 subjects had taken IPX203 for at least 12 months at any single dose, and no subjects had taken ≥600mg/2400mg per day for at least one year. Therefore, the exposure of subjects in Studies B16-02 and B16-03 is not sufficient to support the safety of IPX203. The Applicant is unable to rely on prior findings of safety for the listed drugs, (Sinemet and Rytary) given the lack of a scientific bridge for PK carbidopa (see Section 4.5).

There were six deaths reported during the development program. One death occurred during the screening period of the Phase 3 controlled trial B16-02, before the subject had received any study drug. The other five occurred during the Phase 3 open-label uncontrolled trial B16-03. These five deaths had diverse causes, although two were gastrointestinal. One of them (a drowning) was considered drug-related but the causal relationship was not clear from our perspective.

In Study B16-02, during the double-blind period of the controlled trial, the overall incidence of treatment-emergent SAEs was 4.7% in the IPX203-treated arm vs 1.6% in the IR CD/LD group. The most frequently reported SAEs were neurological but none of the individual adverse events exceeded 1% frequency.

During the double-blind period of Study B16-02, 5.5% (n=14) of IPX203 subjects withdrew because of TEAEs, vs 1.2% in the IR CD/LD group. During the initial open-label phases of this study, 0.6% of subjects withdrew because of TEAEs during the introductory IR CD/LD dose adjustment period, whereas 5.9% (n=35) subjects subsequently withdrew because of TEAEs during the IPX203 dose conversion stage. The most frequently cited events leading to discontinuation were dyskinesia, dizziness, nausea, and sleep problems.

The serious adverse event and treatment emergent adverse event results of Study B16-03 did not change the conclusions about safety for IPX203.

Certain adverse events of special interest (AESIs) were specifically evaluated. The AESIs were evaluated mostly with respect to Study B16-02 because of the lack of comparator in Study B16-03. Within Study B16-02, results were pooled across study periods for these AEs of special interest. AESIs assessed in Studies B16-02 and B16-03 included dyskinesia, hallucinations/ illusions, somnolence, impulse control disorders, and hypotension.

Dyskinesia was the most frequently reported AESI. At baseline, subjects with moderate to advanced Parkinson's disease with motor fluctuations, who were the substrate for this study, have some degree of dyskinesia resulting from levodopa exposure by definition. IPX203 is formulated to result in a longer exposure to higher amounts of levodopa and resulting greater "on" time; an associated increase in dyskinesia is not surprising and was seen in every stage of the Phase 3 studies involving IPX203. The rate of dyskinesia in the double-blind period of Study

B16-02 was 2% vs. 0.4% in subjects taking IPX203 vs IR CD/LD. It was 1.7% in the dose conversion period for subjects taking IR CD/LD but rose to 6.8% when those subjects converted to IPX203 during the dose conversion period. The overall rate of dyskinesia was 7.6% and 1.9% for any subject taking IPX203 or IR CD/LD, respectively, in Study B16-02.

Hallucinations and illusions occurred in 7 subjects treated with IPX203 (2.7%) vs 1 taking IR CD/LD (0.3%) during the double-blind period of Study B16-02, similar to the incidences when totaled across all periods in this study (2.7% vs 0.3%).

Somnolence was reported in 9 (3.5%) subjects taking IPX203 and 5 (2.0%) taking IR CD/LD in the Study B16-02 double-blind period, and in 20 (3.4%) taking IPX203 vs 9 (1.4%) of subjects taking IR CD/LD across all periods of this study.

Impulse Control Disorders were reported in 2 subjects taking IPX203 vs one taking IR CD/LD during all stages of Study B16-02. One subject reported 2 separate events in the IR CD/LD treated group in blinded treatment. Two subjects reported a single impulse control event on IPX203 during the dose conversion period. These are not appreciably different results.

Hypotension is a common, non-motor feature of PD that can be exacerbated by treatment with levodopa. Analysis of this symptom included complaints of dizziness, postural dizziness, pre-syncope and syncope as well as measured blood pressure abnormalities. In the double-blind period of Study B16-02, 10 (3.9%) of subjects taking IPX203 reported any hypotension-associated symptoms, vs 4 (1.6%) taking IR CD/LD in the blinded period. In total during Study B16-02, 23 subjects (4%) taking IPX203 reported dizziness specifically but 5 (0.8%) of subjects who took IR CD/LD reported dizziness. Overall, in all phases of Study B16-02, 42 (7.1%) subjects on IPX203 reported symptoms in this category vs 13 (2.1%) taking IR CD/LD.

There were no recorded suicides in the Phase 3 studies. During the double-blind period of Study B16-02, slightly more subjects in the IPX203-treated group reported suicidal ideation than in the IR CD/LD-treated group (n=3, 1.2% vs. 0). One subject in the IPX203-treated group had suicidal behavior that developed after 70 days on the medication. These numbers did not raise specific concern.

There were scattered differences in blood pressure in the treatment and control groups that did not amount to discernable differences because of differences that had also been present at baseline in some of the subjects. There were no hematologic differences seen with treatment. There were no cases that met criteria for Hy's law. No subjects discontinued treatment as a result of LFT abnormalities or liver dysfunction.

In summary, there were no adverse events of specific concern associated with IPX203 treatment. Subjects who received the treatment reported more dyskinesia, hallucinations/ illusions, somnolence, and hypotension than those taking IR CD/LD, during the double-blind period of Study B16-02.

However, based on the modal daily dose, there was an insufficient number of subjects with 1 year exposure at any dose (n=67), and no subjects at the proposed maximal dose to support the safety of chronic treatment with IPX203 for the proposed indication. For this reason, we cannot determine or support the chronic safety of IPX203 in the treatment of moderate to advanced PD with motor fluctuations.

# 9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for this submission.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

Deficiencies preclude labeling discussions with the sponsor during this review cycle.

## 10.2. Nonprescription Drug Labeling

Not applicable.

# 11. Risk Evaluation and Mitigation Strategies (REMS)

A decision about a REMS is deferred.

# 12. Post-marketing Requirements and Commitments

Deferred.

# 13. Appendices

## 13.1. References

See footnotes throughout document.

## 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): IPX203-B16-02**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 519 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 19 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 19<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 13.3. UK Parkinson's Disease Society Brain Bank Diagnostic Criteria

**Step 1. Diagnosis of Parkinsonian Syndrome**

- Bradykinesia
- At least one of the following
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

**Step 2 Exclusion criteria for Parkinson's disease**

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

**Step 3 supportive prospective positive criteria for Parkinson's disease**

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.

## 13.4. Study Tables

**Table 38: Protocol Violations/Deviations by Period, Study B16-02 (Full Safety Population)**

| | | Category for Protocol Deviation | | |
|---|---|---|---|---|
| **Epoch** | **Protocol Deviation Coded Term** | **Major** | **Minor** | **All** |
| **Screening** | Concomitant Medication / Administration of prohibited medication | 0 | 2 | 2 |
| | Concomitant Medications | 0 | 2 | 2 |
| | Enrollment Criteria | 5 | 6 | 11 |
| | Inclusion or Exclusion Criteria | 5 | 2 | 7 |
| | Informed Consent | 13 | 18 | 31 |
| | Informed Consent / Other | 1 | 5 | 6 |
| | Investigational Product / IP Dosing | 0 | 1 | 1 |
| | Laboratory | 0 | 22 | 22 |
| | Met Withdrawal Criteria but was not Withdrawn | 1 | 0 | 1 |
| | Non-compliance | 11 | 1 | 12 |
| | Other | 2 | 6 | 8 |
| | Study Procedure / Missed procedure | 3 | 50 | 53 |
| | Study Procedure / Other | 4 | 8 | 12 |
| | Study Procedure / Site Staff Authorization, Delegation, Training | 18 | 0 | 18 |
| | Study Procedure / Visit Missing | 2 | 4 | 6 |
| | Visit Schedule | 0 | 3 | 3 |
| | Visit Window | 0 | 7 | 7 |
| | Visit/Procedure Required | 11 | 57 | 68 |
| | All | 76 | 194 | 270 |
| **Dose Adjustment** | Concomitant Medications | 0 | 3 | 3 |
| | Dosing | 1 | 3 | 4 |
| | Enrollment Criteria | 2 | 0 | 2 |
| | Inclusion or Exclusion Criteria | 3 | 0 | 3 |
| | Informed Consent | 0 | 2 | 2 |
| | Investigational Product / IP Dosing | 0 | 3 | 3 |
| | Investigational Product / Other | 1 | 8 | 9 |
| | Laboratory | 0 | 3 | 3 |
| | Met Withdrawal Criteria but was not Withdrawn | 5 | 0 | 5 |
| | Non-compliance | 6 | 1 | 7 |
| | Other | 4 | 0 | 4 |
| | Study Procedure / Missed procedure | 10 | 17 | 27 |
| | Study Procedure / Other | 6 | 10 | 16 |
| | Study Procedure / Site Staff Authorization, Delegation, Training | 24 | 0 | 24 |
| | Study Procedure / Subject compliance | 2 | 1 | 3 |
| | Study Procedure / Visit Missing | 9 | 3 | 12 |
| | Visit Schedule | 7 | 9 | 16 |
| | Visit Window | 2 | 23 | 25 |
| | Visit/Procedure Required | 10 | 44 | 54 |
| | All | 92 | 130 | 222 |
| **IPX203** | Concomitant Medication / Administration of prohibited | 3 | 1 | 4 |

| | | Category for Protocol Deviation | | |
|---|---|---|---|---|
| **Epoch** | **Protocol Deviation Coded Term** | **Major** | **Minor** | **All** |
| **Conversion** | medication | | | |
| | Concomitant Medications | 0 | 2 | 2 |
| | Dosing | 5 | 12 | 17 |
| | Inclusion or Exclusion Criteria | 0 | 1 | 1 |
| | Informed Consent | 0 | 3 | 3 |
| | Investigational Product / IP Dosing | 0 | 7 | 7 |
| | Investigational Product / Other | 0 | 20 | 20 |
| | Laboratory | 0 | 3 | 3 |
| | Met Withdrawal Criteria but was not Withdrawn | 2 | 0 | 2 |
| | Non-compliance | 4 | 3 | 7 |
| | Other | 0 | 5 | 5 |
| | SAE not reported or reported late | 1 | 0 | 1 |
| | Study Procedure / Missed procedure | 20 | 38 | 58 |
| | Study Procedure / Other | 3 | 7 | 10 |
| | Study Procedure / Site Staff Authorization, Delegation, Training | 21 | 0 | 21 |
| | Study Procedure / Subject compliance | 2 | 3 | 5 |
| | Study Procedure / Visit Missing | 2 | 7 | 9 |
| | Visit Schedule | 4 | 28 | 32 |
| | Visit Window | 4 | 70 | 74 |
| | Visit/Procedure Required | 20 | 59 | 79 |
| | All | 91 | 269 | 360 |
| **Blinded Treatment** | Concomitant Medication / Administration of prohibited medication | 1 | 1 | 2 |
| | Dosing | 8 | 6 | 14 |
| | Enrollment Criteria | 1 | 0 | 1 |
| | Informed Consent | 1 | 3 | 4 |
| | Investigational Product / Incorrect IP kit given to subject | 1 | 1 | 2 |
| | Investigational Product / IP Dosing | 7 | 4 | 11 |
| | Investigational Product / Other | 5 | 23 | 28 |
| | Laboratory | 1 | 29 | 30 |
| | Non-compliance | 16 | 5 | 21 |
| | Other | 2 | 9 | 11 |
| | Study Procedure / Missed procedure | 75 | 70 | 145 |
| | Study Procedure / Other | 10 | 27 | 37 |
| | Study Procedure / Site Staff Authorization, Delegation, Training | 53 | 4 | 57 |
| | Study Procedure / Subject compliance | 5 | 1 | 6 |
| | Study Procedure / Visit Missing | 13 | 20 | 33 |
| | Visit Schedule | 6 | 37 | 43 |
| | Visit Window | 3 | 88 | 91 |
| | Visit/Procedure Required | 33 | 62 | 95 |
| | All | 241 | 390 | 631 |
| **Follow-Up** | Informed Consent / Other | 1 | 1 | 2 |
| | Investigational Product / IP Dosing | 1 | 1 | 2 |
| | Investigational Product / Other | 0 | 3 | 3 |
| | Laboratory | 0 | 4 | 4 |
| | Non-compliance | 2 | 0 | 2 |

| | | Category for Protocol Deviation | | |
|---|---|---|---|---|
| **Epoch** | **Protocol Deviation Coded Term** | **Major** | **Minor** | **All** |
| | Study Procedure / Missed procedure | 5 | 24 | 29 |
| | Study Procedure / Other | 3 | 6 | 9 |
| | Study Procedure / Site Staff Authorization, Delegation, Training | 12 | 0 | 12 |
| | Study Procedure / Subject compliance | 1 | 0 | 1 |
| | Study Procedure / Visit Missing | 2 | 4 | 6 |
| | Visit Schedule | 2 | 0 | 2 |
| | Visit Window | 1 | 23 | 24 |
| | Visit/Procedure Required | 29 | 28 | 57 |
| | All | 59 | 94 | 153 |
| **All Protocol Violations** | | 559 | 1077 | 1636 |

**Table 39: All Treatment Emergent Adverse Events, Study B16-03 (Open-Label Safety Population)**

| **Body System or Organ Class** | **Dictionary-Derived Term** | **IPX203 N=419 n (%)** |
|---|---|---|
| **Nervous system disorders** | Dyskinesia | 21 (5.0) |
| | Syncope | 7 (1.7) |
| | Dizziness | 6 (1.4) |
| | On and off phenomenon | 6 (1.4) |
| | Restless legs syndrome | 5 (1.2) |
| | Sciatica | 5 (1.2) |
| | Carpal tunnel syndrome | 4 (1.0) |
| | Headache | 4 (1.0) |
| | Paresthesia | 4 (1.0) |
| | Cognitive disorder | 3 (0.7) |
| | Hypoesthesia | 3 (0.7) |
| | Polyneuropathy | 3 (0.7) |
| | Seizure | 3 (0.7) |
| | Somnolence | 3 (0.7) |
| | Dysesthesia | 2 (0.5) |
| | Dystonia | 2 (0.5) |
| | Freezing phenomenon | 2 (0.5) |
| | Motor neuron disease | 2 (0.5) |
| | Neuropathy peripheral | 2 (0.5) |
| | Tremor | 2 (0.5) |
| | Brachial plexopathy | 1 (0.2) |
| | Bradykinesia | 1 (0.2) |
| | Cauda equina syndrome | 1 (0.2) |
| | Stroke | 1 (0.2) |
| | Drop attacks | 1 (0.2) |
| | Epilepsy | 1 (0.2) |
| | Hyperkinesia | 1 (0.2) |
| | Hypokinesia | 1 (0.2) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| | Memory impairment | 1 (0.2) |
| | Nerve compression | 1 (0.2) |
| | Orthostatic hypertension | 1 (0.2) |
| | Parkinson's disease | 1 (0.2) |
| | Parkinsonism | 1 (0.2) |
| | Peripheral sensorimotor neuropathy | 1 (0.2) |
| | Peripheral sensory neuropathy | 1 (0.2) |
| | Subarachnoid hemorrhage | 1 (0.2) |
| | Taste disorder | 1 (0.2) |
| | Tongue biting | 1 (0.2) |
| **Psychiatric disorders** | Hallucination | 8 (1.9) |
| | Depression | 7 (1.7) |
| | Insomnia | 6 (1.4) |
| | Confusional state | 5 (1.2) |
| | Anxiety | 4 (1.0) |
| | Delirium | 3 (0.7) |
| | Psychotic disorder | 3 (0.7) |
| | Sleep disorder | 3 (0.7) |
| | Compulsions | 2 (0.5) |
| | Delusion | 2 (0.5) |
| | Hallucination, visual | 2 (0.5) |
| | Hypersexuality | 2 (0.5) |
| | Restlessness | 2 (0.5) |
| | Abnormal dreams | 1 (0.2) |
| | Acute psychosis | 1 (0.2) |
| | Affect lability | 1 (0.2) |
| | Depressed mood | 1 (0.2) |
| | Depressive symptom | 1 (0.2) |
| | Inappropriate affect | 1 (0.2) |
| | Loss of libido | 1 (0.2) |
| | Mental status changes | 1 (0.2) |
| | Obsessive-compulsive disorder | 1 (0.2) |
| | Obsessive-compulsive personality disorder | 1 (0.2) |
| | Panic attack | 1 (0.2) |
| | Rapid eye movement sleep behavior disorder | 1 (0.2) |
| | Rapid eye movements sleep abnormal | 1 (0.2) |
| | Suicidal ideation | 1 (0.2) |
| **Infections and infestations** | Urinary tract infection | 21 (5.0) |
| | COVID-19 | 10 (2.4) |
| | Cystitis | 3 (0.7) |
| | Pneumonia | 3 (0.7) |
| | Cellulitis | 2 (0.5) |
| | Abscess limb | 1 (0.2) |
| | Bronchitis | 1 (0.2) |
| | COVID-19 pneumonia | 1 (0.2) |
| | Candida infection | 1 (0.2) |
| | Ear infection viral | 1 (0.2) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| | Encephalitis | 1 (0.2) |
| | Eye infection bacterial | 1 (0.2) |
| | Eyelid infection | 1 (0.2) |
| | Folliculitis | 1 (0.2) |
| | Gastritis viral | 1 (0.2) |
| | Gastroenteritis | 1 (0.2) |
| | Gastroenteritis viral | 1 (0.2) |
| | Gastrointestinal infection | 1 (0.2) |
| | Herpes zoster | 1 (0.2) |
| | Lower respiratory tract infection | 1 (0.2) |
| | Nasopharyngitis | 1 (0.2) |
| | Otitis media | 1 (0.2) |
| | Post procedural infection | 1 (0.2) |
| | Rhinitis | 1 (0.2) |
| | Sepsis | 1 (0.2) |
| | Tooth abscess | 1 (0.2) |
| | Tooth infection | 1 (0.2) |
| **Gastrointestinal disorders** | Constipation | 11 (2.6) |
| | Nausea | 8 (1.9) |
| | Vomiting | 6 (1.4) |
| | Gastroesophageal reflux disease | 4 (1.0) |
| | Diarrhea | 3 (0.7) |
| | Abdominal distension | 2 (0.5) |
| | Abdominal pain upper | 2 (0.5) |
| | Colitis | 2 (0.5) |
| | Dry mouth | 2 (0.5) |
| | Volvulus | 2 (0.5) |
| | Abdominal discomfort | 1 (0.2) |
| | Aptyalism | 1 (0.2) |
| | Dental caries | 1 (0.2) |
| | Dyspepsia | 1 (0.2) |
| | Dysphagia | 1 (0.2) |
| | Food poisoning | 1 (0.2) |
| | Hiatus hernia | 1 (0.2) |
| | Hyperchlorhydria | 1 (0.2) |
| | Periodontal disease | 1 (0.2) |
| **Injury, poisoning and procedural complications** | Fall | 21 (5.0) |
| | Contusion | 4 (1.0) |
| | Skin laceration | 3 (0.7) |
| | Concussion | 2 (0.5) |
| | Femur fracture | 2 (0.5) |
| | Joint dislocation | 2 (0.5) |
| | Overdose | 2 (0.5) |
| | Skin abrasion | 2 (0.5) |
| | Facial bones fracture | 1 (0.2) |
| | Foot fracture | 1 (0.2) |
| | Head injury | 1 (0.2) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| | Injury | 1 (0.2) |
| | Ligament rupture | 1 (0.2) |
| | Muscle strain | 1 (0.2) |
| | Post procedural hypotension | 1 (0.2) |
| | Procedural pain | 1 (0.2) |
| | Spinal column injury | 1 (0.2) |
| | Spinal cord injury cervical | 1 (0.2) |
| | Upper limb fracture | 1 (0.2) |
| **Musculoskeletal and connective tissue disorders** | Back pain | 15 (3.6) |
| | Musculoskeletal pain | 5 (1.2) |
| | Arthralgia | 4 (1.0) |
| | Muscle spasms | 4 (1.0) |
| | Neck pain | 3 (0.7) |
| | Pain in extremity | 3 (0.7) |
| | Tendonitis | 2 (0.5) |
| | Arthritis | 1 (0.2) |
| | Bursa disorder | 1 (0.2) |
| | Bursitis | 1 (0.2) |
| | Flank pain | 1 (0.2) |
| | Lumbar spinal stenosis | 1 (0.2) |
| | Muscular weakness | 1 (0.2) |
| | Myopathy | 1 (0.2) |
| | Osteoarthritis | 1 (0.2) |
| | Plantar fasciitis | 1 (0.2) |
| | Scoliosis | 1 (0.2) |
| **Investigations** | Weight decreased | 5 (1.2) |
| | Blood creatine phosphokinase increased | 3 (0.7) |
| | Cardiac murmur | 2 (0.5) |
| | Lymphocyte count decreased | 2 (0.5) |
| | Neutrophil count increased | 2 (0.5) |
| | Biopsy skin | 1 (0.2) |
| | Blood alkaline phosphatase increased | 1 (0.2) |
| | Blood bilirubin increased | 1 (0.2) |
| | Blood creatinine increased | 1 (0.2) |
| | Blood glucose increased | 1 (0.2) |
| | Blood potassium increased | 1 (0.2) |
| | Blood urea increased | 1 (0.2) |
| | Electrocardiogram QRS complex prolonged | 1 (0.2) |
| | Electrocardiogram abnormal | 1 (0.2) |
| | Electrocardiogram low voltage | 1 (0.2) |
| | Red blood cell count decreased | 1 (0.2) |
| | Respiratory rate decreased | 1 (0.2) |
| | Respiratory rate increased | 1 (0.2) |
| | Urine uric acid increased | 1 (0.2) |
| | White blood cell count increased | 1 (0.2) |
| **General disorders and administration site** | Edema peripheral | 5 (1.2) |
| | Pyrexia | 4 (1.0) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| **conditions** | Pain | 3 (0.7) |
| | Chest pain | 2 (0.5) |
| | Asthenia | 1 (0.2) |
| | Chest discomfort | 1 (0.2) |
| | Chills | 1 (0.2) |
| | Drowning | 1 (0.2) |
| | Drug ineffective | 1 (0.2) |
| | Fatigue | 1 (0.2) |
| | Malaise | 1 (0.2) |
| | Non-cardiac chest pain | 1 (0.2) |
| **Renal and urinary disorders** | Nephrolithiasis | 5 (1.2) |
| | Chronic kidney disease | 2 (0.5) |
| | Acute kidney injury | 1 (0.2) |
| | Bladder dysfunction | 1 (0.2) |
| | Dysuria | 1 (0.2) |
| | Hematuria | 1 (0.2) |
| | Hypertonic bladder | 1 (0.2) |
| | Incontinence | 1 (0.2) |
| | Ketonuria | 1 (0.2) |
| | Micturition urgency | 1 (0.2) |
| | Neurogenic bladder | 1 (0.2) |
| | Frequent daytime urination | 1 (0.2) |
| | Renal cyst | 1 (0.2) |
| | Ureterolithiasis | 1 (0.2) |
| | Urinary incontinence | 1 (0.2) |
| | Urinary retention | 1 (0.2) |
| | Urinary tract inflammation | 1 (0.2) |
| **Vascular disorders** | Hypertension | 6 (1.4) |
| | Orthostatic hypotension | 6 (1.4) |
| | Hypotension | 3 (0.7) |
| | Hematoma | 2 (0.5) |
| | Deep vein thrombosis | 1 (0.2) |
| | Hypertensive crisis | 1 (0.2) |
| | Peripheral venous disease | 1 (0.2) |
| **Respiratory, thoracic and mediastinal disorders** | Chronic obstructive pulmonary disease | 2 (0.5) |
| | Dysphonia | 2 (0.5) |
| | Dyspnea | 2 (0.5) |
| | Pulmonary embolism | 2 (0.5) |
| | Aspiration | 1 (0.2) |
| | Asthma | 1 (0.2) |
| | Bronchospasm | 1 (0.2) |
| | Cough | 1 (0.2) |
| | Hypoxia | 1 (0.2) |
| | Lower respiratory tract congestion | 1 (0.2) |
| | Pleural effusion | 1 (0.2) |
| | Rhinitis allergic | 1 (0.2) |
| | Rhinorrhea | 1 (0.2) |

