9. DOCUMENTATION OF STATISTICAL METHODS

- Statistical Analysis Plan, Version 1, 29 September 2017

STATISTICAL ANALYSIS PLAN

Study Title:	**A RANDOMIZED, MULTIPLE DOSE STUDY TO ASSESS THE PHARMACOKINETICS AND PHARMACODYNAMICS OF IPX203 IN SUBJECTS WITH ADVANCED PARKINSON'S DISEASE**
Name of Test Drug:	IPX203
Protocol Number:	IPX203-B16-01
Protocol Version (Date):	Original, 08Aug16 Amendment 1, 01Sep16 Amendment 2, 05Oct16
Analysis Type:	Final
Analysis Plan Version:	Version 1
Analysis Plan Date:	29Sep17
Analysis Plan Author:	Phillip Dinh, PhD

SPONSOR
Impax Laboratories, Inc.,
acting through its Impax Specialty Pharma division (Impax)
30831 Huntwood Ave.
Hayward, CA 94544

SIGNATURE PAGE

Authored by:

Phillip Dinh, PhD
Director, Statistics
29 SEP 17
Date

Reviewed and Approved by:

Nishit Modi, PhD
Vice President, Clinical Pharmacology
29 SEP 17
Date

Robert Rubens, MD, MBA
Senior Director, Clinical Development
29 SEP 17
Date

Elizabeth Lindemulder, MS
Senior Statistical Analyst, Programming
29SEP17
Date

Sarita Khanna, PhD
Senior Director, Biostatistics and Data Management
29SEP17
Date

Michelle Landolfi, PhD
Senior Director, Regulatory
29 SEP 17
Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BLOCF	baseline observation carried forward
BLQ	below the limit of quantification
BMI	body mass index
CD	carbidopa
CLE	carbidopa/levodopa/entacapone
CR	controlled release
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
ECG	electrocardiogram
ER	extended release
IR	immediate release
IWRS	interactive web response system
LD	levodopa
LOCF	last observation carried forward
LOQ	lower limit of quantification
MAO	monoamine oxidase
MDS-UPDRS	Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
PK	pharmacokinetic(s)
QTc	corrected QT

QTcF	Fridericia's corrected QT
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TLFs	tables, listings, figures

PHARMACOKINETIC TERMS AND DEFINITIONS

Accumulation ratio	parameter used to quantify the extent to which a compound accumulates after repeated dosing relative to the first dose, defined as the ratio of AUC over a dosing interval at steady state divided by AUC over the same interval following a single dose, calculated as (AUC_{tau}(Day 15)/AUC_{tau}(Day 1)).
AUC	area under the curve
AUC_{s-t} or AUC(s-t)	area under the curve from time s to time t, denote partial AUC values
AUC_{inf} or $AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to time infinity for one treatment dose
AUC_{last}	area under the plasma concentration-time curve up to the last measurable concentration
$AUC_{\%ext}$	area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of AUC_{0-inf}
AUC_{tau}	area under the plasma concentration-time curve over a dosing interval
BA	bioavailability [defined as (AUC_{inf}/dose) of test treatment/(AUC_{inf}/dose of reference treatment)]
C_{avg}	average observed plasma concentration (calculated on Day 15 of treatment as AUC_{0-10}/10)
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
C_{tau}	observed plasma concentration at time tau following first dose on a treatment day at the nearest sampling time prior to the subsequent (2nd) dose
Dur(>50%C_{max})	duration of plasma concentrations above 50% of C_{max} value
Fluctuation index	peak-trough fluctuation, calculated as [(C_{max}(Day15)-C_{min}(Day15)) /C_{avg}(Day15)]
k	apparent elimination rate constant (denoted by λ_z in the protocol)
T(430ng/mL)	time to reach a concentration of 430 ng/mL
T(50%Cmax)	time to reach a concentration of 50% of C_{max}
T(1000ng/mL)	time to reach a concentration of 1000 ng/mL
Tau	dosing interval (defined as the interval between first and second doses on a treatment day (Day 15))

Time invariance ratio	parameter used to assess if the pharmacokinetics vary over time during repeated dosing, quantifies how the concentration-time profile at steady state compares to the profile on Day 1, calculated as AUC_{tau}(Day 15) / AUC_{inf}(Day 1)
T_{max}	time to maximum observed plasma concentration
$t_{1/2}$	apparent elimination half-life

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, listings, and figures (TLFs) in the clinical study report (CSR) for Study IPX203-B16-01. This SAP is based on the study protocol amendment 2 dated 05OCT16. The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

This is a randomized, open-label, rater-blinded, multicenter, 2-treatment, 2-period, multiple-dose crossover study. Approximately 30 advanced Parkinson's disease (PD) subjects will be randomized to 1 of 2 dosing sequences. The study duration will be approximately 8 weeks, including the screening period.