| Body System or Organ Class | Dictionary-Derived Term | IPX203 N=419 n (%) |
|---|---|---|
| | Sleep apnea syndrome | 1 (0.2) |
| | Wheezing | 1 (0.2) |
| **Cardiac disorders** | Atrial fibrillation | 5 (1.2) |
| | Acute myocardial infarction | 1 (0.2) |
| | Aortic valve incompetence | 1 (0.2) |
| | Atrioventricular block first degree | 1 (0.2) |
| | Bundle branch block left | 1 (0.2) |
| | Cardiac failure | 1 (0.2) |
| | Cardiogenic shock | 1 (0.2) |
| | Cardiovascular disorder | 1 (0.2) |
| | Tachyarrhythmia | 1 (0.2) |
| | Tachycardia | 1 (0.2) |
| **Metabolism and nutrition disorders** | Dehydration | 2 (0.5) |
| | Hypokalemia | 2 (0.5) |
| | Decreased appetite | 1 (0.2) |
| | Fluid retention | 1 (0.2) |
| | Gout | 1 (0.2) |
| | Hyperglycemia | 1 (0.2) |
| | Hyperuricemia | 1 (0.2) |
| | Overweight | 1 (0.2) |
| | Vitamin D deficiency | 1 (0.2) |
| **Skin and subcutaneous tissue disorders** | Rash | 5 (1.2) |
| | Pruritus | 2 (0.5) |
| | Dermatitis | 1 (0.2) |
| | Erythema | 1 (0.2) |
| | Pain of skin | 1 (0.2) |
| **Blood and lymphatic system disorders** | Anemia | 5 (1.2) |
| | Lymphadenopathy | 1 (0.2) |
| | Microcytic anemia | 1 (0.2) |
| | Normochromic normocytic anemia | 1 (0.2) |
| **Eye disorders** | Cataract | 4 (1.0) |
| | Intraocular hematoma | 1 (0.2) |
| | Uveitis | 1 (0.2) |
| **Ear and labyrinth disorders** | Vertigo | 4 (1.0) |
| | Ear disorder | 1 (0.2) |
| **Surgical and medical procedures** | Abscess drainage | 1 (0.2) |
| | Knee arthroplasty | 1 (0.2) |
| | Tooth extraction | 1 (0.2) |
| **Neoplasms** | Bladder neoplasm | 1 (0.2) |
| | Lung neoplasm malignant | 1 (0.2) |
| **Reproductive system and breast disorders** | Prostatitis | 1 (0.2) |
| | Vaginal odor | 1 (0.2) |
| **Endocrine disorders** | Hyperthyroidism | 1 (0.2) |
| **Hepatobiliary disorders** | Hepatic cyst | 1 (0.2) |
| **Immune system disorders** | Hypersensitivity | 1 (0.2) |

Source: FDA analysis

**Table 40: Chemistry Descriptive Analysis, Study B16-02 (Controlled Safety Population)**

| | | Planned Arm | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IPX203 | | | | | IR CD/LD | | | | | Not Assigned | | | | |
| | | Analysis Value | | | | | Analysis Value | | | | | Analysis Value | | | | |
| Analysis Visit | Parameter | N | Mean | Min | Max | Median | N | Mean | Min | Max | Median | N | Mean | Min | Max | Median |
| STUDY ENTRY BASELINE | Alanine Aminotransferase | 256.00 | 14.85 | 5.00 | 66.00 | 12.50 | 250.00 | 15.60 | 5.00 | 49.00 | 13.00 | 124.00 | 13.25 | 5.00 | 40.00 | 12.00 |
| | Albumin | 256.00 | 44.40 | 35.00 | 52.00 | 44.00 | 250.00 | 44.49 | 35.00 | 51.00 | 45.00 | 124.00 | 44.41 | 37.00 | 51.00 | 44.50 |
| | Alkaline Phosphatase | 256.00 | 78.10 | 21.00 | 184.00 | 74.50 | 250.00 | 78.62 | 33.00 | 166.00 | 75.00 | 124.00 | 84.67 | 21.00 | 200.00 | 81.50 |
| | Aspartate Aminotransferase | 253.00 | 18.58 | 8.00 | 74.00 | 17.00 | 248.00 | 19.32 | 9.00 | 42.00 | 19.00 | 122.00 | 18.07 | 6.00 | 35.00 | 18.00 |
| | Bicarbonate | 256.00 | 23.62 | 17.00 | 34.00 | 23.50 | 250.00 | 23.70 | 16.00 | 33.00 | 24.00 | 124.00 | 23.57 | 15.00 | 35.00 | 23.00 |
| | Bilirubin | 256.00 | 8.13 | 3.00 | 28.00 | 7.00 | 250.00 | 8.56 | 3.00 | 29.00 | 7.00 | 124.00 | 8.15 | 3.00 | 27.00 | 7.00 |
| | Calcium | 256.00 | 2.36 | 2.12 | 2.70 | 2.36 | 250.00 | 2.36 | 2.18 | 2.65 | 2.36 | 124.00 | 2.35 | 2.10 | 2.63 | 2.35 |
| | Chloride | 256.00 | 101.17 | 89.00 | 107.00 | 101.00 | 250.00 | 101.06 | 93.00 | 108.00 | 101.00 | 124.00 | 101.18 | 92.00 | 110.00 | 101.00 |
| | Creatine Kinase | 256.00 | 117.56 | 23.00 | 550.00 | 94.00 | 250.00 | 127.88 | 29.00 | 931.00 | 100.50 | 124.00 | 114.94 | 25.00 | 328.00 | 94.50 |
| | Creatinine | 256.00 | 79.77 | 44.00 | 162.00 | 78.00 | 250.00 | 79.41 | 45.00 | 153.00 | 77.00 | 124.00 | 84.47 | 45.00 | 783.00 | 74.00 |
| | Direct Bilirubin | 249.00 | 2.88 | 0.00 | 10.00 | 3.00 | 246.00 | 3.00 | 1.00 | 11.00 | 3.00 | 121.00 | 2.69 | 1.00 | 10.00 | 2.00 |
| | Glucose | 256.00 | 5.81 | 2.90 | 14.40 | 5.50 | 250.00 | 5.84 | 3.00 | 16.40 | 5.50 | 124.00 | 5.77 | 3.70 | 16.50 | 5.50 |
| | Indirect Bilirubin | 249.00 | 5.24 | 0.00 | 19.00 | 4.00 | 246.00 | 5.61 | 1.00 | 20.00 | 5.00 | 121.00 | 5.49 | 1.00 | 22.00 | 5.00 |
| | Lactate Dehydrogenase | 238.00 | 173.57 | 95.00 | 343.00 | 168.00 | 234.00 | 171.90 | 107.00 | 265.00 | 168.50 | 114.00 | 177.39 | 99.00 | 309.00 | 172.50 |
| | Phosphate | 256.00 | 1.11 | 0.60 | 1.46 | 1.13 | 250.00 | 1.10 | 0.71 | 1.61 | 1.11 | 124.00 | 1.12 | 0.48 | 3.25 | 1.12 |
| | Potassium | 253.00 | 4.44 | 3.30 | 5.70 | 4.40 | 244.00 | 4.43 | 3.30 | 5.60 | 4.40 | 121.00 | 4.43 | 3.60 | 8.00 | 4.40 |
| | Protein | 256.00 | 67.84 | 55.00 | 80.00 | 68.00 | 250.00 | 68.62 | 55.00 | 81.00 | 68.50 | 124.00 | 67.42 | 57.00 | 83.00 | 68.00 |
| | Sodium | 256.00 | 140.08 | 130.00 | 148.00 | 140.00 | 250.00 | 140.02 | 130.00 | 147.00 | 140.00 | 124.00 | 140.11 | 130.00 | 145.00 | 140.00 |
| | Urate | 256.00 | 0.29 | 0.09 | 0.71 | 0.28 | 250.00 | 0.29 | 0.10 | 0.60 | 0.29 | 124.00 | 0.28 | 0.13 | 0.48 | 0.27 |
| | Urea Nitrogen | 256.00 | 6.52 | 2.60 | 17.20 | 6.25 | 250.00 | 6.29 | 3.00 | 14.90 | 6.00 | 124.00 | 6.64 | 3.10 | 19.30 | 6.35 |
| VISIT 5 | Alanine Aminotransferase | 226.00 | 10.05 | 5.00 | 65.00 | 8.00 | 224.00 | 12.41 | 5.00 | 57.00 | 10.00 | 0.00 | . | . | . | . |
| | Albumin | 227.00 | 43.50 | 32.00 | 50.00 | 44.00 | 227.00 | 43.49 | 35.00 | 50.00 | 44.00 | 0.00 | . | . | . | . |
| | Alkaline Phosphatase | 227.00 | 80.78 | 27.00 | 167.00 | 78.00 | 225.00 | 80.23 | 35.00 | 191.00 | 75.00 | 0.00 | . | . | . | . |
| | Aspartate Aminotransferase | 222.00 | 16.38 | 7.00 | 60.00 | 15.00 | 223.00 | 17.93 | 5.00 | 42.00 | 16.00 | 0.00 | . | . | . | . |
| | Bicarbonate | 226.00 | 23.81 | 16.00 | 33.00 | 24.00 | 224.00 | 23.99 | 16.00 | 31.00 | 24.00 | 0.00 | . | . | . | . |
| | Bilirubin | 226.00 | 7.66 | 3.00 | 29.00 | 7.00 | 224.00 | 7.94 | 3.00 | 32.00 | 7.00 | 0.00 | . | . | . | . |
| | Calcium | 227.00 | 2.35 | 2.12 | 2.64 | 2.34 | 225.00 | 2.33 | 2.14 | 2.59 | 2.34 | 0.00 | . | . | . | . |
| | Chloride | 227.00 | 101.00 | 91.00 | 107.00 | 101.00 | 225.00 | 101.16 | 94.00 | 108.00 | 101.00 | 0.00 | . | . | . | . |
| | Creatine Kinase | 225.00 | 112.77 | 26.00 | 868.00 | 93.00 | 224.00 | 121.76 | 18.00 | 497.00 | 96.00 | 0.00 | . | . | . | . |
| | Creatinine | 227.00 | 77.62 | 38.00 | 137.00 | 75.00 | 225.00 | 78.94 | 44.00 | 154.00 | 78.00 | 0.00 | . | . | . | . |
| | Direct Bilirubin | 221.00 | 2.84 | 0.00 | 12.00 | 3.00 | 219.00 | 2.74 | 1.00 | 10.00 | 2.00 | 0.00 | . | . | . | . |

| | | Planned Arm | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IPX203 | | | | | IR CD/LD | | | | | Not Assigned | | | | |
| | | Analysis Value | | | | | Analysis Value | | | | | Analysis Value | | | | |
| Analysis Visit | Parameter | N | Mean | Min | Max | Median | N | Mean | Min | Max | Median | N | Mean | Min | Max | Median |
| | Glucose | 226.00 | 5.85 | 3.70 | 24.80 | 5.50 | 222.00 | 5.75 | 2.70 | 15.70 | 5.40 | 0.00 | . | . | . | . |
| | Indirect Bilirubin | 221.00 | 4.84 | 1.00 | 21.00 | 4.00 | 219.00 | 5.15 | 1.00 | 25.00 | 4.00 | 0.00 | . | . | . | . |
| | Lactate Dehydrogenase | 211.00 | 171.00 | 80.00 | 328.00 | 165.00 | 206.00 | 167.80 | 87.00 | 281.00 | 168.00 | 0.00 | . | . | . | . |
| | Phosphate | 226.00 | 1.10 | 0.67 | 1.45 | 1.09 | 224.00 | 1.11 | 0.60 | 1.73 | 1.11 | 0.00 | . | . | . | . |
| | Potassium | 223.00 | 4.44 | 3.50 | 6.20 | 4.40 | 223.00 | 4.38 | 3.20 | 5.50 | 4.30 | 0.00 | . | . | . | . |
| | Protein | 227.00 | 66.75 | 49.00 | 83.00 | 67.00 | 225.00 | 67.46 | 57.00 | 79.00 | 67.00 | 0.00 | . | . | . | . |
| | Sodium | 227.00 | 139.40 | 131.00 | 149.00 | 139.00 | 227.00 | 139.66 | 132.00 | 146.00 | 140.00 | 0.00 | . | . | . | . |
| | Urate | 226.00 | 0.27 | 0.09 | 0.55 | 0.26 | 224.00 | 0.29 | 0.12 | 0.49 | 0.28 | 0.00 | . | . | . | . |
| | Urea Nitrogen | 227.00 | 6.54 | 2.80 | 12.60 | 6.50 | 225.00 | 6.40 | 2.60 | 15.50 | 6.10 | 0.00 | . | . | . | . |
| VISIT 7/ET | Alanine Aminotransferase | 247.00 | 9.69 | 5.00 | 39.00 | 8.00 | 242.00 | 13.17 | 5.00 | 112.00 | 10.00 | 85.00 | 12.14 | 5.00 | 40.00 | 10.00 |
| | Albumin | 248.00 | 43.75 | 35.00 | 52.00 | 44.00 | 244.00 | 43.86 | 36.00 | 51.00 | 44.00 | 87.00 | 43.64 | 35.00 | 52.00 | 44.00 |
| | Alkaline Phosphatase | 248.00 | 81.85 | 26.00 | 173.00 | 79.00 | 244.00 | 81.14 | 40.00 | 170.00 | 77.50 | 86.00 | 89.78 | 37.00 | 314.00 | 84.50 |
| | Aspartate Aminotransferase | 245.00 | 15.80 | 5.00 | 46.00 | 15.00 | 241.00 | 18.00 | 6.00 | 43.00 | 17.00 | 85.00 | 17.47 | 6.00 | 56.00 | 16.00 |
| | Bicarbonate | 248.00 | 24.02 | 16.00 | 36.00 | 24.00 | 244.00 | 23.70 | 17.00 | 31.00 | 23.50 | 87.00 | 23.71 | 15.00 | 33.00 | 24.00 |
| | Bilirubin | 247.00 | 8.20 | 3.00 | 28.00 | 7.00 | 244.00 | 8.38 | 3.00 | 34.00 | 8.00 | 87.00 | 7.70 | 3.00 | 34.00 | 6.00 |
| | Calcium | 247.00 | 2.34 | 2.09 | 2.58 | 2.33 | 244.00 | 2.34 | 2.05 | 2.65 | 2.33 | 87.00 | 2.36 | 2.11 | 2.91 | 2.36 |
| | Chloride | 247.00 | 101.26 | 90.00 | 108.00 | 101.00 | 244.00 | 101.28 | 93.00 | 107.00 | 101.00 | 87.00 | 100.82 | 92.00 | 108.00 | 101.00 |
| | Creatine Kinase | 248.00 | 112.78 | 24.00 | 530.00 | 98.50 | 243.00 | 122.04 | 18.00 | 741.00 | 98.00 | 85.00 | 131.33 | 26.00 | 1788.00 | 87.00 |
| | Creatinine | 248.00 | 77.65 | 37.00 | 173.00 | 75.00 | 244.00 | 78.87 | 41.00 | 146.00 | 77.00 | 87.00 | 77.93 | 47.00 | 164.00 | 73.00 |
| | Direct Bilirubin | 243.00 | 2.93 | 1.00 | 11.00 | 3.00 | 237.00 | 2.84 | 1.00 | 11.00 | 2.00 | 83.00 | 2.54 | 1.00 | 8.00 | 2.00 |
| | Glucose | 245.00 | 5.74 | 3.00 | 14.60 | 5.40 | 244.00 | 5.98 | 3.10 | 17.80 | 5.50 | 87.00 | 5.67 | 4.10 | 14.30 | 5.30 |
| | Indirect Bilirubin | 243.00 | 5.22 | 1.00 | 21.00 | 4.00 | 237.00 | 5.51 | 1.00 | 23.00 | 5.00 | 83.00 | 5.24 | 1.00 | 29.00 | 4.00 |
| | Lactate Dehydrogenase | 226.00 | 173.41 | 97.00 | 313.00 | 168.50 | 220.00 | 172.51 | 86.00 | 326.00 | 169.00 | 78.00 | 176.65 | 123.00 | 512.00 | 171.50 |
| | Phosphate | 247.00 | 1.11 | 0.70 | 1.58 | 1.11 | 244.00 | 1.10 | 0.73 | 1.60 | 1.10 | 86.00 | 1.13 | 0.72 | 1.49 | 1.12 |
| | Potassium | 243.00 | 4.42 | 3.20 | 6.00 | 4.40 | 237.00 | 4.43 | 3.40 | 5.90 | 4.40 | 82.00 | 4.40 | 3.20 | 5.30 | 4.40 |
| | Protein | 247.00 | 66.67 | 55.00 | 84.00 | 67.00 | 244.00 | 67.42 | 56.00 | 80.00 | 67.00 | 87.00 | 67.36 | 59.00 | 77.00 | 67.00 |
| | Sodium | 247.00 | 139.43 | 132.00 | 146.00 | 140.00 | 244.00 | 139.55 | 129.00 | 146.00 | 140.00 | 87.00 | 139.48 | 131.00 | 147.00 | 139.00 |
| | Urate | 247.00 | 0.27 | 0.11 | 0.57 | 0.27 | 244.00 | 0.29 | 0.12 | 0.51 | 0.29 | 87.00 | 0.27 | 0.11 | 0.62 | 0.27 |
| | Urea Nitrogen | 247.00 | 6.67 | 2.30 | 18.20 | 6.50 | 244.00 | 6.46 | 3.20 | 16.60 | 6.10 | 87.00 | 6.32 | 2.30 | 18.70 | 6.10 |