As shown in Figure 1, this study will consist of 4 study visits after Screening: Day 1 of each treatment period (Visits 1 and 3), and Day 15 of each treatment period (Visits 2 and 4). Study Exit procedures are done at the end of Visit 4 or within 3 days of Visit 4, or during an early withdrawal. Between treatment periods, subjects will return to their prestudy PD medication regimen during the 1-week (± 2 days) washout period. Subjects may continue to take allowed non-carbidopa (CD)-levodopa (LD) based PD medications throughout the study if documented in their prestudy regimen and if dosing regimens have been stable for at least 4 weeks prior to Visit 1.

Within 2 weeks following Screening, on each of the 3 days prior to Visit 1, eligible subjects will complete their PD and Dosing diaries, and will wear the Kinesia 360 sensor bands on the more affected side at home immediately after waking. Subjects will be instructed to take their last dose of CD-LD no later than 10:00 PM on the evening prior to Visits 1 and 3. The first morning dose of study medication will be administered at the study site. On Day 1 of the immediate release (IR) CD-LD treatment period, subjects will start with a single dose of their usual prestudy first morning IR CD-LD dose. On Day 1 of the IPX203 treatment period, subjects will start with a single dose of IPX203 based on their usual prestudy first morning IR CD-LD dose according to the guidance provided in Table 1. During each treatment period subjects will dose for 15 days with study medication. During the IR CD-LD treatment period, the initial dosing regimen of IR CD-LD will be the same as the subject's stable prestudy regimen unless they were taking a single daily bedtime dose of controlled release (CR) CD-LD, either alone or in combination with IR CD-LD, in which case, the CR CD-LD dose will be discontinued and substituted with a 1:1 milligram-equivalent IR CD-LD dose. A "bedtime dose" is defined as a dose of CR CD-LD taken within 1 hour of the subject's normal nighttime sleep period. During the IPX203 treatment period, subjects are assigned their initial IPX203 dosing regimen according to the guidance provided in Table 1 and Table 2. This regimen is based on each individual's prestudy IR CD-LD morning dose and daily dosing regimen. The typical dosing regimen for IPX203 will be three times a day, dosed approximately every 7 to 8 hours. Some subjects may require more or less frequent dosing to optimize therapeutic effect (minimize "Off" time without causing troublesome dyskinesia or other dopaminergic side effects). Nighttime dosing of study medication is allowed as needed with the exception of the evening prior to Day 15 (withhold dosing for at least 5 hours before arriving at the site) of each treatment period. Subjects may continue to take allowed non-

CD-LD based PD medications throughout the study if documented in their prestudy regimen and if dosing regimens have been stable for at least 4 weeks prior to Visit 1.

During Days 1 through 9 of both treatment periods, investigators may adjust each subject's study medication regimen if necessary to optimize efficacy and safety.

Pharmacokinetic and pharmacodynamic measures are assessed in the clinic for up to 8 hours postdose on Day 1 of each treatment period (Visits 1 and 3), and for up to 10 hours on Day 15 of each treatment period (Visits 2 and 4). Additionally, on each of the 3 days prior to Visits 1, 2, and 4, subjects will complete the PD and Dosing diaries, and use the Kinesia 360 sensor bands on the ankle and wrist of their more affected side immediately after waking.