Source: FDA Analysis

**Table 41: Chemistry Laboratory Shift Table, Study B16-02 (Controlled Safety Population)**

| | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| Alanine Aminotransferase | IPX203 | Normal | 0 | 251 | 3 | 254 |
| | IR CD/LD | Normal | 0 | 243 | 1 | 244 |
| | | High | 0 | 5 | 0 | 5 |
| Albumin | IPX203 | Normal | 0 | 255 | 0 | 255 |
| | IR CD/LD | Normal | 0 | 249 | 0 | 249 |
| Alkaline Phosphatase | IPX203 | Low | 1 | 0 | 0 | 1 |
| | | Normal | 0 | 223 | 7 | 230 |
| | | High | 0 | 8 | 16 | 24 |
| | IR CD/LD | Normal | 4 | 220 | 4 | 228 |
| | | High | 0 | 9 | 12 | 21 |
| Aspartate Aminotransferase | IPX203 | Normal | 0 | 247 | 2 | 249 |
| | | High | 0 | 1 | 1 | 2 |
| | IR CD/LD | Normal | 0 | 243 | 1 | 244 |
| | | High | 0 | 0 | 1 | 1 |
| Bicarbonate | IPX203 | Low | 21 | 27 | 0 | 48 |
| | | Normal | 36 | 165 | 3 | 204 |
| | | High | 0 | 2 | 1 | 3 |
| | IR CD/LD | Low | 21 | 26 | 0 | 47 |
| | | Normal | 28 | 173 | 1 | 202 |
| Bilirubin | IPX203 | Normal | 0 | 245 | 5 | 250 |
| | | High | 0 | 3 | 1 | 4 |
| | IR CD/LD | Normal | 0 | 242 | 4 | 246 |
| | | High | 0 | 1 | 2 | 3 |
| Calcium | IPX203 | Low | 0 | 2 | 0 | 2 |
| | | Normal | 2 | 249 | 1 | 252 |
| | IR CD/LD | Low | 0 | 2 | 0 | 2 |
| | | Normal | 0 | 243 | 1 | 244 |
| | | High | 0 | 3 | 0 | 3 |
| Chloride | IPX203 | Low | 6 | 11 | 0 | 17 |
| | | Normal | 10 | 227 | 0 | 237 |
| | IR CD/LD | Low | 3 | 7 | 0 | 10 |
| | | Normal | 13 | 226 | 0 | 239 |
| Creatine Kinase | IPX203 | Normal | 0 | 215 | 15 | 230 |
| | | High | 0 | 16 | 9 | 25 |
| | IR CD/LD | Low | 0 | 1 | 0 | 1 |
| | | Normal | 0 | 200 | 16 | 216 |
| | | High | 0 | 17 | 15 | 32 |
| Creatinine | IPX203 | Low | 3 | 8 | 0 | 11 |
| | | Normal | 0 | 207 | 9 | 216 |
| | | High | 0 | 9 | 19 | 28 |
| | IR CD/LD | Low | 2 | 10 | 0 | 12 |
| | | Normal | 3 | 200 | 9 | 212 |
| | | High | 0 | 10 | 15 | 25 |
| Direct Bilirubin | IPX203 | Normal | 0 | 241 | 3 | 244 |
| | | High | 0 | 2 | 1 | 3 |

| | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| | IR CD/LD | Normal | 0 | 233 | 1 | 234 |
| | | High | 0 | 1 | 5 | 6 |
| Glucose | IPX203 | Low | 0 | 2 | 0 | 2 |
| | | Normal | 1 | 221 | 10 | 232 |
| | | High | 0 | 13 | 7 | 20 |
| | IR CD/LD | Low | 0 | 2 | 0 | 2 |
| | | Normal | 3 | 214 | 5 | 222 |
| | | High | 0 | 13 | 12 | 25 |
| Indirect Bilirubin | IPX203 | Normal | 0 | 229 | 4 | 233 |
| | | High | 0 | 9 | 5 | 14 |
| | IR CD/LD | Normal | 0 | 223 | 6 | 229 |
| | | High | 0 | 6 | 5 | 11 |
| Lactate Dehydrogenase | IPX203 | Low | 1 | 0 | 0 | 1 |
| | | Normal | 1 | 213 | 6 | 220 |
| | | High | 0 | 9 | 4 | 13 |
| | IR CD/LD | Low | 0 | 1 | 0 | 1 |
| | | Normal | 0 | 206 | 7 | 213 |
| | | High | 0 | 5 | 5 | 10 |
| Phosphate | IPX203 | Low | 5 | 1 | 0 | 6 |
| | | Normal | 4 | 244 | 0 | 248 |
| | IR CD/LD | Low | 3 | 3 | 0 | 6 |
| | | Normal | 1 | 242 | 0 | 243 |
| Potassium | IPX203 | Low | 0 | 1 | 0 | 1 |
| | | Normal | 2 | 241 | 4 | 247 |
| | | High | 0 | 3 | 1 | 4 |
| | IR CD/LD | Low | 1 | 0 | 0 | 1 |
| | | Normal | 0 | 234 | 3 | 237 |
| | | High | 0 | 4 | 0 | 4 |
| Protein | IPX203 | Low | 5 | 12 | 0 | 17 |
| | | Normal | 4 | 233 | 0 | 237 |
| | IR CD/LD | Low | 1 | 9 | 0 | 10 |
| | | Normal | 1 | 238 | 0 | 239 |
| Sodium | IPX203 | Low | 4 | 3 | 0 | 7 |
| | | Normal | 3 | 244 | 0 | 247 |
| | IR CD/LD | Low | 2 | 2 | 0 | 4 |
| | | Normal | 2 | 243 | 0 | 245 |
| Urate | IPX203 | Low | 10 | 15 | 0 | 25 |
| | | Normal | 5 | 221 | 2 | 228 |
| | | High | 0 | 0 | 1 | 1 |
| | IR CD/LD | Low | 7 | 6 | 0 | 13 |
| | | Normal | 4 | 230 | 2 | 236 |
| Urea Nitrogen | IPX203 | Normal | 0 | 218 | 10 | 228 |
| | | High | 0 | 13 | 13 | 26 |
| | IR CD/LD | Normal | 0 | 222 | 8 | 230 |
| | | High | 0 | 9 | 10 | 19 |
| All | All | All | 223 | 9435 | 314 | 9972 |

**Table 42: Hematology Values Descriptive Analysis, Study B16-02 (Controlled Safety Population)**

| | | Description of Planned Arm | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IR CD/LD | | | | | IPX203 | | | | | Not Assigned | | | | |
| | | Analysis Value | | | | | Analysis Value | | | | | Analysis Value | | | | |
| **Analysis Visit** | **Parameter** | **N** | **Mean** | **Min** | **Max** | **Median** | **N** | **Mean** | **Min** | **Max** | **Median** | **N** | **Mean** | **Min** | **Max** | **Median** |
| Study Entry Baseline | Hematocrit | 250.00 | 0.46 | 0.36 | 0.56 | 0.45 | 255.00 | 0.45 | 0.33 | 0.59 | 0.45 | 124.00 | 0.44 | 0.34 | 0.53 | 0.44 |
| | Hemoglobin | 250.00 | 143.15 | 106.00 | 177.00 | 143.00 | 256.00 | 140.88 | 90.00 | 179.00 | 142.00 | 124.00 | 139.02 | 108.00 | 169.00 | 138.00 |
| | Platelets | 250.00 | 226.63 | 84.00 | 369.00 | 223.00 | 254.00 | 231.14 | 42.00 | 494.00 | 227.50 | 124.00 | 243.25 | 133.00 | 438.00 | 242.50 |
| | Neutrophils | 249.00 | 4.48 | 1.20 | 18.70 | 4.30 | 255.00 | 4.50 | 0.90 | 14.90 | 4.20 | 123.00 | 4.53 | 2.00 | 8.40 | 4.30 |
| | Basophils | 249.00 | 0.05 | 0.00 | 0.30 | 0.00 | 255.00 | 0.05 | 0.00 | 0.30 | 0.00 | 123.00 | 0.05 | 0.00 | 0.20 | 0.00 |
| | Basophils/ Leukocytes | 249.00 | 0.88 | 0.00 | 6.00 | 1.00 | 255.00 | 0.83 | 0.00 | 3.00 | 1.00 | 123.00 | 0.80 | 0.00 | 3.00 | 1.00 |
| | Eosinophils | 249.00 | 0.15 | 0.00 | 1.50 | 0.10 | 255.00 | 0.12 | 0.00 | 0.60 | 0.10 | 123.00 | 0.13 | 0.00 | 0.50 | 0.10 |
| | Eosinophils/ Leukocytes | 249.00 | 2.29 | 0.00 | 18.00 | 2.00 | 255.00 | 1.79 | 0.00 | 7.00 | 2.00 | 123.00 | 1.89 | 0.00 | 7.00 | 2.00 |
| | Erythrocytes | 250.00 | 4.68 | 3.60 | 5.80 | 4.70 | 255.00 | 4.65 | 3.20 | 5.90 | 4.70 | 124.00 | 4.57 | 3.50 | 5.70 | 4.55 |
| | Leukocytes | 250.00 | 6.77 | 2.90 | 19.60 | 6.60 | 255.00 | 6.83 | 2.10 | 18.20 | 6.50 | 124.00 | 6.75 | 3.60 | 11.30 | 6.70 |
| | Lymphocytes | 249.00 | 1.69 | 0.40 | 4.10 | 1.60 | 255.00 | 1.76 | 0.60 | 4.80 | 1.60 | 123.00 | 1.65 | 0.70 | 3.30 | 1.60 |
| | Lymphocytes/ Leukocytes | 249.00 | 25.65 | 2.00 | 53.00 | 25.00 | 255.00 | 26.35 | 9.00 | 54.00 | 25.00 | 123.00 | 24.95 | 10.00 | 50.00 | 24.00 |
| | Monocytes | 249.00 | 0.43 | 0.10 | 1.30 | 0.40 | 255.00 | 0.42 | 0.20 | 1.70 | 0.40 | 123.00 | 0.40 | 0.10 | 0.90 | 0.40 |
| | Monocytes/ Leukocytes | 249.00 | 6.41 | 2.00 | 19.00 | 6.00 | 255.00 | 6.20 | 2.00 | 20.00 | 6.00 | 123.00 | 6.06 | 2.00 | 12.00 | 6.00 |
| | Neutrophils/ Leukocytes | 249.00 | 65.18 | 35.00 | 95.00 | 66.00 | 255.00 | 65.21 | 40.00 | 86.00 | 66.00 | 123.00 | 66.67 | 40.00 | 83.00 | 69.00 |
| VISIT 5 | Hematocrit | 218.00 | 0.45 | 0.34 | 0.54 | 0.45 | 228.00 | 0.44 | 0.33 | 0.54 | 0.44 | 0.00 | . | . | . | . |
| | Hemoglobin | 223.00 | 141.74 | 108.00 | 174.00 | 142.00 | 228.00 | 139.00 | 97.00 | 177.00 | 140.00 | 0.00 | . | . | . | . |
| | Platelets | 215.00 | 226.65 | 99.00 | 370.00 | 223.00 | 228.00 | 232.59 | 46.00 | 612.00 | 220.00 | 0.00 | . | . | . | . |
| | Neutrophils | 212.00 | 4.42 | 1.90 | 15.00 | 4.20 | 228.00 | 4.36 | 0.70 | 12.00 | 4.20 | 0.00 | . | . | . | . |
| | Basophils | 212.00 | 0.04 | 0.00 | 0.20 | 0.00 | 228.00 | 0.05 | 0.00 | 0.30 | 0.00 | 0.00 | . | . | . | . |
| | Basophils/ Leukocytes | 212.00 | 0.89 | 0.00 | 3.00 | 1.00 | 228.00 | 0.83 | 0.00 | 4.00 | 1.00 | 0.00 | . | . | . | . |
| | Eosinophils | 212.00 | 0.15 | 0.00 | 0.80 | 0.10 | 228.00 | 0.13 | 0.00 | 0.50 | 0.10 | 0.00 | . | . | . | . |
| | Eosinophils/ | 212.00 | 2.30 | 0.00 | 12.00 | 2.00 | 228.00 | 1.94 | 0.00 | 7.00 | 2.00 | 0.00 | . | . | . | . |

| | | Description of Planned Arm | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | IR CD/LD | | | | | IPX203 | | | | | Not Assigned | | | | |
| | | Analysis Value | | | | | Analysis Value | | | | | Analysis Value | | | | |
| Analysis Visit | Parameter | N | Mean | Min | Max | Median | N | Mean | Min | Max | Median | N | Mean | Min | Max | Median |
| | Leukocytes | | | | | | | | | | | | | | | |
| | Erythrocytes | 218.00 | 4.63 | 3.30 | 5.80 | 4.60 | 228.00 | 4.60 | 3.50 | 5.70 | 4.60 | 0.00 | . | . | . | . |
| | Leukocytes | 215.00 | 6.74 | 3.30 | 19.50 | 6.50 | 228.00 | 6.66 | 1.80 | 16.00 | 6.60 | 0.00 | . | . | . | . |
| | Lymphocytes | 212.00 | 1.72 | 0.50 | 5.10 | 1.60 | 228.00 | 1.71 | 0.50 | 4.40 | 1.60 | 0.00 | . | . | . | . |
| | Lymphocytes/ Leukocytes | 212.00 | 25.82 | 7.00 | 51.00 | 25.00 | 228.00 | 26.31 | 8.00 | 52.00 | 26.00 | 0.00 | . | . | . | . |
| | Monocytes | 212.00 | 0.43 | 0.10 | 1.20 | 0.40 | 228.00 | 0.42 | 0.10 | 1.70 | 0.40 | 0.00 | . | . | . | . |
| | Monocytes/ Leukocytes | 212.00 | 6.37 | 3.00 | 19.00 | 6.00 | 228.00 | 6.36 | 3.00 | 20.00 | 6.00 | 0.00 | . | . | . | . |
| | Neutrophils/ Leukocytes | 212.00 | 64.91 | 33.00 | 87.00 | 65.50 | 228.00 | 64.82 | 40.00 | 88.00 | 65.00 | 0.00 | . | . | . | . |
| VISIT 7/ET | Hematocrit | 244.00 | 0.45 | 0.34 | 0.60 | 0.45 | 247.00 | 0.44 | 0.32 | 0.57 | 0.44 | 88.00 | 0.43 | 0.35 | 0.53 | 0.43 |
| | Hemoglobin | 246.00 | 141.61 | 101.00 | 184.00 | 142.00 | 248.00 | 138.49 | 85.00 | 177.00 | 138.00 | 88.00 | 136.15 | 106.00 | 166.00 | 134.50 |
| | Platelets | 241.00 | 221.08 | 38.00 | 374.00 | 215.00 | 246.00 | 227.93 | 32.00 | 459.00 | 222.50 | 88.00 | 251.80 | 137.00 | 453.00 | 241.00 |
| | Neutrophils | 238.00 | 4.30 | 1.40 | 9.80 | 4.10 | 244.00 | 4.45 | 0.70 | 11.10 | 4.30 | 88.00 | 4.50 | 1.90 | 8.10 | 4.30 |
| | Basophils | 238.00 | 0.04 | 0.00 | 0.30 | 0.00 | 244.00 | 0.04 | 0.00 | 0.30 | 0.00 | 88.00 | 0.04 | 0.00 | 0.10 | 0.00 |
| | Basophils/ Leukocytes | 238.00 | 0.84 | 0.00 | 3.00 | 1.00 | 244.00 | 0.78 | 0.00 | 3.00 | 1.00 | 88.00 | 0.76 | 0.00 | 2.00 | 1.00 |
| | Eosinophils | 238.00 | 0.16 | 0.00 | 0.60 | 0.10 | 244.00 | 0.13 | 0.00 | 0.70 | 0.10 | 88.00 | 0.13 | 0.00 | 0.60 | 0.10 |
| | Eosinophils/ Leukocytes | 238.00 | 2.37 | 0.00 | 11.00 | 2.00 | 244.00 | 1.91 | 0.00 | 11.00 | 2.00 | 88.00 | 1.88 | 0.00 | 8.00 | 2.00 |
| | Erythrocytes | 244.00 | 4.62 | 3.40 | 5.80 | 4.70 | 247.00 | 4.60 | 3.50 | 6.00 | 4.60 | 88.00 | 4.51 | 3.60 | 5.80 | 4.50 |
| | Leukocytes | 239.00 | 6.63 | 3.40 | 11.70 | 6.40 | 245.00 | 6.72 | 1.60 | 14.20 | 6.40 | 88.00 | 6.64 | 3.50 | 11.00 | 6.55 |
| | Lymphocytes | 238.00 | 1.70 | 0.30 | 4.70 | 1.60 | 244.00 | 1.69 | 0.60 | 5.10 | 1.60 | 88.00 | 1.60 | 0.80 | 3.00 | 1.50 |
| | Lymphocytes/ Leukocytes | 238.00 | 26.31 | 3.00 | 53.00 | 25.00 | 244.00 | 25.74 | 8.00 | 52.00 | 25.00 | 88.00 | 24.60 | 11.00 | 46.00 | 23.00 |
| | Monocytes | 238.00 | 0.43 | 0.20 | 1.40 | 0.40 | 244.00 | 0.42 | 0.10 | 1.20 | 0.40 | 88.00 | 0.40 | 0.10 | 1.20 | 0.40 |
| | Monocytes/ Leukocytes | 238.00 | 6.63 | 2.00 | 17.00 | 6.00 | 244.00 | 6.27 | 1.00 | 16.00 | 6.00 | 88.00 | 6.03 | 2.00 | 13.00 | 6.00 |
| | Neutrophils/ Leukocytes | 238.00 | 64.13 | 29.00 | 92.00 | 65.00 | 244.00 | 65.55 | 42.00 | 85.00 | 66.00 | 88.00 | 67.08 | 44.00 | 84.00 | 68.00 |

**Table 43: Hematology Parameter Shifts, Study B16-02 (Controlled Safety Population)**

| | | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| Study Entry Baseline | Basophils | IPX203 | Normal | 0 | 254 | 0 | 254 |
| | | | High | 0 | 0 | 1 | 1 |
| | | | All | 0 | 254 | 1 | 255 |
| | | IR CD/LD | Normal | 0 | 247 | 0 | 247 |
| | | | High | 0 | 0 | 2 | 2 |
| | | | All | 0 | 247 | 2 | 249 |
| | Basophils/ Leukocytes | IPX203 | Normal | 0 | 252 | 0 | 252 |
| | | | High | 0 | 0 | 3 | 3 |
| | | | All | 0 | 252 | 3 | 255 |
| | | IR CD/LD | Normal | 0 | 245 | 0 | 245 |
| | | | High | 0 | 0 | 4 | 4 |
| | | | All | 0 | 245 | 4 | 249 |
| | Eosinophils | IPX203 | Normal | 0 | 255 | 0 | 255 |
| | | | All | 0 | 255 | 0 | 255 |
| | | IR CD/LD | Normal | 0 | 247 | 0 | 247 |
| | | | High | 0 | 0 | 2 | 2 |
| | | | All | 0 | 247 | 2 | 249 |
| | Eosinophils/ Leukocytes | IPX203 | Normal | 0 | 255 | 0 | 255 |
| | | | All | 0 | 255 | 0 | 255 |
| | | IR CD/LD | Normal | 0 | 243 | 0 | 243 |
| | | | High | 0 | 0 | 6 | 6 |
| | | | All | 0 | 243 | 6 | 249 |
| | Erythrocytes | IPX203 | Low | 55 | 0 | 0 | 55 |
| | | | Normal | 0 | 198 | 0 | 198 |
| | | | High | 0 | 0 | 2 | 2 |
| | | | All | 55 | 198 | 2 | 255 |
| | | IR CD/LD | Low | 55 | 0 | 0 | 55 |
| | | | Normal | 0 | 192 | 0 | 192 |
| | | | High | 0 | 0 | 3 | 3 |
| | | | All | 55 | 192 | 3 | 250 |
| | Hematocrit | IPX203 | Low | 7 | 0 | 0 | 7 |
| | | | Normal | 0 | 228 | 0 | 228 |
| | | | High | 0 | 0 | 20 | 20 |
| | | | All | 7 | 228 | 20 | 255 |
| | | IR CD/LD | Low | 9 | 0 | 0 | 9 |
| | | | Normal | 0 | 216 | 0 | 216 |
| | | | High | 0 | 0 | 25 | 25 |
| | | | All | 9 | 216 | 25 | 250 |
| | Hemoglobin | IPX203 | Low | 40 | 0 | 0 | 40 |
| | | | Normal | 0 | 213 | 0 | 213 |
| | | | High | 0 | 0 | 3 | 3 |
| | | | All | 40 | 213 | 3 | 256 |

| | | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| | | IR CD/LD | Low | 33 | 0 | 0 | 33 |
| | | | Normal | 0 | 216 | 0 | 216 |
| | | | High | 0 | 0 | 1 | 1 |
| | | | All | 33 | 216 | 1 | 250 |
| | Leukocytes | IPX203 | Low | 6 | 0 | 0 | 6 |
| | | | Normal | 0 | 242 | 0 | 242 |
| | | | High | 0 | 0 | 7 | 7 |
| | | | All | 6 | 242 | 7 | 255 |
| | | IR CD/LD | Low | 8 | 0 | 0 | 8 |
| | | | Normal | 0 | 238 | 0 | 238 |
| | | | High | 0 | 0 | 4 | 4 |
| | | | All | 8 | 238 | 4 | 250 |
| | Lymphocytes | IPX203 | Low | 8 | 0 | 0 | 8 |
| | | | Normal | 0 | 244 | 0 | 244 |
| | | | High | 0 | 0 | 3 | 3 |
| | | | All | 8 | 244 | 3 | 255 |
| | | IR CD/LD | Low | 19 | 0 | 0 | 19 |
| | | | Normal | 0 | 229 | 0 | 229 |
| | | | High | 0 | 0 | 1 | 1 |
| | | | All | 19 | 229 | 1 | 249 |
| | Lymphocytes/ Leukocytes | IPX203 | Low | 46 | 0 | 0 | 46 |
| | | | Normal | 0 | 204 | 0 | 204 |
| | | | High | 0 | 0 | 5 | 5 |
| | | | All | 46 | 204 | 5 | 255 |
| | | IR CD/LD | Low | 55 | 0 | 0 | 55 |
| | | | Normal | 0 | 187 | 0 | 187 |
| | | | High | 0 | 0 | 7 | 7 |
| | | | All | 55 | 187 | 7 | 249 |
| | Monocytes | IPX203 | Normal | 0 | 253 | 0 | 253 |
| | | | High | 0 | 0 | 2 | 2 |
| | | | All | 0 | 253 | 2 | 255 |
| | | IR CD/LD | Normal | 0 | 246 | 0 | 246 |
| | | | High | 0 | 0 | 3 | 3 |
| | | | All | 0 | 246 | 3 | 249 |
| | Monocytes/ Leukocytes | IPX203 | Low | 3 | 0 | 0 | 3 |
| | | | Normal | 0 | 246 | 0 | 246 |
| | | | High | 0 | 0 | 6 | 6 |
| | | | All | 3 | 246 | 6 | 255 |
| | | IR CD/LD | Low | 1 | 0 | 0 | 1 |
| | | | Normal | 0 | 236 | 0 | 236 |
| | | | High | 0 | 0 | 12 | 12 |
| | | | All | 1 | 236 | 12 | 249 |
| | Neutrophils | IPX203 | Low | 1 | 0 | 0 | 1 |
| | | | Normal | 0 | 245 | 0 | 245 |

| | | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| | | | High | 0 | 0 | 9 | 9 |
| | | | All | 1 | 245 | 9 | 255 |
| | | IR CD/LD | Low | 3 | 0 | 0 | 3 |
| | | | Normal | 0 | 237 | 0 | 237 |
| | | | High | 0 | 0 | 9 | 9 |
| | | | All | 3 | 237 | 9 | 249 |
| | Neutrophils/ Leukocytes | IPX203 | Low | 2 | 0 | 0 | 2 |
| | | | Normal | 0 | 230 | 0 | 230 |
| | | | High | 0 | 0 | 23 | 23 |
| | | | All | 2 | 230 | 23 | 255 |
| | | IR CD/LD | Low | 7 | 0 | 0 | 7 |
| | | | Normal | 0 | 211 | 0 | 211 |
| | | | High | 0 | 0 | 31 | 31 |
| | | | All | 7 | 211 | 31 | 249 |
| | Platelets | IPX203 | Low | 17 | 0 | 0 | 17 |
| | | | Normal | 0 | 225 | 0 | 225 |
| | | | High | 0 | 0 | 12 | 12 |
| | | | All | 17 | 225 | 12 | 254 |
| | | IR CD/LD | Low | 13 | 0 | 0 | 13 |
| | | | Normal | 0 | 235 | 0 | 235 |
| | | | High | 0 | 0 | 2 | 2 |
| | | | All | 13 | 235 | 2 | 250 |
| | All | All | All | 388 | 6969 | 208 | 7565 |
| VISIT 7/ET | Basophils | IPX203 | Normal | 0 | 253 | 1 | 254 |
| | | | High | 0 | 1 | 0 | 1 |
| | | | All | 0 | 254 | 1 | 255 |
| | | IR CD/LD | Normal | 0 | 243 | 2 | 245 |
| | | | High | 0 | 1 | 0 | 1 |
| | | | All | 0 | 244 | 2 | 246 |
| | Basophils/ Leukocytes | IPX203 | Normal | 0 | 249 | 3 | 252 |
| | | | High | 0 | 3 | 0 | 3 |
| | | | All | 0 | 252 | 3 | 255 |
| | | IR CD/LD | Normal | 0 | 239 | 4 | 243 |
| | | | High | 0 | 3 | 0 | 3 |
| | | | All | 0 | 242 | 4 | 246 |
| | Eosinophils | IPX203 | Normal | 0 | 255 | 0 | 255 |
| | | | All | 0 | 255 | 0 | 255 |
| | | IR CD/LD | Normal | 0 | 244 | 2 | 246 |
| | | | All | 0 | 244 | 2 | 246 |
| | Eosinophils/ Leukocytes | IPX203 | Normal | 0 | 253 | 0 | 253 |
| | | | High | 0 | 2 | 0 | 2 |
| | | | All | 0 | 255 | 0 | 255 |
| | | IR CD/LD | Normal | 0 | 240 | 3 | 243 |
| | | | High | 0 | 0 | 3 | 3 |

| | | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| | | | All | 0 | 240 | 6 | 246 |
| | Erythrocytes | IPX203 | Low | 43 | 30 | 0 | 73 |
| | | | Normal | 12 | 166 | 1 | 179 |
| | | | High | 0 | 2 | 1 | 3 |
| | | | All | 55 | 198 | 2 | 255 |
| | | IR CD/LD | Low | 43 | 24 | 0 | 67 |
| | | | Normal | 12 | 166 | 2 | 180 |
| | | | High | 0 | 0 | 1 | 1 |
| | | | All | 55 | 190 | 3 | 248 |
| | Hematocrit | IPX203 | Low | 3 | 9 | 0 | 12 |
| | | | Normal | 4 | 213 | 13 | 230 |
| | | | High | 0 | 6 | 7 | 13 |
| | | | All | 7 | 228 | 20 | 255 |
| | | IR CD/LD | Low | 5 | 8 | 0 | 13 |
| | | | Normal | 4 | 194 | 15 | 213 |
| | | | High | 0 | 12 | 10 | 22 |
| | | | All | 9 | 214 | 25 | 248 |
| | Hemoglobin | IPX203 | Low | 26 | 20 | 0 | 46 |
| | | | Normal | 14 | 193 | 2 | 209 |
| | | | High | 0 | 0 | 1 | 1 |
| | | | All | 40 | 213 | 3 | 256 |
| | | IR CD/LD | Low | 22 | 17 | 0 | 39 |
| | | | Normal | 11 | 196 | 0 | 207 |
| | | | High | 0 | 1 | 1 | 2 |
| | | | All | 33 | 214 | 1 | 248 |
| | Leukocytes | IPX203 | Low | 2 | 6 | 0 | 8 |
| | | | Normal | 4 | 231 | 4 | 239 |
| | | | High | 0 | 5 | 3 | 8 |
| | | | All | 6 | 242 | 7 | 255 |
| | | IR CD/LD | Low | 1 | 6 | 0 | 7 |
| | | | Normal | 7 | 228 | 4 | 239 |
| | | | High | 0 | 2 | 0 | 2 |
| | | | All | 8 | 236 | 4 | 248 |
| | Lymphocytes | IPX203 | Low | 4 | 14 | 0 | 18 |
| | | | Normal | 4 | 230 | 1 | 235 |
| | | | High | 0 | 0 | 2 | 2 |
| | | | All | 8 | 244 | 3 | 255 |
| | | IR CD/LD | Low | 7 | 4 | 0 | 11 |
| | | | Normal | 12 | 221 | 0 | 233 |
| | | | High | 0 | 1 | 1 | 2 |
| | | | All | 19 | 226 | 1 | 246 |
| | Lymphocytes/ Leukocytes | IPX203 | Low | 25 | 28 | 0 | 53 |
| | | | Normal | 20 | 171 | 4 | 195 |
| | | | High | 1 | 5 | 1 | 7 |

| | | | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Double-Blind Period** | **Analysis Reference Range Indicator** | **LOW** | **NORMAL** | **HIGH** | **All** |
| | | | All | 46 | 204 | 5 | 255 |
| | | IR CD/LD | Low | 29 | 19 | 0 | 48 |
| | | | Normal | 26 | 160 | 4 | 190 |
| | | | High | 0 | 5 | 3 | 8 |
| | | | All | 55 | 184 | 7 | 246 |
| | Monocytes | IPX203 | Normal | 0 | 253 | 1 | 254 |
| | | | High | 0 | 0 | 1 | 1 |
| | | | All | 0 | 253 | 2 | 255 |
| | | IR CD/LD | Normal | 0 | 239 | 2 | 241 |
| | | | High | 0 | 4 | 1 | 5 |
| | | | All | 0 | 243 | 3 | 246 |
| | Monocytes/ Leukocytes | IPX203 | Low | 0 | 2 | 0 | 2 |
| | | | Normal | 3 | 240 | 4 | 247 |
| | | | High | 0 | 4 | 2 | 6 |
| | | | All | 3 | 246 | 6 | 255 |
| | | IR CD/LD | Low | 0 | 2 | 0 | 2 |
| | | | Normal | 1 | 226 | 8 | 235 |
| | | | High | 0 | 5 | 4 | 9 |
| | | | All | 1 | 233 | 12 | 246 |
| | Neutrophils | IPX203 | Low | 1 | 0 | 0 | 1 |
| | | | Normal | 0 | 241 | 4 | 245 |
| | | | High | 0 | 4 | 5 | 9 |
| | | | All | 1 | 245 | 9 | 255 |
| | | IR CD/LD | Low | 1 | 1 | 0 | 2 |
| | | | Normal | 2 | 228 | 8 | 238 |
| | | | High | 0 | 5 | 1 | 6 |
| | | | All | 3 | 234 | 9 | 246 |
| | Neutrophils/ Leukocytes | IPX203 | Low | 0 | 1 | 0 | 1 |
| | | | Normal | 2 | 212 | 8 | 222 |
| | | | High | 0 | 17 | 15 | 32 |
| | | | All | 2 | 230 | 23 | 255 |
| | | IR CD/LD | Low | 2 | 2 | 0 | 4 |
| | | | Normal | 5 | 194 | 16 | 215 |
| | | | High | 0 | 12 | 15 | 27 |
| | | | All | 7 | 208 | 31 | 246 |
| | Platelets | IPX203 | Low | 11 | 10 | 0 | 21 |
| | | | Normal | 6 | 211 | 4 | 221 |
| | | | High | 0 | 4 | 8 | 12 |
| | | | All | 17 | 225 | 12 | 254 |
| | | IR CD/LD | Low | 9 | 9 | 0 | 18 |
| | | | Normal | 4 | 221 | 0 | 225 |
| | | | High | 0 | 3 | 2 | 5 |
| | | | All | 13 | 233 | 2 | 248 |
| | All | All | All | 388 | 6929 | 208 | 7525 |

**Table 44: Descriptive Statistics Chemistry Results by Visit, Study B16-03 (Open-Label Safety Population)**

| | | | | Analysis Value | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Standard Units** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| **Alanine Aminotransferase** | U/L | BASELINE | 409.00 | 11.56 | 5.00 | 112.00 | 9.00 |
| | | VISIT 2 | 356.00 | 9.92 | 5.00 | 38.00 | 8.00 |
| | | VISIT 3 | 340.00 | 9.60 | 5.00 | 46.00 | 7.00 |
| | | VISIT 4 | 335.00 | 9.67 | 5.00 | 49.00 | 7.00 |
| | | VISIT 4/ET | 376.00 | 9.90 | 5.00 | 52.00 | 7.00 |
| **Albumin** | g/L | BASELINE | 412.00 | 43.79 | 36.00 | 52.00 | 44.00 |
| | | VISIT 2 | 360.00 | 43.31 | 29.00 | 51.00 | 43.00 |
| | | VISIT 3 | 344.00 | 43.60 | 34.00 | 53.00 | 44.00 |
| | | VISIT 4 | 338.00 | 43.75 | 30.00 | 53.00 | 44.00 |
| | | VISIT 4/ET | 380.00 | 43.69 | 30.00 | 53.00 | 44.00 |
| **Alkaline Phosphatase** | U/L | BASELINE | 412.00 | 81.90 | 26.00 | 173.00 | 79.00 |
| | | VISIT 2 | 359.00 | 84.09 | 27.00 | 183.00 | 80.00 |
| | | VISIT 3 | 341.00 | 84.74 | 36.00 | 169.00 | 82.00 |
| | | VISIT 4 | 337.00 | 84.77 | 37.00 | 187.00 | 80.00 |
| | | VISIT 4/ET | 379.00 | 84.44 | 27.00 | 187.00 | 80.00 |
| **Aspartate Aminotransferase** | U/L | BASELINE | 407.00 | 16.96 | 5.00 | 46.00 | 16.00 |
| | | VISIT 2 | 354.00 | 16.42 | 5.00 | 75.00 | 15.00 |
| | | VISIT 3 | 337.00 | 16.68 | 5.00 | 76.00 | 15.00 |
| | | VISIT 4 | 331.00 | 16.47 | 5.00 | 54.00 | 16.00 |
| | | VISIT 4/ET | 372.00 | 16.57 | 5.00 | 54.00 | 16.00 |
| **Bicarbonate** | mmol/L | BASELINE | 412.00 | 23.84 | 16.00 | 33.00 | 24.00 |
| | | VISIT 2 | 358.00 | 24.18 | 14.00 | 35.00 | 24.00 |
| | | VISIT 3 | 342.00 | 24.36 | 16.00 | 32.00 | 24.00 |
| | | VISIT 4 | 337.00 | 24.10 | 16.00 | 35.00 | 24.00 |
| | | VISIT 4/ET | 379.00 | 24.07 | 16.00 | 35.00 | 24.00 |
| **Bilirubin** | umol/L | BASELINE | 411.00 | 8.27 | 3.00 | 34.00 | 7.00 |
| | | VISIT 2 | 358.00 | 8.27 | 3.00 | 49.00 | 7.00 |
| | | VISIT 3 | 343.00 | 8.24 | 3.00 | 43.00 | 7.00 |
| | | VISIT 4 | 337.00 | 8.16 | 3.00 | 36.00 | 7.00 |
| | | VISIT 4/ET | 379.00 | 8.07 | 3.00 | 36.00 | 7.00 |
| **Calcium** | mmol/L | BASELINE | 411.00 | 2.33 | 2.05 | 2.65 | 2.33 |
| | | VISIT 2 | 360.00 | 2.34 | 1.99 | 2.72 | 2.34 |
| | | VISIT 3 | 343.00 | 2.35 | 2.06 | 2.66 | 2.34 |
| | | VISIT 4 | 337.00 | 2.34 | 2.09 | 2.73 | 2.34 |
| | | VISIT 4/ET | 379.00 | 2.34 | 2.09 | 2.73 | 2.34 |
| **Chloride** | mmol/L | BASELINE | 411.00 | 101.25 | 90.00 | 108.00 | 101.00 |
| | | VISIT 2 | 359.00 | 101.39 | 92.00 | 111.00 | 102.00 |
| | | VISIT 3 | 343.00 | 101.32 | 93.00 | 109.00 | 102.00 |
| | | VISIT 4 | 337.00 | 101.50 | 93.00 | 108.00 | 102.00 |
| | | VISIT 4/ET | 379.00 | 101.51 | 93.00 | 108.00 | 102.00 |
| **Creatine Kinase** | U/L | BASELINE | 411.00 | 120.56 | 24.00 | 741.00 | 101.00 |
| | | VISIT 2 | 356.00 | 122.79 | 23.00 | 616.00 | 96.50 |
| | | VISIT 3 | 339.00 | 133.39 | 23.00 | 2332.00 | 97.00 |

| | | | | Analysis Value | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Standard Units** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| | | VISIT 4 | 337.00 | 116.09 | 19.00 | 722.00 | 96.00 |
| | | VISIT 4/ET | 379.00 | 118.32 | 19.00 | 722.00 | 97.00 |
| **Creatinine** | umol/L | BASELINE | 412.00 | 78.33 | 37.00 | 173.00 | 76.00 |
| | | VISIT 2 | 359.00 | 79.28 | 38.00 | 161.00 | 78.00 |
| | | VISIT 3 | 342.00 | 78.56 | 38.00 | 192.00 | 75.00 |
| | | VISIT 4 | 336.00 | 78.57 | 29.00 | 199.00 | 76.00 |
| | | VISIT 4/ET | 378.00 | 77.85 | 29.00 | 199.00 | 76.00 |
| **Direct Bilirubin** | umol/L | BASELINE | 402.00 | 2.90 | 1.00 | 11.00 | 3.00 |
| | | VISIT 2 | 347.00 | 2.97 | 0.00 | 13.00 | 3.00 |
| | | VISIT 3 | 332.00 | 2.86 | 1.00 | 13.00 | 2.00 |
| | | VISIT 4 | 325.00 | 2.91 | 1.00 | 11.00 | 2.00 |
| | | VISIT 4/ET | 366.00 | 2.87 | 1.00 | 11.00 | 2.00 |
| **Glucose** | mmol/L | BASELINE | 409.00 | 5.86 | 3.00 | 17.80 | 5.50 |
| | | VISIT 2 | 358.00 | 5.76 | 2.70 | 20.30 | 5.40 |
| | | VISIT 3 | 343.00 | 5.86 | 3.10 | 20.50 | 5.40 |
| | | VISIT 4 | 337.00 | 5.90 | 2.20 | 18.50 | 5.50 |
| | | VISIT 4/ET | 379.00 | 5.86 | 2.20 | 18.50 | 5.50 |
| **Indirect Bilirubin** | umol/L | BASELINE | 402.00 | 5.37 | 1.00 | 23.00 | 5.00 |
| | | VISIT 2 | 347.00 | 5.37 | 1.00 | 36.00 | 5.00 |
| | | VISIT 3 | 332.00 | 5.34 | 1.00 | 30.00 | 5.00 |
| | | VISIT 4 | 325.00 | 5.26 | 1.00 | 28.00 | 4.00 |
| | | VISIT 4/ET | 366.00 | 5.16 | 1.00 | 28.00 | 4.00 |
| **Lactate Dehydrogenase** | U/L | BASELINE | 372.00 | 173.91 | 86.00 | 318.00 | 170.00 |
| | | VISIT 2 | 325.00 | 176.02 | 88.00 | 304.00 | 171.00 |
| | | VISIT 3 | 319.00 | 174.22 | 85.00 | 398.00 | 171.00 |
| | | VISIT 4 | 300.00 | 171.98 | 87.00 | 356.00 | 166.00 |
| | | VISIT 4/ET | 340.00 | 173.51 | 87.00 | 356.00 | 168.00 |
| **Phosphate** | mmol/L | BASELINE | 411.00 | 1.11 | 0.70 | 1.60 | 1.11 |
| | | VISIT 2 | 358.00 | 1.11 | 0.67 | 1.68 | 1.11 |
| | | VISIT 3 | 343.00 | 1.11 | 0.66 | 1.64 | 1.11 |
| | | VISIT 4 | 337.00 | 1.12 | 0.66 | 1.62 | 1.11 |
| | | VISIT 4/ET | 379.00 | 1.11 | 0.66 | 1.65 | 1.10 |
| **Potassium** | mmol/L | BASELINE | 402.00 | 4.43 | 3.20 | 6.00 | 4.40 |
| | | VISIT 2 | 347.00 | 4.40 | 3.00 | 6.00 | 4.40 |
| | | VISIT 3 | 332.00 | 4.45 | 3.30 | 6.00 | 4.40 |
| | | VISIT 4 | 319.00 | 4.42 | 3.20 | 5.90 | 4.40 |
| | | VISIT 4/ET | 359.00 | 4.42 | 3.20 | 5.90 | 4.40 |
| **Protein** | g/L | BASELINE | 411.00 | 67.02 | 55.00 | 81.00 | 67.00 |
| | | VISIT 2 | 359.00 | 66.69 | 56.00 | 79.00 | 67.00 |
| | | VISIT 3 | 343.00 | 66.66 | 53.00 | 80.00 | 67.00 |
| | | VISIT 4 | 337.00 | 66.83 | 51.00 | 84.00 | 67.00 |
| | | VISIT 4/ET | 379.00 | 66.63 | 51.00 | 84.00 | 67.00 |
| **Sodium** | mmol/L | BASELINE | 411.00 | 139.49 | 129.00 | 146.00 | 140.00 |
| | | VISIT 2 | 360.00 | 139.41 | 130.00 | 145.00 | 140.00 |
| | | VISIT 3 | 344.00 | 139.34 | 130.00 | 150.00 | 140.00 |
| | | VISIT 4 | 338.00 | 139.54 | 131.00 | 146.00 | 140.00 |
| | | VISIT 4/ET | 380.00 | 139.54 | 131.00 | 146.00 | 140.00 |

| | | | | Analysis Value | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Standard Units** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| **Urate** | mmol/L | BASELINE | 411.00 | 0.28 | 0.11 | 0.57 | 0.28 |
| | | VISIT 2 | 358.00 | 0.28 | 0.08 | 0.55 | 0.27 |
| | | VISIT 3 | 343.00 | 0.27 | 0.08 | 0.68 | 0.27 |
| | | VISIT 4 | 337.00 | 0.27 | 0.08 | 0.66 | 0.26 |
| | | VISIT 4/ET | 379.00 | 0.27 | 0.08 | 0.66 | 0.26 |
| **Urea Nitrogen** | mmol/L | BASELINE | 411.00 | 6.61 | 2.30 | 18.20 | 6.30 |
| | | VISIT 2 | 359.00 | 6.69 | 2.30 | 16.40 | 6.40 |
| | | VISIT 3 | 343.00 | 6.74 | 2.70 | 16.50 | 6.40 |
| | | VISIT 4 | 337.00 | 6.80 | 2.80 | 16.60 | 6.50 |
| | | VISIT 4/ET | 379.00 | 6.77 | 2.80 | 16.60 | 6.50 |

Source: FDA analysis

**Table 45: Chemistry Shift, Study B16-03 (Open-Label Safety Population)**

| | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|
| **Parameter** | **Analysis Reference Range Indicator** | **Low** | **Normal** | **High** | **All** |
| **Alanine Aminotransferase** | Normal | 0 | 393 | 5 | 398 |
| | High | 0 | 2 | 0 | 2 |
| | All | 0 | 395 | 5 | 400 |
| **Albumin** | Low | 0 | 2 | 0 | 2 |
| | Normal | 0 | 401 | 0 | 401 |
| | All | 0 | 403 | 0 | 403 |
| **Alkaline Phosphatase** | Low | 1 | 1 | 0 | 2 |
| | Normal | 0 | 351 | 8 | 359 |
| | High | 0 | 13 | 29 | 42 |
| | All | 1 | 365 | 37 | 403 |
| **Aspartate Aminotransferase** | Normal | 0 | 393 | 1 | 394 |
| | High | 0 | 3 | 1 | 4 |
| | All | 0 | 396 | 2 | 398 |
| **Bicarbonate** | Low | 25 | 44 | 0 | 69 |
| | Normal | 47 | 283 | 1 | 331 |
| | High | 0 | 3 | 0 | 3 |
| | All | 72 | 330 | 1 | 403 |
| **Bilirubin** | Normal | 0 | 389 | 5 | 394 |
| | High | 0 | 6 | 2 | 8 |
| | All | 0 | 395 | 7 | 402 |
| **Calcium** | Low | 2 | 2 | 0 | 4 |
| | Normal | 2 | 391 | 3 | 396 |
| | High | 0 | 2 | 0 | 2 |
| | All | 4 | 395 | 3 | 402 |
| **Chloride** | Low | 8 | 17 | 0 | 25 |
| | Normal | 16 | 361 | 0 | 377 |
| | All | 24 | 378 | 0 | 402 |
| **Creatine Kinase** | Low | 0 | 0 | 1 | 1 |
| | Normal | 0 | 321 | 31 | 352 |
| | High | 0 | 28 | 21 | 49 |
| | All | 0 | 349 | 53 | 402 |

| Parameter | Analysis Reference Range Indicator | Baseline Reference Range Indicator Low | Normal | High | All |
|---|---|---|---|---|---|
| **Creatinine** | Low | 10 | 8 | 0 | 18 |
| | Normal | 7 | 316 | 18 | 341 |
| | High | 0 | 15 | 29 | 44 |
| | All | 17 | 339 | 47 | 403 |
| **Direct Bilirubin** | Normal | 0 | 381 | 2 | 383 |
| | High | 0 | 4 | 5 | 9 |
| | All | 0 | 385 | 7 | 392 |
| **Glucose** | Low | 0 | 4 | 3 | 7 |
| | Normal | 4 | 345 | 15 | 364 |
| | High | 0 | 10 | 19 | 29 |
| | All | 4 | 359 | 37 | 400 |
| **Indirect Bilirubin** | Normal | 0 | 364 | 10 | 374 |
| | High | 0 | 8 | 10 | 18 |
| | All | 0 | 372 | 20 | 392 |
| **Lactate Dehydrogenase** | Low | 1 | 1 | 0 | 2 |
| | Normal | 1 | 323 | 6 | 330 |
| | High | 0 | 15 | 13 | 28 |
| | All | 2 | 339 | 19 | 360 |
| **Phosphate** | Low | 3 | 5 | 0 | 8 |
| | Normal | 6 | 387 | 0 | 393 |
| | High | 0 | 1 | 0 | 1 |
| | All | 9 | 393 | 0 | 402 |
| **Potassium** | Low | 1 | 1 | 0 | 2 |
| | Normal | 1 | 374 | 6 | 381 |
| | High | 0 | 8 | 1 | 9 |
| | All | 2 | 383 | 7 | 392 |
| **Protein** | Low | 9 | 12 | 0 | 21 |
| | Normal | 11 | 370 | 0 | 381 |
| | All | 20 | 382 | 0 | 402 |
| **Sodium** | Low | 3 | 7 | 0 | 10 |
| | Normal | 6 | 386 | 0 | 392 |
| | All | 9 | 393 | 0 | 402 |
| **Urate** | Low | 21 | 19 | 0 | 40 |
| | Normal | 9 | 351 | 0 | 360 |
| | High | 0 | 1 | 1 | 2 |
| | All | 30 | 371 | 1 | 402 |
| **Urea Nitrogen** | Normal | 0 | 335 | 17 | 352 |
| | High | 0 | 28 | 22 | 50 |
| | All | 0 | 363 | 39 | 402 |