Figure 1: Study Flow Chart

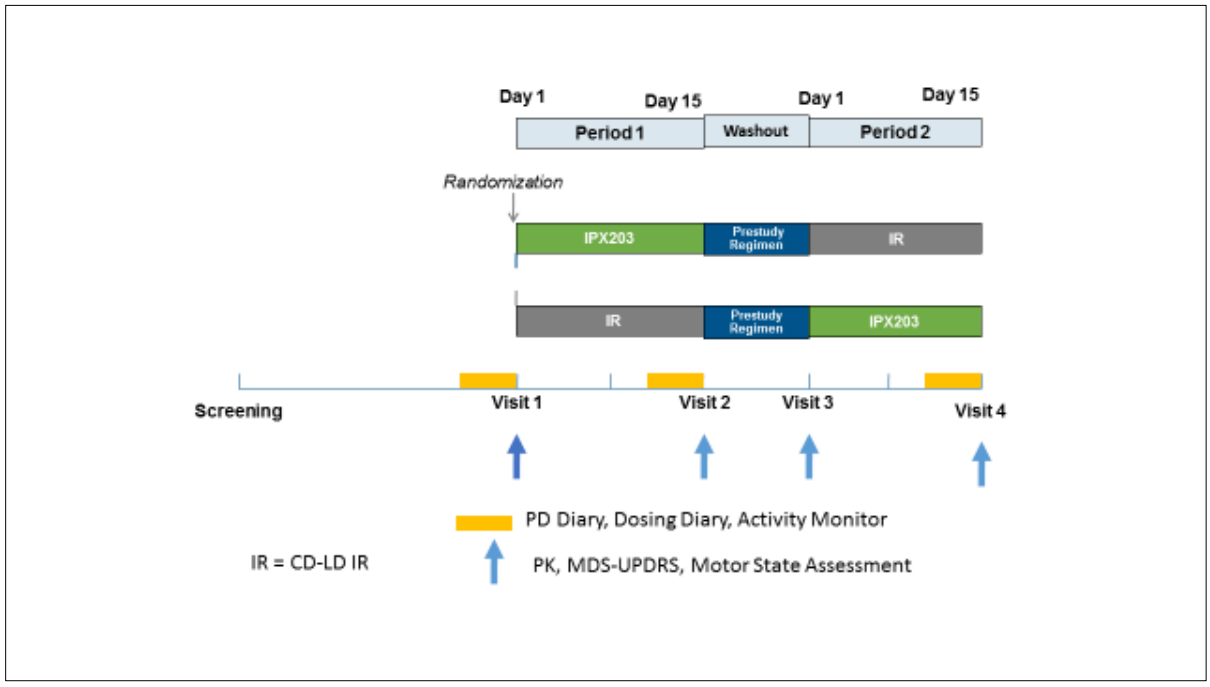

Table 1: Day 1 In-clinic Dosing — First Morning Dose of Study Medication

Prestudy Morning IR LD Dose (mg)	IR CD-LD LD (mg) (100 mg Tablets)	IPX203 LD (mg) (180 mg and 270 mg Capsules)
100	100 (1 tablet)	360 (180 mg × 2 capsules)
150	150 (1.5 tablets)	540 (270 mg × 2 capsules)
200	200 (2 tablets)	720 (270 mg × 2 capsules plus 180 mg × 1 capsule)
250	250 (2.5 tablets)	900 (270 mg × 2 capsules plus 180 mg × 2 capsules)

Table 2: Initial IPX203 LD Dosing Regimen Subsequent to IPX203 Morning Dose Based on Prestudy Regimen of LD

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

1.2. Sample Size and Power

Assuming a difference of 1.75 hours between the treatments in "Off" time and the standard deviation of the treatment differences to be 3 hours, this 2-way crossover design will have 80% power to detect a difference between IPX203 and IR CD-LD with at least 26 subjects completing the study (level of significance = 0.05).

To allow for a dropout rate of approximately 15%, at least 30 subjects will be randomized to ensure at least 26 completers.

2. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

The database will be locked and final analysis of the data will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, descriptive statistics (the number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level, without multiplicity adjustment.

2.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, listing, and figure.

2.1.1. Screened Analysis Set

The screened analysis set (Screened) includes all subjects who were screened for the study.

2.1.2. Screened but Not Treated Analysis Set

The screened but not treated analysis set includes all subjects who were screened for the study but were not dosed with a study drug.

2.1.3. Randomized Analysis Set

The randomized analysis set (Randomized) includes all subjects who were randomized into the study and received at least one dose of study drug.

2.1.4. Completers Analysis Set

The completers analysis set (Completers) includes all subjects who completed both treatment periods of the study and were indicated as “Completed” on the case report form (CRF) study disposition form.