Source: FDA analysis

**Table 46: Hematology Descriptive Analysis by Visit, Study B16-03 (Open-Label Safety Population) (SAS)**

| | | Analysis Value | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| **Basophils** | Baseline | 404.00 | 0.04 | 0.00 | 0.30 | 0.00 |

| | | Analysis Value | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| | Visit 2 | 361.00 | 0.04 | 0.00 | 0.20 | 0.00 |
| | Visit 3 | 345.00 | 0.04 | 0.00 | 0.20 | 0.00 |
| | Visit 4 | 335.00 | 0.04 | 0.00 | 0.20 | 0.00 |
| | Visit 4/Et | 374.00 | 0.04 | 0.00 | 0.20 | 0.00 |
| **Basophils/ Leukocytes** | Baseline | 404.00 | 0.82 | 0.00 | 3.00 | 1.00 |
| | Visit 2 | 361.00 | 0.84 | 0.00 | 3.00 | 1.00 |
| | Visit 3 | 345.00 | 0.78 | 0.00 | 5.00 | 1.00 |
| | Visit 4 | 335.00 | 0.75 | 0.00 | 4.00 | 1.00 |
| | Visit 4/Et | 374.00 | 0.75 | 0.00 | 4.00 | 1.00 |
| **Eosinophils** | Baseline | 404.00 | 0.15 | 0.00 | 0.70 | 0.10 |
| | Visit 2 | 361.00 | 0.15 | 0.00 | 0.90 | 0.10 |
| | Visit 3 | 345.00 | 0.15 | 0.00 | 1.10 | 0.10 |
| | Visit 4 | 335.00 | 0.15 | 0.00 | 0.80 | 0.10 |
| | Visit 4/Et | 374.00 | 0.15 | 0.00 | 0.80 | 0.10 |
| **Eosinophils/ Leukocytes** | Baseline | 404.00 | 2.17 | 0.00 | 11.00 | 2.00 |
| | Visit 2 | 361.00 | 2.14 | 0.00 | 13.00 | 2.00 |
| | Visit 3 | 345.00 | 2.20 | 0.00 | 13.00 | 2.00 |
| | Visit 4 | 335.00 | 2.20 | 0.00 | 16.00 | 2.00 |
| | Visit 4/Et | 374.00 | 2.25 | 0.00 | 16.00 | 2.00 |
| **Erythrocytes** | Baseline | 410.00 | 4.62 | 3.50 | 6.00 | 4.60 |
| | Visit 2 | 362.00 | 4.60 | 3.40 | 5.90 | 4.60 |
| | Visit 3 | 345.00 | 4.59 | 3.40 | 5.70 | 4.60 |
| | Visit 4 | 337.00 | 4.59 | 3.20 | 5.60 | 4.60 |
| | Visit 4/Et | 378.00 | 4.58 | 3.20 | 5.80 | 4.60 |
| **Hematocrit** | Baseline | 410.00 | 0.45 | 0.32 | 0.59 | 0.45 |
| | Visit 2 | 362.00 | 0.45 | 0.33 | 0.60 | 0.45 |
| | Visit 3 | 345.00 | 0.45 | 0.33 | 0.56 | 0.45 |
| | Visit 4 | 337.00 | 0.44 | 0.32 | 0.54 | 0.45 |
| | Visit 4/Et | 378.00 | 0.44 | 0.32 | 0.56 | 0.45 |
| **Hemoglobin** | Baseline | 413.00 | 140.41 | 85.00 | 182.00 | 142.00 |
| | Visit 2 | 362.00 | 139.82 | 81.00 | 187.00 | 140.00 |
| | Visit 3 | 346.00 | 139.55 | 87.00 | 172.00 | 140.00 |
| | Visit 4 | 337.00 | 139.45 | 92.00 | 166.00 | 140.00 |
| | Visit 4/Et | 379.00 | 139.25 | 92.00 | 180.00 | 140.00 |
| **Leukocytes** | Baseline | 406.00 | 6.71 | 3.40 | 14.20 | 6.40 |
| | Visit 2 | 362.00 | 6.79 | 3.00 | 14.80 | 6.50 |
| | Visit 3 | 345.00 | 6.65 | 2.00 | 16.90 | 6.60 |
| | Visit 4 | 337.00 | 6.77 | 3.10 | 14.10 | 6.70 |
| | Visit 4/Et | 376.00 | 6.78 | 3.10 | 14.10 | 6.65 |
| **Lymphocytes** | Baseline | 404.00 | 1.72 | 0.30 | 4.90 | 1.60 |
| | Visit 2 | 361.00 | 1.68 | 0.60 | 4.60 | 1.50 |
| | Visit 3 | 345.00 | 1.67 | 0.60 | 4.00 | 1.60 |
| | Visit 4 | 335.00 | 1.68 | 0.50 | 5.10 | 1.60 |
| | Visit 4/Et | 374.00 | 1.69 | 0.50 | 5.10 | 1.60 |
| **Lymphocytes/ Leukocytes** | Baseline | 404.00 | 26.18 | 3.00 | 53.00 | 25.00 |
| | Visit 2 | 361.00 | 25.38 | 6.00 | 51.00 | 24.00 |
| | Visit 3 | 345.00 | 25.63 | 7.00 | 51.00 | 25.00 |
| | Visit 4 | 335.00 | 25.47 | 6.00 | 55.00 | 24.00 |

| | | Analysis Value | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| | Visit 4/Et | 374.00 | 25.52 | 6.00 | 55.00 | 25.00 |
| **Monocytes** | Baseline | 404.00 | 0.43 | 0.10 | 1.40 | 0.40 |
| | Visit 2 | 361.00 | 0.44 | 0.10 | 1.30 | 0.40 |
| | Visit 3 | 345.00 | 0.43 | 0.10 | 1.50 | 0.40 |
| | Visit 4 | 335.00 | 0.43 | 0.10 | 1.00 | 0.40 |
| | Visit 4/Et | 374.00 | 0.44 | 0.10 | 1.30 | 0.40 |
| **Monocytes/ Leukocytes** | Baseline | 404.00 | 6.48 | 1.00 | 17.00 | 6.00 |
| | Visit 2 | 361.00 | 6.51 | 2.00 | 15.00 | 6.00 |
| | Visit 3 | 345.00 | 6.64 | 3.00 | 20.00 | 6.00 |
| | Visit 4 | 335.00 | 6.47 | 2.00 | 18.00 | 6.00 |
| | Visit 4/Et | 374.00 | 6.46 | 2.00 | 18.00 | 6.00 |
| **Neutrophils** | Baseline | 404.00 | 4.39 | 1.40 | 11.10 | 4.20 |
| | Visit 2 | 361.00 | 4.50 | 1.50 | 12.70 | 4.30 |
| | Visit 3 | 345.00 | 4.38 | 0.40 | 13.60 | 4.20 |
| | Visit 4 | 335.00 | 4.48 | 1.60 | 11.70 | 4.30 |
| | Visit 4/Et | 374.00 | 4.48 | 1.60 | 11.70 | 4.30 |
| **Neutrophils/ Leukocytes** | Baseline | 404.00 | 64.60 | 29.00 | 92.00 | 65.00 |
| | Visit 2 | 361.00 | 65.51 | 40.00 | 90.00 | 66.00 |
| | Visit 3 | 345.00 | 65.16 | 19.00 | 91.00 | 66.00 |
| | Visit 4 | 335.00 | 65.47 | 33.00 | 86.00 | 66.00 |
| | Visit 4/Et | 374.00 | 65.37 | 33.00 | 86.00 | 66.00 |
| **Platelets** | Baseline | 407.00 | 225.49 | 38.00 | 459.00 | 216.00 |
| | Visit 2 | 361.00 | 222.43 | 100.00 | 500.00 | 213.00 |
| | Visit 3 | 344.00 | 221.86 | 94.00 | 484.00 | 219.50 |
| | Visit 4 | 337.00 | 232.66 | 112.00 | 468.00 | 223.00 |
| | Visit 4/Et | 377.00 | 231.92 | 112.00 | 468.00 | 223.00 |

Source: FDA analysis

**Table 47: Hematology Shift Table, Study B16-03 (Open-Label Safety Population)**

| | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|
| **Parameter** | **Analysis Reference Range Indicator** | **Low** | **Normal** | **High** | **All** |
| **Basophils** | Normal | 0 | 391 | 2 | 393 |
| | All | 0 | 391 | 2 | 393 |
| **Basophils/Leukocytes** | Normal | 0 | 381 | 5 | 386 |
| | High | 0 | 7 | 0 | 7 |
| | All | 0 | 388 | 5 | 393 |
| **Eosinophils** | Normal | 0 | 391 | 0 | 391 |
| | High | 0 | 2 | 0 | 2 |
| | All | 0 | 393 | 0 | 393 |
| **Eosinophils/Leukocytes** | Normal | 0 | 387 | 3 | 390 |
| | High | 0 | 2 | 1 | 3 |
| | All | 0 | 389 | 4 | 393 |
| **Erythrocytes** | Low | 83 | 46 | 0 | 129 |
| | Normal | 24 | 242 | 2 | 268 |
| | High | 0 | 1 | 2 | 3 |
| | All | 107 | 289 | 4 | 400 |

| | | Baseline Reference Range Indicator | | | |
|---|---|---|---|---|---|
| **Parameter** | **Analysis Reference Range Indicator** | **Low** | **Normal** | **High** | **All** |
| **Hematocrit** | Low | 12 | 9 | 0 | 21 |
| | Normal | 5 | 328 | 19 | 352 |
| | High | 0 | 15 | 12 | 27 |
| | All | 17 | 352 | 31 | 400 |
| **Hemoglobin** | Low | 46 | 36 | 0 | 82 |
| | Normal | 18 | 301 | 2 | 321 |
| | High | 0 | 0 | 1 | 1 |
| | All | 64 | 337 | 3 | 404 |
| **Leukocytes** | Low | 3 | 8 | 0 | 11 |
| | Normal | 3 | 366 | 4 | 373 |
| | High | 0 | 7 | 4 | 11 |
| | All | 6 | 381 | 8 | 395 |
| **Lymphocytes** | Low | 4 | 19 | 0 | 23 |
| | Normal | 16 | 350 | 2 | 368 |
| | High | 0 | 0 | 2 | 2 |
| | All | 20 | 369 | 4 | 393 |
| **Lymphocytes/Leukocytes** | Low | 46 | 42 | 0 | 88 |
| | Normal | 31 | 256 | 10 | 297 |
| | High | 0 | 5 | 3 | 8 |
| | All | 77 | 303 | 13 | 393 |
| **Monocytes** | Normal | 0 | 387 | 4 | 391 |
| | High | 0 | 2 | 0 | 2 |
| | All | 0 | 389 | 4 | 393 |
| **Monocytes/Leukocytes** | Low | 1 | 1 | 0 | 2 |
| | Normal | 2 | 370 | 10 | 382 |
| | High | 0 | 5 | 4 | 9 |
| | All | 3 | 376 | 14 | 393 |
| **Neutrophils** | Normal | 1 | 369 | 8 | 378 |
| | High | 0 | 10 | 5 | 15 |
| | All | 1 | 379 | 13 | 393 |
| **Neutrophils/Leukocytes** | Low | 0 | 5 | 0 | 5 |
| | Normal | 3 | 304 | 22 | 329 |
| | High | 0 | 34 | 25 | 59 |
| | All | 3 | 343 | 47 | 393 |
| **Platelets** | Low | 16 | 18 | 0 | 34 |
| | Normal | 11 | 325 | 7 | 343 |
| | High | 1 | 11 | 7 | 19 |
| | All | 28 | 354 | 14 | 396 |

Source: FDA analysis

**Table 48: Vital Signs Descriptive Analysis by Visit, Study B16-02 (Controlled Safety Population)**

| | | | IPX203 | | | | | IR CD/LD | | | | | Not Assigned | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Units** | **N** | **Mean** | **Min** | **Max** | **Median** | **N** | **Mean** | **Min** | **Max** | **Median** | **N** | **Mean** | **Min** | **Max** | **Median** |
| Study entry | HEIGHT | cm | 256.0 | 169.1 | 124.5 | 195.4 | 170.0 | 250.0 | 171.7 | 145.0 | 193.0 | 172.7 | 123.0 | 166.4 | 139.7 | 190.0 | 165.1 |
| baseline | RESP | breaths/min | 256.0 | 16.5 | 11.0 | 25.0 | 16.0 | 250.0 | 16.2 | 10.0 | 24.0 | 16.0 | 124.0 | 16.6 | 12.0 | 28.0 | 16.0 |
| | STDIABP | mmHg | 256.0 | 77.6 | 50.0 | 120.0 | 77.5 | 250.0 | 77.2 | 50.0 | 101.0 | 77.0 | 123.0 | 77.3 | 50.0 | 107.0 | 77.0 |
| | STHR | beats/min | 256.0 | 76.1 | 41.0 | 125.0 | 76.0 | 250.0 | 75.0 | 54.0 | 104.0 | 75.0 | 123.0 | 76.0 | 54.0 | 102.0 | 76.0 |
| | STSYSBP | mmHg | 256.0 | 125.0 | 86.0 | 218.0 | 124.5 | 250.0 | 123.6 | 88.0 | 187.0 | 123.0 | 123.0 | 125.4 | 83.0 | 174.0 | 124.0 |
| | SUDIABP | mmHg | 256.0 | 76.9 | 51.0 | 110.0 | 76.5 | 250.0 | 77.7 | 52.0 | 107.0 | 77.0 | 124.0 | 76.9 | 54.0 | 111.0 | 76.0 |
| | SUHR | beats/min | 256.0 | 70.8 | 40.0 | 99.0 | 71.0 | 250.0 | 70.0 | 51.0 | 100.0 | 70.0 | 124.0 | 70.6 | 49.0 | 97.0 | 70.0 |
| | SUSYSBP | mmHg | 256.0 | 127.4 | 91.0 | 203.0 | 127.0 | 250.0 | 128.5 | 98.0 | 188.0 | 128.5 | 124.0 | 128.8 | 87.0 | 198.0 | 126.5 |
| | TEMP | °C | 254.0 | 36.5 | 34.8 | 37.3 | 36.5 | 250.0 | 36.5 | 34.6 | 37.8 | 36.5 | 124.0 | 36.5 | 35.7 | 37.9 | 36.5 |
| | WEIGHT | kg | 255.0 | 78.7 | 41.8 | 139.2 | 77.4 | 250.0 | 80.7 | 45.0 | 140.1 | 78.6 | 123.0 | 75.3 | 44.8 | 165.5 | 75.0 |
| Visit 2 | RESP | breaths/min | 255.0 | 16.4 | 12.0 | 24.0 | 16.0 | 249.0 | 16.4 | 11.0 | 24.0 | 16.0 | 86.0 | 16.5 | 13.0 | 26.0 | 16.0 |
| | STDIABP | mmHg | 255.0 | 77.1 | 46.0 | 116.0 | 78.0 | 249.0 | 76.7 | 51.0 | 118.0 | 76.0 | 87.0 | 77.7 | 50.0 | 101.0 | 78.0 |
| | STHR | beats/min | 255.0 | 77.1 | 51.0 | 112.0 | 76.0 | 249.0 | 76.2 | 35.0 | 110.0 | 75.0 | 87.0 | 76.3 | 55.0 | 105.0 | 76.0 |
| | STSYSBP | mmHg | 255.0 | 123.7 | 76.0 | 192.0 | 122.0 | 249.0 | 123.2 | 83.0 | 189.0 | 122.0 | 87.0 | 126.5 | 70.0 | 175.0 | 126.0 |
| | SUDIABP | mmHg | 255.0 | 76.2 | 54.0 | 104.0 | 77.0 | 249.0 | 77.0 | 52.0 | 105.0 | 77.0 | 87.0 | 77.0 | 50.0 | 99.0 | 76.0 |
| | SUHR | beats/min | 255.0 | 71.9 | 47.0 | 109.0 | 71.0 | 249.0 | 71.3 | 50.0 | 100.0 | 70.0 | 87.0 | 70.2 | 46.0 | 97.0 | 69.0 |
| | SUSYSBP | mmHg | 255.0 | 126.6 | 92.0 | 194.0 | 125.0 | 249.0 | 128.2 | 90.0 | 171.0 | 128.0 | 87.0 | 131.0 | 106.0 | 169.0 | 131.0 |
| | TEMP | °C | 128.0 | 36.5 | 35.0 | 37.7 | 36.6 | 130.0 | 36.5 | 35.4 | 37.2 | 36.6 | 29.0 | 36.5 | 36.1 | 37.1 | 36.5 |
| | WEIGHT | kg | 112.0 | 75.8 | 47.4 | 118.0 | 75.5 | 117.0 | 78.8 | 45.0 | 129.8 | 77.0 | 24.0 | 71.5 | 46.8 | 116.0 | 71.5 |
| Visit 3 | RESP | breaths/min | 248.0 | 16.5 | 12.0 | 24.0 | 16.0 | 241.0 | 16.2 | 10.0 | 27.0 | 16.0 | 37.0 | 16.6 | 12.0 | 28.0 | 16.0 |
| | STDIABP | mmHg | 249.0 | 76.0 | 40.0 | 102.0 | 77.0 | 242.0 | 76.4 | 46.0 | 108.0 | 76.5 | 37.0 | 74.8 | 46.0 | 94.0 | 77.0 |
| | STHR | beats/min | 249.0 | 75.9 | 44.0 | 110.0 | 75.0 | 242.0 | 75.0 | 47.0 | 105.0 | 74.0 | 36.0 | 77.0 | 51.0 | 98.0 | 77.5 |
| | STSYSBP | mmHg | 249.0 | 122.2 | 80.0 | 168.0 | 121.0 | 242.0 | 122.5 | 81.0 | 168.0 | 120.5 | 37.0 | 125.5 | 87.0 | 162.0 | 125.0 |
| | SUDIABP | mmHg | 249.0 | 76.1 | 48.0 | 102.0 | 77.0 | 242.0 | 76.6 | 54.0 | 98.0 | 78.0 | 37.0 | 76.2 | 53.0 | 98.0 | 76.0 |
| | SUHR | beats/min | 249.0 | 71.5 | 45.0 | 101.0 | 71.0 | 242.0 | 70.1 | 43.0 | 105.0 | 70.0 | 37.0 | 70.9 | 45.0 | 92.0 | 71.0 |
| | SUSYSBP | mmHg | 249.0 | 125.5 | 90.0 | 179.0 | 125.0 | 242.0 | 126.9 | 94.0 | 172.0 | 126.0 | 37.0 | 131.3 | 105.0 | 169.0 | 129.0 |
| | TEMP | °C | 115.0 | 36.5 | 35.2 | 37.3 | 36.5 | 124.0 | 36.5 | 35.8 | 37.3 | 36.5 | 15.0 | 36.5 | 35.8 | 37.1 | 36.5 |
| | WEIGHT | kg | 93.0 | 75.8 | 42.4 | 119.0 | 75.0 | 105.0 | 78.2 | 45.0 | 129.7 | 76.2 | 7.0 | 67.2 | 53.1 | 87.1 | 58.9 |
| Visit 4 | RESP | breaths/min | 254.0 | 16.5 | 12.0 | 26.0 | 16.0 | 248.0 | 16.3 | 12.0 | 22.0 | 16.0 | 1.0 | 16.0 | 16.0 | 16.0 | 16.0 |
| | STDIABP | mmHg | 255.0 | 76.0 | 47.0 | 103.0 | 76.0 | 248.0 | 75.2 | 55.0 | 113.0 | 75.0 | 1.0 | 101.0 | 101.0 | 101.0 | 101.0 |
| | STHR | beats/min | 255.0 | 73.7 | 43.0 | 102.0 | 73.0 | 248.0 | 74.2 | 50.0 | 102.0 | 74.0 | 1.0 | 77.0 | 77.0 | 77.0 | 77.0 |

| | | | IPX203 | | | | | IR CD/LD | | | | | Not Assigned | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Units** | **N** | **Mean** | **Min** | **Max** | **Median** | **N** | **Mean** | **Min** | **Max** | **Median** | **N** | **Mean** | **Min** | **Max** | **Median** |
| | STSYSBP | mmHg | 255.0 | 122.6 | 72.0 | 167.0 | 122.0 | 248.0 | 120.4 | 81.0 | 175.0 | 120.0 | 1.0 | 147.0 | 147.0 | 147.0 | 147.0 |
| | SUDIABP | mmHg | 255.0 | 75.5 | 51.0 | 105.0 | 75.0 | 248.0 | 75.7 | 55.0 | 95.0 | 75.0 | 1.0 | 112.0 | 112.0 | 112.0 | 112.0 |
| | SUHR | beats/min | 255.0 | 69.0 | 45.0 | 95.0 | 69.0 | 248.0 | 69.4 | 47.0 | 107.0 | 69.0 | 1.0 | 77.0 | 77.0 | 77.0 | 77.0 |
| | SUSYSBP | mmHg | 255.0 | 125.9 | 84.0 | 179.0 | 126.0 | 248.0 | 125.2 | 94.0 | 163.0 | 125.0 | 1.0 | 171.0 | 171.0 | 171.0 | 171.0 |
| Visit 5 | RESP | breaths/min | 229.0 | 16.6 | 12.0 | 27.0 | 16.0 | 223.0 | 16.5 | 12.0 | 26.0 | 16.0 | 0.0 | . | . | . | . |
| | STDIABP | mmHg | 230.0 | 76.3 | 46.0 | 113.0 | 77.0 | 226.0 | 76.6 | 50.0 | 100.0 | 76.0 | 0.0 | . | . | . | . |
| | STHR | beats/min | 230.0 | 76.7 | 45.0 | 104.0 | 76.5 | 226.0 | 76.2 | 51.0 | 109.0 | 75.0 | 0.0 | . | . | . | . |
| | STSYSBP | mmHg | 230.0 | 122.0 | 80.0 | 170.0 | 121.0 | 226.0 | 122.9 | 70.0 | 158.0 | 124.0 | 0.0 | . | . | . | . |
| | SUDIABP | mmHg | 230.0 | 76.6 | 48.0 | 107.0 | 77.0 | 226.0 | 77.1 | 55.0 | 98.0 | 78.0 | 0.0 | . | . | . | . |
| | SUHR | beats/min | 230.0 | 70.9 | 46.0 | 104.0 | 70.0 | 226.0 | 71.1 | 49.0 | 103.0 | 70.0 | 0.0 | . | . | . | . |
| | SUSYSBP | mmHg | 230.0 | 126.3 | 90.0 | 172.0 | 127.0 | 226.0 | 128.1 | 81.0 | 173.0 | 129.0 | 0.0 | . | . | . | . |
| | TEMP | °C | 119.0 | 36.5 | 35.5 | 37.2 | 36.5 | 121.0 | 36.6 | 35.7 | 37.1 | 36.6 | 0.0 | . | . | . | . |
| | WEIGHT | kg | 230.0 | 79.0 | 43.1 | 140.1 | 78.0 | 225.0 | 80.7 | 45.0 | 130.2 | 78.5 | 0.0 | . | . | . | . |
| Visit 6 | RESP | breaths/min | 214.0 | 16.3 | 12.0 | 24.0 | 16.0 | 218.0 | 16.3 | 11.0 | 22.0 | 16.0 | 0.0 | . | . | . | . |
| | STDIABP | mmHg | 213.0 | 76.1 | 47.0 | 117.0 | 75.0 | 219.0 | 76.5 | 50.0 | 108.0 | 76.0 | 0.0 | . | . | . | . |
| | STHR | beats/min | 213.0 | 75.9 | 48.0 | 107.0 | 76.0 | 219.0 | 75.5 | 51.0 | 108.0 | 74.0 | 0.0 | . | . | . | . |
| | STSYSBP | mmHg | 213.0 | 122.6 | 73.0 | 170.0 | 122.0 | 219.0 | 123.5 | 77.0 | 170.0 | 124.0 | 0.0 | . | . | . | . |
| | SUDIABP | mmHg | 215.0 | 75.5 | 50.0 | 111.0 | 75.0 | 219.0 | 77.1 | 55.0 | 116.0 | 77.0 | 0.0 | . | . | . | . |
| | SUHR | beats/min | 214.0 | 71.2 | 49.0 | 97.0 | 70.5 | 219.0 | 71.1 | 50.0 | 100.0 | 71.0 | 0.0 | . | . | . | . |
| | SUSYSBP | mmHg | 215.0 | 126.0 | 85.0 | 180.0 | 125.0 | 219.0 | 128.0 | 97.0 | 172.0 | 128.0 | 0.0 | . | . | . | . |
| | TEMP | °C | 111.0 | 36.5 | 35.5 | 37.1 | 36.5 | 114.0 | 36.5 | 35.7 | 37.4 | 36.6 | 0.0 | . | . | . | . |
| | WEIGHT | kg | 91.0 | 75.1 | 43.2 | 118.0 | 74.7 | 102.0 | 79.3 | 45.0 | 121.0 | 77.1 | 0.0 | . | . | . | . |
| Visit 7/et | RESP | breaths/min | 252.0 | 16.4 | 12.0 | 22.0 | 16.0 | 249.0 | 16.5 | 12.0 | 26.0 | 16.0 | 95.0 | 17.0 | 12.0 | 36.0 | 16.0 |
| | STDIABP | mmHg | 253.0 | 76.4 | 50.0 | 117.0 | 77.0 | 249.0 | 76.9 | 55.0 | 103.0 | 77.0 | 96.0 | 75.7 | 42.0 | 104.0 | 76.0 |
| | STHR | beats/min | 253.0 | 75.2 | 48.0 | 107.0 | 74.0 | 248.0 | 75.1 | 49.0 | 109.0 | 75.5 | 96.0 | 77.1 | 43.0 | 101.0 | 77.5 |
| | STSYSBP | mmHg | 253.0 | 123.0 | 77.0 | 176.0 | 123.0 | 249.0 | 124.3 | 84.0 | 170.0 | 125.0 | 96.0 | 122.6 | 86.0 | 169.0 | 122.0 |
| | SUDIABP | mmHg | 253.0 | 76.6 | 51.0 | 109.0 | 76.0 | 249.0 | 77.3 | 55.0 | 105.0 | 78.0 | 96.0 | 75.6 | 52.0 | 102.0 | 74.5 |
| | SUHR | beats/min | 253.0 | 70.6 | 47.0 | 100.0 | 70.0 | 249.0 | 70.1 | 43.0 | 108.0 | 71.0 | 96.0 | 70.9 | 43.0 | 106.0 | 70.0 |
| | SUSYSBP | mmHg | 253.0 | 127.4 | 93.0 | 181.0 | 127.0 | 249.0 | 128.7 | 96.0 | 168.0 | 128.0 | 96.0 | 127.5 | 99.0 | 175.0 | 126.0 |
| | TEMP | °C | 250.0 | 36.5 | 35.0 | 37.3 | 36.5 | 249.0 | 36.5 | 35.0 | 37.3 | 36.5 | 94.0 | 36.6 | 35.7 | 37.6 | 36.6 |
| | WEIGHT | kg | 253.0 | 78.6 | 42.3 | 140.6 | 78.0 | 248.0 | 80.7 | 46.0 | 150.6 | 78.7 | 95.0 | 74.9 | 44.3 | 153.3 | 75.0 |

RESP= Respirations, STDIABP= Standing Diastolic blood pressure, STHR=Standing heart rate, STSYSBP = Standing systolic blood pressure, SUDIABP Supine diastolic blood pressure, SUHR= Supine heart rate, SUSYSBP=Supine systolic blood pressure and TEMP= Temperature
Source: FDA analysis

**Table 49: Categorical Summary of Vital Signs, Study B16-02 (Controlled Safety Population)**

| Analysis Visit | Parameter | Analysis Value Category 1 | Units | IPX203 | IR CD/LD | Not Assigned |
|---|---|---|---|---|---|---|
| **Study Entry Baseline** | Respiratory Rate | 9 - < 20 | breaths/min | 231 | 234 | 113 |
| | Respiratory Rate | ≥ 20 | breaths/min | 25 | 16 | 11 |
| | Temperature | < 36.5 | °C | 108 | 97 | 50 |
| | Temperature | 36.5 - < 37.5 | °C | 146 | 151 | 73 |
| | Temperature | 37.5 - < 38.5 | °C | 0 | 2 | 1 |
| | Supine Heart Rate | < 60 | beats/min | 25 | 28 | 18 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 231 | 221 | 106 |
| | Supine Heart Rate | ≥ 100 | beats/min | 0 | 1 | 0 |
| | Standing Heart Rate | < 60 | beats/min | 10 | 9 | 8 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 240 | 237 | 112 |
| | Standing Heart Rate | ≥ 100 | beats/min | 6 | 4 | 3 |
| | Supine Systolic Blood Pressure | < 90 | mm Hg | 0 | 0 | 1 |
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 205 | 203 | 97 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 51 | 47 | 26 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 5 | 3 | 2 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 206 | 218 | 101 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 45 | 29 | 20 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 10 | 3 | 2 |
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 224 | 224 | 112 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 22 | 23 | 10 |
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 12 | 4 | 6 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 214 | 227 | 104 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 30 | 19 | 13 |
| **Visit 2** | Respiratory Rate | 9 - < 20 | breaths/min | 229 | 229 | 78 |
| | Respiratory Rate | ≥ 20 | breaths/min | 26 | 20 | 8 |
| | Temperature | < 36.5 | °C | 50 | 46 | 13 |
| | Temperature | 36.5 - < 37.5 | °C | 77 | 84 | 16 |
| | Temperature | 37.5 - < 38.5 | °C | 1 | 0 | 0 |
| | Supine Heart Rate | < 60 | beats/min | 17 | 26 | 13 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 236 | 221 | 74 |
| | Supine Heart Rate | ≥ 100 | beats/min | 2 | 2 | 0 |
| | Standing Heart Rate | < 60 | beats/min | 9 | 7 | 5 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 242 | 235 | 81 |
| | Standing Heart Rate | ≥ 100 | beats/min | 4 | 7 | 1 |

| Analysis Visit | Parameter | Analysis Value Category 1 | Units | IPX203 | IR CD/LD | Not Assigned |
|---|---|---|---|---|---|---|
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 205 | 200 | 64 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 50 | 49 | 23 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 3 | 5 | 1 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 207 | 208 | 67 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 45 | 36 | 19 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 10 | 5 | 2 |
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 225 | 221 | 78 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 20 | 23 | 7 |
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 14 | 8 | 4 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 212 | 212 | 73 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 29 | 29 | 10 |
| **Visit 3** | Respiratory Rate | 9 - < 20 | breaths/min | 221 | 221 | 34 |
| | Respiratory Rate | ≥ 20 | breaths/min | 27 | 20 | 3 |
| | Temperature | < 36.5 | °C | 49 | 47 | 7 |
| | Temperature | 36.5 - < 37.5 | °C | 66 | 77 | 8 |
| | Supine Heart Rate | < 60 | beats/min | 23 | 30 | 3 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 224 | 210 | 34 |
| | Supine Heart Rate | ≥ 100 | beats/min | 2 | 2 | 0 |
| | Standing Heart Rate | < 60 | beats/min | 10 | 11 | 3 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 232 | 228 | 33 |
| | Standing Heart Rate | ≥ 100 | beats/min | 7 | 3 | 0 |
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 199 | 195 | 27 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 50 | 47 | 10 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 5 | 4 | 1 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 209 | 206 | 29 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 35 | 32 | 7 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 12 | 5 | 4 |
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 218 | 224 | 29 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 19 | 13 | 4 |

| Analysis Visit | Parameter | Analysis Value Category 1 | Units | IPX203 | IR CD/LD | Not Assigned |
|---|---|---|---|---|---|---|
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 12 | 10 | 3 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 219 | 213 | 33 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 18 | 19 | 1 |
| **Visit 4** | Respiratory Rate | 9 - < 20 | breaths/min | 234 | 231 | 1 |
| | Respiratory Rate | ≥ 20 | breaths/min | 20 | 17 | 0 |
| | Supine Heart Rate | < 60 | beats/min | 23 | 32 | 0 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 232 | 215 | 1 |
| | Supine Heart Rate | ≥ 100 | beats/min | 0 | 1 | 0 |
| | Standing Heart Rate | < 60 | beats/min | 10 | 10 | 0 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 242 | 236 | 1 |
| | Standing Heart Rate | ≥ 100 | beats/min | 3 | 2 | 0 |
| | Supine Systolic Blood Pressure | < 90 | mm Hg | 1 | 0 | 0 |
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 207 | 217 | 0 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 47 | 31 | 1 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 5 | 8 | 0 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 213 | 214 | 0 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 37 | 26 | 1 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 13 | 4 | 0 |
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 225 | 236 | 0 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 17 | 8 | 1 |
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 15 | 6 | 0 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 214 | 228 | 0 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 26 | 14 | 1 |
| **Visit 5** | Respiratory Rate | 9 - < 20 | breaths/min | 206 | 203 | 0 |
| | Respiratory Rate | ≥ 20 | breaths/min | 23 | 20 | 0 |
| | Temperature | < 36.5 | °C | 54 | 42 | 0 |
| | Temperature | 36.5 - < 37.5 | °C | 65 | 79 | 0 |
| | Supine Heart Rate | < 60 | beats/min | 27 | 27 | 0 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 202 | 198 | 0 |
| | Supine Heart Rate | ≥ 100 | beats/min | 1 | 1 | 0 |
| | Standing Heart Rate | < 60 | beats/min | 11 | 9 | 0 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 214 | 212 | 0 |
| | Standing Heart Rate | ≥ 100 | beats/min | 5 | 5 | 0 |

| Analysis Visit | Parameter | Analysis Value Category 1 | Units | IPX203 | IR CD/LD | Not Assigned |
|---|---|---|---|---|---|---|
| | Supine Systolic Blood Pressure | < 90 | mm Hg | 0 | 1 | 0 |
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 186 | 172 | 0 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 44 | 53 | 0 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 4 | 4 | 0 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 196 | 186 | 0 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 30 | 36 | 0 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 9 | 7 | 0 |
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 198 | 200 | 0 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 23 | 19 | 0 |
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 15 | 12 | 0 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 192 | 187 | 0 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 23 | 27 | 0 |
| **Visit 6** | Respiratory Rate | 9 - < 20 | breaths/min | 202 | 200 | 0 |
| | Respiratory Rate | ≥ 20 | breaths/min | 12 | 18 | 0 |
| | Temperature | < 36.5 | °C | 47 | 46 | 0 |
| | Temperature | 36.5 - < 37.5 | °C | 64 | 68 | 0 |
| | Supine Heart Rate | < 60 | beats/min | 19 | 25 | 0 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 195 | 193 | 0 |
| | Supine Heart Rate | ≥ 100 | beats/min | 0 | 1 | 0 |
| | Standing Heart Rate | < 60 | beats/min | 5 | 14 | 0 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 204 | 200 | 0 |
| | Standing Heart Rate | ≥ 100 | beats/min | 4 | 5 | 0 |
| | Supine Systolic Blood Pressure | < 90 | mm Hg | 1 | 0 | 0 |
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 175 | 175 | 0 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 39 | 44 | 0 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 3 | 2 | 0 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 183 | 191 | 0 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 27 | 26 | 0 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 12 | 5 | 0 |

| Analysis Visit | Parameter | Analysis Value Category 1 | Units | IPX203 | IR CD/LD | Not Assigned |
|---|---|---|---|---|---|---|
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 189 | 203 | 0 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 14 | 11 | 0 |
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 10 | 8 | 0 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 186 | 197 | 0 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 17 | 14 | 0 |
| **Visit 7/ET** | Respiratory Rate | 9 - < 20 | breaths/min | 235 | 226 | 82 |
| | Respiratory Rate | ≥ 20 | breaths/min | 17 | 23 | 13 |
| | Temperature | < 36.5 | °C | 98 | 109 | 33 |
| | Temperature | 36.5 - < 37.5 | °C | 152 | 140 | 60 |
| | Temperature | 37.5 - < 38.5 | °C | 0 | 0 | 1 |
| | Supine Heart Rate | < 60 | beats/min | 34 | 34 | 13 |
| | Supine Heart Rate | 60 - < 100 | beats/min | 217 | 213 | 82 |
| | Supine Heart Rate | ≥ 100 | beats/min | 2 | 2 | 1 |
| | Standing Heart Rate | < 60 | beats/min | 18 | 14 | 7 |
| | Standing Heart Rate | 60 - < 100 | beats/min | 230 | 231 | 87 |
| | Standing Heart Rate | ≥ 100 | beats/min | 5 | 3 | 2 |
| | Supine Systolic Blood Pressure | 90 - < 140 | mm Hg | 204 | 194 | 75 |
| | Supine Systolic Blood Pressure | ≥ 140 | mm Hg | 49 | 55 | 21 |
| | Standing Systolic Blood Pressure | < 90 | mm Hg | 5 | 1 | 1 |
| | Standing Systolic Blood Pressure | 90 - < 140 | mm Hg | 208 | 208 | 85 |
| | Standing Systolic Blood Pressure | ≥ 140 | mm Hg | 40 | 40 | 10 |
| | Supine Diastolic Blood Pressure | < 60 | mm Hg | 9 | 1 | 2 |
| | Supine Diastolic Blood Pressure | 60 - < 90 | mm Hg | 216 | 231 | 86 |
| | Supine Diastolic Blood Pressure | ≥ 90 | mm Hg | 28 | 17 | 8 |
| | Standing Diastolic Blood Pressure | < 60 | mm Hg | 18 | 6 | 6 |
| | Standing Diastolic Blood Pressure | 60 - < 90 | mm Hg | 213 | 228 | 80 |
| | Standing Diastolic Blood Pressure | ≥ 90 | mm Hg | 22 | 15 | 10 |

Source: FDA analysis

**Table 50: Vital Signs by Visit, Study B16-03 (Open-Label Safety Population)**

| | | Analysis Value | | | | |
|---|---|---|---|---|---|---|
| **Parameter (unit)** | **Analysis Visit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| Supine Heart Rate (beats/min) | BASELINE | 418.0 | 70.5 | 47.0 | 108.0 | 70.0 |
| | VISIT 2 | 374.0 | 70.5 | 48.0 | 112.0 | 70.0 |
| | VISIT 3 | 358.0 | 70.6 | 40.0 | 104.0 | 71.0 |
| | VISIT 4 | 350.0 | 71.0 | 47.0 | 101.0 | 71.0 |
| | VISIT 4/ET | 392.0 | 70.7 | 43.0 | 101.0 | 70.0 |
| Standing Heart Rate (beats/min) | BASELINE | 417.0 | 75.0 | 49.0 | 109.0 | 75.0 |
| | VISIT 2 | 373.0 | 74.8 | 49.0 | 119.0 | 75.0 |
| | VISIT 3 | 358.0 | 74.9 | 45.0 | 103.0 | 75.0 |
| | VISIT 4 | 350.0 | 76.0 | 47.0 | 104.0 | 75.0 |
| | VISIT 4/ET | 391.0 | 75.5 | 47.0 | 104.0 | 75.0 |
| Supine Systolic Blood Pressure (mmHg) | BASELINE | 418.0 | 128.4 | 93.0 | 181.0 | 128.0 |
| | VISIT 2 | 374.0 | 127.0 | 82.0 | 176.0 | 126.5 |
| | VISIT 3 | 358.0 | 128.1 | 89.0 | 181.0 | 127.0 |
| | VISIT 4 | 350.0 | 127.3 | 86.0 | 173.0 | 126.0 |
| | VISIT 4/ET | 392.0 | 127.5 | 86.0 | 173.0 | 126.0 |
| Standing Systolic Blood Pressure (mmHg) | BASELINE | 418.0 | 124.2 | 77.0 | 176.0 | 124.0 |
| | VISIT 2 | 374.0 | 121.9 | 68.0 | 166.0 | 122.0 |
| | VISIT 3 | 358.0 | 123.7 | 74.0 | 171.0 | 123.0 |
| | VISIT 4 | 350.0 | 121.7 | 66.0 | 175.0 | 120.0 |
| | VISIT 4/ET | 392.0 | 122.2 | 66.0 | 175.0 | 121.0 |
| Supine Diastolic Blood Pressure (mmHg) | BASELINE | 418.0 | 77.1 | 51.0 | 109.0 | 77.0 |
| | VISIT 2 | 374.0 | 76.9 | 47.0 | 102.0 | 76.0 |
| | VISIT 3 | 358.0 | 77.2 | 51.0 | 118.0 | 77.0 |
| | VISIT 4 | 350.0 | 76.6 | 47.0 | 102.0 | 77.0 |
| | VISIT 4/ET | 392.0 | 76.6 | 47.0 | 105.0 | 76.0 |
| Standing Diastolic Blood Pressure (mmHg) | BASELINE | 418.0 | 76.8 | 50.0 | 117.0 | 77.0 |
| | VISIT 2 | 374.0 | 76.3 | 45.0 | 107.0 | 76.0 |
| | VISIT 3 | 358.0 | 76.4 | 44.0 | 113.0 | 76.0 |
| | VISIT 4 | 350.0 | 76.1 | 44.0 | 109.0 | 76.0 |
| | VISIT 4/ET | 392.0 | 76.3 | 44.0 | 109.0 | 76.0 |
| Temperature (°C) | BASELINE | 417.0 | 36.5 | 35.0 | 37.3 | 36.5 |
| | VISIT 2 | 370.0 | 36.5 | 35.1 | 37.6 | 36.5 |
| | VISIT 3 | 354.0 | 36.5 | 35.4 | 37.3 | 36.5 |
| | VISIT 4 | 347.0 | 36.5 | 34.6 | 37.5 | 36.5 |
| | VISIT 4/ET | 389.0 | 36.5 | 34.6 | 37.5 | 36.5 |
| Respiratory Rate (breaths/min) | BASELINE | 418.0 | 16.5 | 12.0 | 26.0 | 16.0 |
| | VISIT 2 | 373.0 | 16.4 | 11.0 | 26.0 | 16.0 |
| | VISIT 3 | 358.0 | 16.2 | 11.0 | 24.0 | 16.0 |
| | VISIT 4 | 350.0 | 16.2 | 11.0 | 30.0 | 16.0 |
| | VISIT 4/ET | 392.0 | 16.3 | 11.0 | 30.0 | 16.0 |
| Weight (kg) | BASELINE | 417.0 | 80.1 | 42.3 | 150.6 | 79.0 |
| | VISIT 2 | 372.0 | 79.5 | 38.3 | 145.6 | 79.0 |
| | VISIT 3 | 358.0 | 79.6 | 40.9 | 147.4 | 79.0 |
| | VISIT 4 | 349.0 | 79.5 | 44.6 | 147.4 | 78.3 |
| | VISIT 4/ET | 390.0 | 79.2 | 44.4 | 147.4 | 78.3 |

**Table 51: Categorical Summary of Vital Signs by Visit, Study B16-03 (Open-Label Safety Population)**

| Analysis Visit | Parameter | Analysis Value Category | N |
|---|---|---|---|
| **Baseline** | Supine Heart Rate (beats/min) | < 60 | 57 |
| | | 60 to < 100 | 357 |
| | | ≥ 100 | 4 |
| | | All | 418 |
| | Standing Heart Rate (beats/min) | < 60 | 30 |
| | | 60 to < 100 | 379 |
| | | ≥ 100 | 8 |
| | | All | 417 |
| | Supine Systolic Blood Pressure (mmHg) | 90 to < 140 | 332 |
| | | ≥ 140 | 86 |
| | | All | 418 |
| | Standing Systolic Blood Pressure (mmHg) | < 90 | 5 |
| | | 90 to < 140 | 345 |
| | | ≥ 140 | 68 |
| | | All | 418 |
| | Supine Diastolic Blood Pressure (mmHg) | < 60 | 9 |
| | | 60 to < 90 | 372 |
| | | ≥ 90 | 37 |
| | | All | 418 |
| | Standing Diastolic Blood Pressure (mmHg) | < 60 | 20 |
| | | 60 to < 90 | 367 |
| | | ≥ 90 | 31 |
| | | All | 418 |
| | Temperature (°C) | < 36.5 | 178 |
| | | 36.5 to < 37.5 | 239 |
| | | All | 417 |
| | Respiratory Rate (breaths/min) | 9 to < 20 | 383 |
| | | ≥ 20 | 35 |
| | | All | 418 |
| **Visit 2** | Supine Heart Rate (beats/min) | < 60 | 45 |
| | | 60 to < 100 | 327 |
| | | ≥ 100 | 2 |
| | | All | 374 |
| | Standing Heart Rate (beats/min) | < 60 | 21 |
| | | 60 to < 100 | 347 |
| | | ≥ 100 | 5 |
| | | All | 373 |
| | Supine Systolic Blood Pressure (mmHg) | < 90 | 1 |
| | | 90 to < 140 | 289 |
| | | ≥ 140 | 84 |
| | | All | 374 |
| | Standing Systolic Blood Pressure (mmHg) | < 90 | 9 |
| | | 90 to < 140 | 311 |
| | | ≥ 140 | 54 |
| | | All | 374 |

| Analysis Visit | Parameter | Analysis Value Category | N |
|---|---|---|---|
| | Supine Diastolic Blood Pressure (mmHg) | < 60 | 11 |
| | | 60 to < 90 | 331 |
| | | ≥ 90 | 32 |
| | | All | 374 |
| | Standing Diastolic Blood Pressure (mmHg) | < 60 | 15 |
| | | 60 to < 90 | 328 |
| | | ≥ 90 | 31 |
| | | All | 374 |
| | Temperature (°C) | < 36.5 | 168 |
| | | 36.5 to < 37.5 | 201 |
| | | 37.5 to < 38.5 | 1 |
| | | All | 370 |
| | Respiratory Rate (breaths/min) | 9 to < 20 | 347 |
| | | ≥ 20 | 26 |
| | | All | 373 |
| **Visit 3** | Supine Heart Rate (beats/min) | < 60 | 49 |
| | | 60 to < 100 | 308 |
| | | ≥ 100 | 1 |
| | | All | 358 |
| | Standing Heart Rate (beats/min) | < 60 | 19 |
| | | 60 to < 100 | 333 |
| | | ≥ 100 | 6 |
| | | All | 358 |
| | Supine Systolic Blood Pressure (mmHg) | < 90 | 1 |
| | | ≥ 140 | 76 |
| | | 90 to < 140 | 281 |
| | | All | 358 |
| | Standing Systolic Blood Pressure (mmHg) | < 90 | 7 |
| | | 90 to < 140 | 299 |
| | | ≥ 140 | 52 |
| | | All | 358 |
| | Supine Diastolic Blood Pressure (mmHg) | < 60 | 10 |
| | | 60 to < 90 | 315 |
| | | ≥ 90 | 33 |
| | | All | 358 |
| | Standing Diastolic Blood Pressure (mmHg) | < 60 | 16 |
| | | 60 to < 90 | 310 |
| | | ≥ 90 | 32 |
| | | All | 358 |
| | Temperature (°C) | < 36.5 | 155 |
| | | 36.5 to < 37.5 | 199 |
| | | All | 354 |
| | Respiratory Rate (breaths/min) | 9 to < 20 | 338 |
| | | ≥ 20 | 20 |
| | | All | 358 |
| **Visit 4/ET** | Supine Heart Rate (beats/min) | < 60 | 54 |
| | | 60 to < 100 | 337 |
| | | ≥ 100 | 1 |
| | | All | 392 |

| Analysis Visit | Parameter | Analysis Value Category | N |
|---|---|---|---|
| | Standing Heart Rate (beats/min) | < 60 | 21 |
| | | 60 to < 100 | 364 |
| | | ≥ 100 | 6 |
| | | All | 391 |
| | Supine Systolic Blood Pressure (mmHg) | < 90 | 1 |
| | | 90 to < 140 | 310 |
| | | ≥ 140 | 81 |
| | | All | 392 |
| | Standing Systolic Blood Pressure (mmHg) | < 90 | 8 |
| | | 90 to < 140 | 330 |
| | | ≥ 140 | 54 |
| | | All | 392 |
| | Supine Diastolic Blood Pressure (mmHg) | < 60 | 16 |
| | | 60 to < 90 | 343 |
| | | ≥ 90 | 33 |
| | | All | 392 |
| | Standing Diastolic Blood Pressure (mmHg) | < 60 | 22 |
| | | 60 to < 90 | 330 |
| | | ≥ 90 | 40 |
| | | All | 392 |
| | Temperature (°C) | < 36.5 | 171 |
| | | 36.5 to < 37.5 | 217 |
| | | 37.5 to < 38.5 | 1 |
| | | All | 389 |
| | Respiratory Rate (breaths/min) | ≥ 20 | 24 |
| | | All | 392 |

Source: FDA analysis

**Table 52: ECG Descriptive Statistics, Study B16-02 (Controlled Safety Population)**

| | | | Planned Arm | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | IPX203 | | IR CD/LD | | Not Assigned | |
| | | | Analysis Visit | | Analysis Visit | | Analysis Visit | |
| Parameter | Analysis Unit | | STUDY ENTRY BASELINE | VISIT 7/ET | STUDY ENTRY BASELINE | VISIT 7/ET | STUDY ENTRY BASELINE | VISIT 7/ET |
| ECG Mean Ventricular Rate | beats/min | N | 256.00 | 247.00 | 249.00 | 248.00 | 124.00 | 87.00 |
| | | Mean | 68.68 | 69.13 | 69.01 | 69.22 | 70.00 | 68.07 |
| | | Min | 46.00 | 41.00 | 45.00 | 43.00 | 47.00 | 40.00 |
| | | Max | 100.00 | 103.00 | 98.00 | 106.00 | 102.00 | 94.00 |
| | | Median | 68.00 | 69.00 | 68.00 | 69.00 | 70.00 | 69.00 |
| PR Interval, Aggregate | msec | N | 254.00 | 243.00 | 249.00 | 245.00 | 122.00 | 83.00 |
| | | Mean | 163.08 | 162.77 | 168.19 | 168.74 | 163.37 | 160.08 |
| | | Min | 0.00 | 0.00 | 0.00 | 0.00 | 96.00 | 110.00 |
| | | Max | 332.00 | 228.00 | 264.00 | 290.00 | 348.00 | 280.00 |
| | | Median | 165.00 | 166.00 | 167.00 | 170.00 | 156.00 | 160.00 |

| | | | Planned Arm | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | IPX203 | | IR CD/LD | | Not Assigned | |
| | | | Analysis Visit | | Analysis Visit | | Analysis Visit | |
| **Parameter** | **Analysis Unit** | | **STUDY ENTRY BASELINE** | **VISIT 7/ET** | **STUDY ENTRY BASELINE** | **VISIT 7/ET** | **STUDY ENTRY BASELINE** | **VISIT 7/ET** |
| QRS Duration, Aggregate | msec | N | 256.00 | 247.00 | 249.00 | 248.00 | 124.00 | 86.00 |
| | | Mean | 96.16 | 95.52 | 99.25 | 99.71 | 93.57 | 90.24 |
| | | Min | 60.00 | 61.00 | 28.00 | 60.00 | 30.00 | -9.00 |
| | | Max | 207.00 | 197.00 | 178.00 | 178.00 | 172.00 | 165.00 |
| | | Median | 93.00 | 93.00 | 95.00 | 96.00 | 93.00 | 89.00 |
| QT Interval, Aggregate | msec | N | 256.00 | 247.00 | 249.00 | 248.00 | 124.00 | 87.00 |
| | | Mean | 395.66 | 394.85 | 393.45 | 393.05 | 396.13 | 396.43 |
| | | Min | 308.00 | 4.00 | 309.00 | 14.00 | 344.00 | 316.00 |
| | | Max | 494.00 | 496.00 | 498.00 | 492.00 | 488.00 | 504.00 |
| | | Median | 394.00 | 394.00 | 392.00 | 394.00 | 394.50 | 393.00 |
| QTcF Interval, Aggregate | msec | N | 255.00 | 245.00 | 246.00 | 247.00 | 122.00 | 85.00 |
| | | Mean | 418.09 | 415.82 | 413.63 | 411.12 | 426.70 | 416.99 |
| | | Min | 326.00 | 4.00 | 323.00 | 15.00 | 374.00 | 330.00 |
| | | Max | 1019.00 | 819.00 | 872.00 | 534.00 | 878.00 | 872.00 |
| | | Median | 410.00 | 412.00 | 409.50 | 411.00 | 414.50 | 410.00 |
| RR Interval, Aggregate | msec | N | 255.00 | 245.00 | 246.00 | 247.00 | 122.00 | 85.00 |
| | | Mean | 878.28 | 876.88 | 878.62 | 881.38 | 859.45 | 893.85 |
| | | Min | 86.00 | 166.00 | 95.00 | 560.00 | 72.00 | 91.00 |
| | | Max | 1287.00 | 1460.00 | 1317.00 | 1393.00 | 1271.00 | 1477.00 |
| | | Median | 871.00 | 868.00 | 875.00 | 866.00 | 858.00 | 870.00 |

Source: FDA analysis

**Table 53: Shift in ECG Parameter, Study B16-02 (Controlled Safety Population)**

| **Parameter** | **Analysis Value Category** | **Analysis Unit** | **IPX203, Study Entry Baseline** | **IPX203, VISIT 7/ET** | **IR CD/LD, Study Entry Baseline** | **IR CD/LD, VISIT 7/ET** | **Not Assigned, Study Entry Baseline** | **Not Assigned, VISIT 7/ET** |
|---|---|---|---|---|---|---|---|---|
| ECG Mean Ventricular Rate | < 60 | beats/ min | 56 | 54 | 48 | 47 | 20 | 13 |
| | 60 - 100 | | 200 | 191 | 201 | 199 | 103 | 74 |
| | > 100 | | 0 | 2 | 0 | 2 | 1 | 0 |
| PR Interval, Aggregate | < 120 | msec | 13 | 11 | 11 | 12 | 2 | 3 |
| | 120 - 200 | | 227 | 214 | 212 | 202 | 109 | 77 |
| | > 200 | | 14 | 18 | 26 | 31 | 11 | 3 |
| QRS Duration, Aggregate | < 60 | msec | 0 | 0 | 1 | 0 | 4 | 3 |
| | 60 - 100 | | 187 | 177 | 163 | 160 | 90 | 68 |
| | > 100 | | 69 | 70 | 85 | 88 | 30 | 15 |
| QT Interval, Aggregate | < 200 | msec | 0 | 1 | 0 | 1 | 0 | 0 |
| | 200 - 430 | | 217 | 208 | 228 | 219 | 110 | 75 |
| | > 430 - 450 | | 30 | 23 | 14 | 20 | 11 | 9 |
| | > 450 - 500 | | 9 | 15 | 7 | 8 | 3 | 2 |
| | > 500 | | 0 | 0 | 0 | 0 | 0 | 1 |

| Parameter | Analysis Value Category | Analysis Unit | IPX203, Study Entry Baseline | IPX203, VISIT 7/ET | IR CD/LD, Study Entry Baseline | IR CD/LD, VISIT 7/ET | Not Assigned, Study Entry Baseline | Not Assigned, VISIT 7/ET |
|---|---|---|---|---|---|---|---|---|
| QTcF Interval, Aggregate | < 200 | msec | 0 | 1 | 0 | 1 | 0 | 0 |
| | 200 - 430 | | 194 | 196 | 199 | 204 | 94 | 66 |
| QTcF Interval, Aggregate | > 430 - 450 | | 43 | 31 | 35 | 28 | 18 | 13 |
| | > 450 - 500 | | 15 | 13 | 9 | 12 | 7 | 5 |
| | > 500 | | 3 | 4 | 3 | 2 | 3 | 1 |
| RR Interval, Aggregate | < 600 | msec | 3 | 5 | 1 | 2 | 4 | 1 |
| | 600 -1000 | msec | 197 | 190 | 199 | 200 | 98 | 70 |
| | > 1000 | msec | 55 | 50 | 46 | 45 | 20 | 14 |

Source: FDA analysis

**Table 54: ECG by Visit, Study B16-03, (Open-Label Safety Population)**

| | | | Analysis Value | | | | |
|---|---|---|---|---|---|---|---|
| Analysis Visit | Parameter | Analysis Unit | N | Mean | Min | Max | Median |
| Baseline | ECG Mean Ventricular Rate | beats/min | 413.00 | 69.43 | 41.00 | 106.00 | 69.00 |
| | PR Interval, Aggregate | msec | 409.00 | 166.21 | 0.00 | 290.00 | 168.00 |
| | QRS Duration, Aggregate | msec | 413.00 | 97.27 | 60.00 | 168.00 | 94.00 |
| | QT Interval, Aggregate | msec | 413.00 | 392.90 | 4.00 | 496.00 | 394.00 |
| | QTcF Interval, Aggregate | msec | 412.00 | 411.16 | 4.00 | 546.00 | 411.00 |
| | RR Interval, Aggregate | msec | 412.00 | 880.93 | 560.00 | 1460.00 | 867.50 |
| Visit 2 | ECG Mean Ventricular Rate | beats/min | 364.00 | 69.29 | 43.00 | 129.00 | 68.00 |
| | PR Interval, Aggregate | msec | 360.00 | 168.48 | 0.00 | 319.00 | 170.00 |
| | QRS Duration, Aggregate | msec | 364.00 | 96.67 | 0.00 | 170.00 | 94.00 |
| | QT Interval, Aggregate | msec | 364.00 | 393.30 | 189.00 | 510.00 | 391.00 |
| | QTcF Interval, Aggregate | msec | 362.00 | 413.34 | 234.00 | 888.00 | 410.00 |
| | RR Interval, Aggregate | msec | 363.00 | 875.76 | 0.00 | 1376.00 | 871.00 |
| Visit 3 | ECG Mean Ventricular Rate | beats/min | 347.00 | 69.08 | 46.00 | 126.00 | 69.00 |
| | PR Interval, Aggregate | msec | 343.00 | 170.13 | 0.00 | 936.00 | 169.00 |
| | QRS Duration, Aggregate | msec | 347.00 | 96.44 | 48.00 | 168.00 | 92.00 |
| | QT Interval, Aggregate | msec | 347.00 | 395.13 | 313.00 | 480.00 | 391.00 |
| | QTcF Interval, Aggregate | msec | 345.00 | 412.67 | 329.00 | 575.00 | 410.00 |
| | RR Interval, Aggregate | msec | 345.00 | 886.60 | 476.00 | 1279.00 | 866.00 |
| Visit 4 | ECG Mean Ventricular Rate | beats/ min | 346.00 | 69.40 | 42.00 | 133.00 | 68.00 |
| | PR Interval, Aggregate | msec | 339.00 | 167.07 | 0.00 | 268.00 | 170.00 |
| | QRS Duration, Aggregate | msec | 346.00 | 96.84 | 7.00 | 196.00 | 94.00 |
| | QT Interval, Aggregate | msec | 346.00 | 394.38 | 279.00 | 498.00 | 394.00 |
| | QTcF Interval, Aggregate | msec | 345.00 | 412.83 | 357.00 | 517.00 | 412.00 |
| | RR Interval, Aggregate | msec | 345.00 | 879.23 | 416.00 | 1428.00 | 874.00 |
| Visit 4/ET | ECG Mean Ventricular Rate | beats/min | 388.00 | 68.91 | 42.00 | 133.00 | 68.00 |
| | PR Interval, Aggregate | msec | 381.00 | 167.25 | 0.00 | 268.00 | 170.00 |

| | | | Analysis Value | | | | |
|---|---|---|---|---|---|---|---|
| **Analysis Visit** | **Parameter** | **Analysis Unit** | **N** | **Mean** | **Min** | **Max** | **Median** |
| | QRS Duration, Aggregate | msec | 388.00 | 96.64 | 7.00 | 196.00 | 94.00 |
| | QT Interval, Aggregate | msec | 388.00 | 394.96 | 279.00 | 498.00 | 394.00 |
| | QTcF Interval, Aggregate | msec | 387.00 | 413.51 | 324.00 | 836.00 | 412.00 |
| | RR Interval, Aggregate | msec | 387.00 | 884.94 | 76.00 | 1428.00 | 880.00 |

Source: FDA analysis

**Table 55: ECG Categorical Values, Study B16-03 (Open-Label Safety Population) (SAS)**

| Analysis Visit | Parameter | Standard Units | Analysis Value Category 1 | N |
|---|---|---|---|---|
| BASELINE | ECG Mean Ventricular Rate | beats/min | All | 413 |
| | | beats/min | < 60 | 83 |
| | | beats/min | 60 - 100 | 326 |
| | | beats/min | > 100 | 4 |
| | QT Interval, Aggregate | msec | All | 413 |
| | | msec | < 200 | 2 |
| | | msec | 200 - 430 | 361 |
| | | msec | > 430 - 450 | 35 |
| | | msec | > 450 - 500 | 15 |
| | QRS Duration, Aggregate | msec | All | 413 |
| | | msec | 60 - 100 | 285 |
| | | msec | > 100 | 128 |
| | RR Interval, Aggregate | msec | All | 412 |
| | | msec | < 600 | 5 |
| | | msec | 600 - 1000 | 325 |
| | | msec | > 1000 | 82 |
| | PR Interval, Aggregate | msec | All | 409 |
| | | msec | < 120 | 17 |
| | | msec | 120 - 200 | 351 |
| | | msec | > 200 | 41 |
| VISIT 2 | ECG Mean Ventricular Rate | beats/min | All | 364 |
| | | beats/min | < 60 | 60 |
| | | beats/min | 60 - 100 | 298 |
| | | beats/min | > 100 | 6 |
| | QT Interval, Aggregate | msec | All | 364 |
| | | msec | < 200 | 1 |
| | | msec | 200 - 430 | 313 |
| | | msec | > 430 - 450 | 37 |
| | | msec | > 450 - 500 | 12 |
| | | msec | > 500 | 1 |
| | QRS Duration, Aggregate | msec | All | 364 |
| | | msec | < 60 | 4 |
| | | msec | 60 - 100 | 248 |
| | | msec | > 100 | 112 |
| | RR Interval, Aggregate | msec | All | 363 |
| | | msec | < 600 | 8 |
| | | msec | 600 - 1000 | 298 |
| | | msec | > 1000 | 57 |

| Analysis Visit | Parameter | Standard Units | Analysis Value Category 1 | N |
|---|---|---|---|---|
| | PR Interval, Aggregate | msec | All | 360 |
| | | msec | < 120 | 13 |
| | | msec | 120 - 200 | 308 |
| | | msec | > 200 | 39 |
| VISIT 3 | ECG Mean Ventricular Rate | beats/min | All | 347 |
| | | beats/min | < 60 | 62 |
| | | beats/min | 60 - 100 | 280 |
| | | beats/min | > 100 | 5 |
| | QT Interval, Aggregate | msec | All | 347 |
| | | msec | 200 - 430 | 311 |
| | | msec | > 430 - 450 | 22 |
| | | msec | > 450 - 500 | 14 |
| | QRS Duration, Aggregate | msec | All | 347 |
| | | msec | < 60 | 1 |
| | | msec | 60 - 100 | 234 |
| | | msec | > 100 | 112 |
| | RR Interval, Aggregate | msec | All | 345 |
| | | msec | < 600 | 5 |
| | | msec | 600 - 1000 | 275 |
| | | msec | > 1000 | 65 |
| | PR Interval, Aggregate | msec | All | 343 |
| | | msec | < 120 | 16 |
| | | msec | 120 - 200 | 285 |
| | | msec | > 200 | 42 |
| VISIT 4 | ECG Mean Ventricular Rate | beats/min | All | 346 |
| | | beats/min | < 60 | 57 |
| | | beats/min | 60 - 100 | 283 |
| | | beats/min | > 100 | 6 |
| | QT Interval, Aggregate | msec | All | 346 |
| | | msec | 200 - 430 | 310 |
| | | msec | > 430 - 450 | 23 |
| | | msec | > 450 - 500 | 13 |
| | QRS Duration, Aggregate | msec | All | 346 |
| | | msec | < 60 | 3 |
| | | msec | 60 - 100 | 227 |
| | | msec | > 100 | 116 |
| | RR Interval, Aggregate | msec | All | 345 |
| | | msec | < 600 | 7 |
| | | msec | 600 - 1000 | 284 |
| | | msec | > 1000 | 54 |
| | PR Interval, Aggregate | msec | All | 339 |
| | | msec | < 120 | 14 |
| | | msec | 120 - 200 | 287 |
| | | msec | > 200 | 38 |
| VISIT 4/ET | ECG Mean Ventricular Rate | beats/min | All | 388 |
| | | beats/min | < 60 | 68 |
| | | beats/min | 60 - 100 | 314 |
| | | beats/min | > 100 | 6 |
| | QT Interval, Aggregate | msec | All | 388 |

| Analysis Visit | Parameter | Standard Units | Analysis Value Category 1 | N |
|---|---|---|---|---|
| | | msec | 200 - 430 | 347 |
| | | msec | > 430 - 450 | 24 |
| | | msec | > 450 - 500 | 17 |
| | QRS Duration, Aggregate | msec | All | 388 |
| | | msec | < 60 | 3 |
| | | msec | 60 - 100 | 258 |
| | | msec | > 100 | 127 |
| | RR Interval, Aggregate | msec | All | 387 |
| | | msec | < 600 | 8 |
| | | msec | 600 - 1000 | 313 |
| | | msec | > 1000 | 66 |
| | PR Interval, Aggregate | msec | All | 381 |
| | | msec | < 120 | 15 |
| | | msec | 120 - 200 | 327 |
| | | msec | > 200 | 39 |

Source: FDA analysis

## 13.5. Clinical Reference Laboratory Reference Ranges



# Appendix IV: Reference ranges and test methodologies

| Reference Interval List v08.2 | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test Name Full (Default report order) | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conventional Reference Interval Low | Conventional Reference Interval High | Conventional Unit | Conversion Factor Conv to SI | Conversion Factor SI to Conv | SI Reference Interval Low | SI Reference Interval High | SI Unit | Instrument Platform | Methodology |
| Hemoglobin | Hematology | 15 | y | 999 | y | M | 13.5 | 17.5 | g/dL | 10 | 0.1 | 135 | 175 | g/L | Siemens Advia | Siemens Cyanmethaemoglobin |
| Hemoglobin | Hematology | 15 | y | 999 | y | F | 12.0 | 16.0 | g/dL | 10 | 0.1 | 120 | 160 | g/L | Siemens Advia | Siemens Cyanmethaemoglobin |
| Hematocrit | Hematology | 15 | y | 999 | y | M | 40 | 52 | % | 0.01 | 100 | 0.40 | 0.52 | L/L | Siemens Advia | Siemens Calculated |
| Hematocrit | Hematology | 15 | y | 999 | y | F | 36 | 46 | % | 0.01 | 100 | 0.36 | 0.46 | L/L | Siemens Advia | Siemens Calculated |
| Red Cell Count | Hematology | 15 | y | 999 | y | M | 4.6 | 5.8 | x10E6/uL | 1 | 1 | 4.6 | 5.8 | x10E12/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Red Cell Count | Hematology | 15 | y | 999 | y | F | 4.1 | 5.2 | x10E6/uL | 1 | 1 | 4.1 | 5.2 | x10E12/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| White Cell Count | Hematology | 5 | y | 999 | y | M/F | 4.0 | 10.7 | x10E3/uL | 1 | 1 | 4.0 | 10.7 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Neutrophils (%) | Hematology | 7 | y | 999 | y | M/F | 43 | 74 | % | 1 | 1 | 43 | 74 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Total Lymphs (%) | Hematology | 13 | y | 999 | y | M/F | 20 | 44 | % | 1 | 1 | 20 | 44 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Monocytes (%) | Hematology | 7 | y | 999 | y | M/F | 3 | 10 | % | 1 | 1 | 3 | 10 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Eosinophils (%) | Hematology | 13 | y | 999 | y | M/F | 0 | 7 | % | 1 | 1 | 0 | 7 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Basophils (%) | Hematology | 31 | d | 999 | y | M/F | 0 | 2 | % | 1 | 1 | 0 | 2 | % | Siemens Advia | Siemens Flow cytometry/Light scatter |
| The Total relative White Cell Count may not equal exactly 100%. This is a consequence of the calculation and rounding of the individual cell type counts that constitute the total count. | | | | | | | | | | | | | | | | |
| Neutrophils (Abs) | Hematology | 7 | y | 999 | y | M/F | 1.6 | 7.4 | x10E3/uL | 1 | 1 | 1.6 | 7.4 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Total Lymphs (Abs) | Hematology | 13 | y | 999 | y | M/F | 1.0 | 4.0 | x10E3/uL | 1 | 1 | 1.0 | 4.0 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Monocytes (Abs) | Hematology | 7 | y | 999 | y | M/F | 0.1 | 0.9 | x10E3/uL | 1 | 1 | 0.1 | 0.9 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Eosinophils (Abs) | Hematology | 13 | y | 999 | y | M/F | 0.0 | 0.7 | x10E3/uL | 1 | 1 | 0.0 | 0.7 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Basophils (Abs) | Hematology | 31 | d | 999 | y | M/F | 0.0 | 0.2 | x10E3/uL | 1 | 1 | 0.0 | 0.2 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Platelets | Hematology | 15 | y | 999 | y | M/F | 150 | 350 | x10E3/uL | 1 | 1 | 150 | 350 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Sodium | Chemistry | 0 | y | 999 | y | M/F | 135 | 148 | mmol/L | 1 | 1 | 135 | 148 | mmol/L | Roche | Roche Indirect Ion Selective Electrode (ISE) |
| Potassium | Chemistry | 0 | y | 999 | y | M/F | 3.5 | 5.3 | mmol/L | 1 | 1 | 3.5 | 5.3 | mmol/L | Roche | Roche Indirect Ion Selective Electrode (ISE) |
| Chloride | Chemistry | 0 | y | 999 | y | M/F | 98 | 110 | mmol/L | 1 | 1 | 98 | 110 | mmol/L | Roche | Roche Indirect Ion Selective Electrode (ISE) |
| Bicarbonate | Chemistry | 0 | y | 999 | y | M/F | 22 | 32 | mmol/L | 1 | 1 | 22 | 32 | mmol/L | Roche | Roche Colorimetric PEP Carboxylase |
| BUN (Urea) | Chemistry | 19 | y | 999 | y | M/F | 6 | 25 | mg/dL | 0.357 | 2.801 | 2.1 | 8.9 | mmol/L | Roche | Roche Kinetic Urease |
| Creatinine | Chemistry | 19 | y | 999 | y | M | 0.7 | 1.2 | mg/dL | 88.4 | 0.0113 | 62 | 106 | umol/L | Roche | Roche Alkaline picrate rate blanked and compensated |
| Creatinine | Chemistry | 19 | y | 999 | y | F | 0.5 | 0.91 | mg/dL | 88.4 | 0.0113 | 44 | 80 | umol/L | Roche | Roche Alkaline picrate rate blanked and compensated |
| Uric Acid | Chemistry | 16 | y | 59 | y | M | 4.0 | 8.5 | mg/dL | 0.05948 | 16.8 | 0.24 | 0.51 | mmol/L | Roche | Roche Uricase/Peroxidase |
| Uric Acid | Chemistry | 16 | y | 999 | y | F | 2.5 | 7.5 | mg/dL | 0.05948 | 16.8 | 0.15 | 0.45 | mmol/L | Roche | Roche Uricase/Peroxidase |
| Uric Acid | Chemistry | 60 | y | 999 | y | M | 3.4 | 8.7 | mg/dL | 0.05948 | 16.8 | 0.20 | 0.52 | mmol/L | Roche | Roche Uricase/Peroxidase |
| Protein (Total) | Chemistry | 0 | y | 999 | y | M/F | 6.0 | 8.5 | g/dL | 10 | 0.1 | 60 | 85 | g/L | Roche | Roche Biuret End Point |
| Albumin | Chemistry | 0 | y | 999 | y | M/F | 3.2 | 5.5 | g/dL | 10 | 0.1 | 32 | 55 | g/L | Roche | Roche Bromocresol Green (BCG) |
| Globulins | Chemistry | 0 | y | 999 | y | M/F | 2.0 | 4.5 | g/dL | 10 | 0.1 | 20 | 45 | g/L | Roche | Calculated |
| Bilirubin (Total) | Chemistry | 8 | d | 999 | y | M/F | 0.0 | 1.2 | mg/dL | 17.1 | 0.0585 | 0 | 21 | umol/L | Roche | Roche DPD |
| Bilirubin (Conj) | Chemistry | 0 | y | 999 | y | M/F | 0.0 | 0.4 | mg/dL | 17.1 | 0.0585 | 0 | 7 | umol/L | Roche | Roche Jendrassik method |
| Bilirubin (Unconj) | Chemistry | 0 | y | 999 | y | M/F | 0.0 | 0.7 | mg/dL | 17.1 | 0.0585 | 0 | 12 | umol/L | Roche | Calculated |
| AST | Chemistry | 7 | y | 999 | y | M/F | 0 | 41 | U/L | 1 | 1 | 0 | 41 | U/L | Roche | Roche tris buffered NADH rate reaction - no P5P |
| ALT | Chemistry | 19 | y | 999 | y | M/F | 0 | 45 | U/L | 1 | 1 | 0 | 45 | U/L | Roche | Roche tris buffered NADH rate reaction - no P5P |
| AP (Alk Phos) | Chemistry | 18 | y | 999 | y | M | 40 | 129 | U/L | 1 | 1 | 40 | 129 | U/L | Roche | Roche AMP buffered pNPP rate reaction |
| AP (Alk Phos) | Chemistry | 18 | y | 999 | y | F | 35 | 104 | U/L | 1 | 1 | 35 | 104 | U/L | Roche | Roche AMP buffered pNPP rate reaction |
| LDH | Chemistry | 16 | y | 999 | y | M | 100 | 242 | U/L | 1 | 1 | 100 | 242 | U/L | Roche | Roche Tris buffered lactate to pyruvate rate reaction |
| LDH | Chemistry | 16 | y | 999 | y | F | 100 | 220 | U/L | 1 | 1 | 100 | 220 | U/L | Roche | Roche Tris buffered lactate to pyruvate rate reaction |
| Glucose | Chemistry | 0 | y | 999 | y | M/F | 70 | 140 | mg/dL | 0.05551 | 18.01477 | 3.9 | 7.8 | mmol/L | Roche | Roche Hexokinase |
| Calcium | Chemistry | 0 | y | 999 | y | M/F | 8.6 | 10.5 | mg/dL | 0.2495 | 4.0 | 2.14 | 2.62 | mmol/L | Roche | Roche Cresolphthalein Complexone |
| Phosphate | Chemistry | 13 | y | 59 | y | M/F | 2.7 | 4.8 | mg/dL | 0.3229 | 3.1 | 0.87 | 1.55 | mmol/L | Roche | Roche Phosphomolybdate complex |
| Phosphate | Chemistry | 60 | y | 999 | y | M/F | 2.1 | 5.0 | mg/dL | 0.3229 | 3.1 | 0.68 | 1.61 | mmol/L | Roche | Roche Phosphomolybdate complex |
| CK | Chemistry | 19 | y | 999 | y | M | 20 | 200 | U/L | 1 | 1 | 20 | 200 | U/L | Roche | Roche Imidazole buffered NADPH rate reaction |
| CK | Chemistry | 19 | y | 999 | y | F | 20 | 180 | U/L | 1 | 1 | 20 | 180 | U/L | Roche | Roche Imidazole buffered NADPH rate reaction |

# 11. (b) (4) Laboratory Reference Ranges and Methodologies

Reference Interval List v06.2

| Test Name Full (Default report order) | Department | Age Low | Age Low Unit | Age High | Age High Unit | Sex | Conventional Reference Interval Low | Conventional Reference Interval High | Conventional Unit | Conversion Factor Conv to SI | Conversion Factor SI to Conv | SI Reference Interval Low | SI Reference Interval High | SI Unit | Instrument Platform | Methodology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hemoglobin | Hematology | 15 | y | 999 | y | M | 13.5 | 17.5 | g/dL | 10 | 0.1 | 135 | 175 | g/L | Siemens Advia | Siemens Cyanmethaemoglobin |
| Hemoglobin | Hematology | 15 | y | 999 | y | F | 12.0 | 16.0 | g/dL | 10 | 0.1 | 120 | 160 | g/L | Siemens Advia | Siemens Cyanmethaemoglobin |
| Hematocrit | Hematology | 15 | y | 999 | y | M | 40 | 52 | % | 0.01 | 100 | 0.40 | 0.52 | L/L | Siemens Advia | Siemens Calculated |
| Hematocrit | Hematology | 15 | y | 999 | y | F | 36 | 46 | % | 0.01 | 100 | 0.36 | 0.46 | L/L | Siemens Advia | Siemens Calculated |
| Red Cell Count | Hematology | 15 | y | 999 | y | M | 4.6 | 6.8 | x10E6/uL | 1 | 1 | 4.6 | 6.8 | x10E12/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Red Cell Count | Hematology | 15 | y | 999 | y | F | 4.1 | 5.2 | x10E6/uL | 1 | 1 | 4.1 | 5.2 | x10E12/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| White Cell Count | Hematology | 5 | y | 999 | y | M/F | 4.0 | 10.7 | x10E3/uL | 1 | 1 | 4.0 | 10.7 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Neutrophils (%) | Hematology | 7 | y | 999 | y | M/F | 43 | 74 | % | 1 | 1 | 43 | 74 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Total Lymphs (%) | Hematology | 13 | y | 999 | y | M/F | 20 | 44 | % | 1 | 1 | 20 | 44 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Monocytes (%) | Hematology | 7 | y | 999 | y | M/F | 3 | 10 | % | 1 | 1 | 3 | 10 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Eosinophils (%) | Hematology | 13 | y | 999 | y | M/F | 0 | 7 | % | 1 | 1 | 0 | 7 | % | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Basophils (%) | Hematology | 31 | d | 999 | y | M/F | 0 | 2 | % | 1 | 1 | 0 | 2 | % | Siemens Advia | Siemens Flow cytometry/Light scatter |
| The Total relative White Cell Count may not equal exactly 100%. This is a consequence of the calculation and rounding of the individual cell type counts that constitute the total count. | | | | | | | | | | | | | | | | |
| Neutrophils (Abs) | Hematology | 7 | y | 999 | y | M/F | 1.6 | 7.4 | x10E3/uL | 1 | 1 | 1.6 | 7.4 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Total Lymphs (Abs) | Hematology | 13 | y | 999 | y | M/F | 1.0 | 4.0 | x10E3/uL | 1 | 1 | 1.0 | 4.0 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Monocytes (Abs) | Hematology | 7 | y | 999 | y | M/F | 0.1 | 0.9 | x10E3/uL | 1 | 1 | 0.1 | 0.9 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Eosinophils (Abs) | Hematology | 13 | y | 999 | y | M/F | 0.0 | 0.7 | x10E3/uL | 1 | 1 | 0.0 | 0.7 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Peroxidase |
| Basophils (Abs) | Hematology | 31 | d | 999 | y | M/F | 0.0 | 0.2 | x10E3/uL | 1 | 1 | 0.0 | 0.2 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Platelets | Hematology | 15 | y | 999 | y | M/F | 150 | 350 | x10E3/uL | 1 | 1 | 150 | 350 | x10E9/L | Siemens Advia | Siemens Flow cytometry/Light scatter |
| Sodium | Chemistry | 0 | y | 999 | y | M/F | 135 | 148 | mmol/L | 1 | 1 | 135 | 148 | mmol/L | Roche | Roche Indirect Ion Selective Electrode (ISE) |
| Potassium | Chemistry | 0 | y | 999 | y | M/F | 3.5 | 5.3 | mmol/L | 1 | 1 | 3.5 | 5.3 | mmol/L | Roche | Roche Indirect Ion Selective Electrode (ISE) |
| Chloride | Chemistry | 0 | y | 999 | y | M/F | 98 | 110 | mmol/L | 1 | 1 | 98 | 110 | mmol/L | Roche | Roche Indirect Ion Selective Electrode (ISE) |
| Bicarbonate | Chemistry | 0 | y | 999 | y | M/F | 22 | 32 | mmol/L | 1 | 1 | 22 | 32 | mmol/L | Roche | Roche Colorimetric PEP Carboxylase |
| BUN (Urea) | Chemistry | 19 | y | 999 | y | M/F | 6 | 25 | mg/dL | 0.357 | 2.801 | 2.1 | 8.9 | mmol/L | Roche | Roche Kinetic Urease |
| Creatinine | Chemistry | 19 | y | 999 | y | M | 0.7 | 1.2 | mg/dL | 88.4 | 0.0113 | 62 | 106 | umol/L | Roche | Roche Alkaline picrate rate blanked and compensated |
| Creatinine | Chemistry | 19 | y | 999 | y | F | 0.5 | 0.91 | mg/dL | 88.4 | 0.0113 | 44 | 80 | umol/L | Roche | Roche Alkaline picrate rate blanked and compensated |
| Uric Acid | Chemistry | 16 | y | 59 | y | M | 4.0 | 8.5 | mg/dL | 0.05948 | 16.8 | 0.24 | 0.51 | mmol/L | Roche | Roche Uricase/Peroxidase |
| Uric Acid | Chemistry | 16 | y | 999 | y | F | 2.5 | 7.5 | mg/dL | 0.05948 | 16.8 | 0.15 | 0.45 | mmol/L | Roche | Roche Uricase/Peroxidase |
| Uric Acid | Chemistry | 60 | y | 999 | y | M | 3.4 | 8.7 | mg/dL | 0.05948 | 16.8 | 0.20 | 0.52 | mmol/L | Roche | Roche Uricase/Peroxidase |
| Protein (Total) | Chemistry | 0 | y | 999 | y | M/F | 6.0 | 8.5 | g/dL | 10 | 0.1 | 60 | 85 | g/L | Roche | Roche Biuret End Point |
| Albumin | Chemistry | 0 | y | 999 | y | M/F | 3.2 | 5.5 | g/dL | 10 | 0.1 | 32 | 55 | g/L | Roche | Roche Bromocresol Green (BCG) |
| Globulins | Chemistry | 0 | y | 999 | y | M/F | 2.0 | 4.5 | g/dL | 10 | 0.1 | 20 | 45 | g/L | Roche | Calculated |
| Bilirubin (Total) | Chemistry | 8 | d | 999 | y | M/F | 0.0 | 1.2 | mg/dL | 17.1 | 0.0585 | 0 | 21 | umol/L | Roche | Roche DPD |
| Bilirubin (Conj) | Chemistry | 0 | y | 999 | y | M/F | 0.0 | 0.4 | mg/dL | 17.1 | 0.0585 | 0 | 7 | umol/L | Roche | Roche Jendrassik method |
| Bilirubin (Unconj) | Chemistry | 0 | y | 999 | y | M/F | 0.0 | 0.7 | mg/dL | 17.1 | 0.0585 | 0 | 12 | umol/L | Roche | Calculated |
| AST | Chemistry | 7 | y | 999 | y | M/F | 0 | 41 | U/L | 1 | 1 | 0 | 41 | U/L | Roche | Roche tris buffered NADH rate reaction - no P5P |
| ALT | Chemistry | 19 | y | 999 | y | M/F | 0 | 45 | U/L | 1 | 1 | 0 | 45 | U/L | Roche | Roche tris buffered NADH rate reaction - no P5P |
| AP (Alk Phos) | Chemistry | 18 | y | 999 | y | M | 40 | 129 | U/L | 1 | 1 | 40 | 129 | U/L | Roche | Roche AMP buffered pNPP rate reaction |
| AP (Alk Phos) | Chemistry | 18 | y | 999 | y | F | 35 | 104 | U/L | 1 | 1 | 35 | 104 | U/L | Roche | Roche AMP buffered pNPP rate reaction |
| LDH | Chemistry | 16 | y | 999 | y | M | 100 | 242 | U/L | 1 | 1 | 100 | 242 | U/L | Roche | Roche Tris buffered lactate to pyruvate rate reaction |
| LDH | Chemistry | 16 | y | 999 | y | F | 100 | 220 | U/L | 1 | 1 | 100 | 220 | U/L | Roche | Roche Tris buffered lactate to pyruvate rate reaction |
| Glucose | Chemistry | 0 | y | 999 | y | M/F | 70 | 140 | mg/dL | 0.05551 | 18.01477 | 3.9 | 7.8 | mmol/L | Roche | Roche Hexokinase |
| Calcium | Chemistry | 0 | y | 999 | y | M/F | 8.6 | 10.5 | mg/dL | 0.2495 | 4.0 | 2.14 | 2.62 | mmol/L | Roche | Roche Cresolphthalein Complexone |
| Phosphate | Chemistry | 13 | y | 59 | y | M/F | 2.7 | 4.8 | mg/dL | 0.3229 | 3.1 | 0.87 | 1.55 | mmol/L | Roche | Roche Phosphomolybdate complex |
| Phosphate | Chemistry | 60 | y | 999 | y | M/F | 2.1 | 5.0 | mg/dL | 0.3229 | 3.1 | 0.68 | 1.61 | mmol/L | Roche | Roche Phosphomolybdate complex |
| CK | Chemistry | 19 | y | 999 | y | M | 20 | 200 | U/L | 1 | 1 | 20 | 200 | U/L | Roche | Roche Imidazole buffered NADPH rate reaction |
| CK | Chemistry | 19 | y | 999 | y | F | 20 | 180 | U/L | 1 | 1 | 20 | 180 | U/L | Roche | Roche Imidazole buffered NADPH rate reaction |

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

ELIZABETH HABERFELD
06/30/2023 04:10:05 PM

NATALIE B GETZOFF
06/30/2023 04:11:29 PM