2.1.5. Diary Completers Analysis Set

The diary completer analysis set (PD Diary Completers) includes all subjects who received both treatments and had 1 day of evaluable PD diary at Visits 1, 2, and 4. An evaluable PD diary day will have no more than 4 half-hour entries missing.

2.1.6. Pharmacodynamic Completers Analysis Set

The pharmacodynamic completer analysis set (Pharmacodynamic completers) includes all subjects who received both treatments and had at least 1 predose and 4 postdose motor state assessments at each visit.

2.1.7. Kinesia 360 Completers Analysis Set

The Kinesia 360 completer analysis set (Kinesia completers) includes all subjects who received both treatments and had 1 day of evaluable Kinesia data at Visits 1, 2, and 4. Evaluable Kinesia data is defined as having at least 2 hours of Kinesia data for the particular day.

2.1.8. Pharmacokinetic (PK) Completers Analysis Set

The PK completers analysis set (PK Completers) includes all subjects for whom at least one PK parameter (AUC_{last} or C_{max}) was calculable on Days 1 and 15 for both treatments.

2.2. Randomization and Description of Study Drug

Subjects are randomly assigned to one of the two treatment sequences via the interactive web response system (IWRS) in a 1:1 ratio. The two treatment sequences are as follows

Table 3: Randomization Schedule for IPX203-B16-01

	Treatment Period 1	Treatment Period 2
Sequence 1	IPX203	IR CD-LD
Sequence 2	IR CD-LD	IPX203

2.3. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy and safety analyses. PK endpoints are evaluated overall and by dose levels.

2.4. Missing Data and Outliers

2.4.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified below.

2.4.1.1. Imputation Method for PD Diary Data

When more than one status is checked at a particular time point in the PD Diary or the Assessment of Subject's Motor State, the worse result is selected as the final reported outcome. The selection order is defined below:

1. Off
2. On with Troublesome Dyskinesia
3. Asleep
4. On with Nontroublesome Dyskinesia
5. On without Dyskinesia

Imputation of missing data for subject PD diaries will be required if the PD diary is incomplete over a 24-hour period (from 6:00 am to 6:00 am the next day). In this case, the method of imputation depends on the amount and pattern of missing data:

- If more than four half-hour time intervals are missing, then that particular day will not be included in the analysis.
- If a half-hour time interval is missing and the observations on either side of the time interval are not missing, then the missing time interval will be imputed by assigning a value of the previous measurement for the first 15 minutes and the value of the next measurement for the second 15 minutes.
- If two or more consecutive half-hour time intervals are missing, not to exceed a total of four, and these time intervals are available from other days of the visit, then the following rules will be applied:
  - For missing values on Day -3, data from Day -2 will be used for imputation for the same time intervals. If Day -2 data is also incomplete then Day -1 data will be used.
  - For missing values on Day -2, data from Day -1 will be used for imputation if available; otherwise Day -3 data will be used.
  - For missing values on Day -1, data from Day -2 will be used for imputation if available; otherwise Day -3 data will be used for imputation.
  - If data at the same time period is missing across all days, the individual missing half-hour intervals will be split into two periods, with the first half-interval being imputed with data from the immediate previous nonmissing time period and the second half-interval being imputed with the next nonmissing time interval.

2.4.1.2. Imputation Method for Assessment of Subject's Motor State

Imputation of missing data for Assessment of Subject's Motor State is affected by whether or not subjects receive rescue medication on Day 1 and whether or not the missingness is monotone. The imputation rules are as follows:

- Prior to or equal to time of rescue medication:
  - If surrounding values exist and are prior to rescue time, the missing results are assigned half the missing time to the previous value and half the missing time to the next value.
  - If the next result occurs after rescue or if next result is not available, then assign the entire missing time to the previous value (a.k.a "last observation carried forward" (LOCF)). For example, if a subject has
    - assessment at hour 4,
    - missing assessment at hour 4.5,
    - rescue at hour 4.75,
    - assessment at hour 5.

In this case, the assessment at hour 4 will be carried forward to the hour 4.5.

- Following rescue medication: Missing results after rescue are assigned "Off." Actual values after rescue are not used in analysis. Instead, values are assigned the "Off" status.

For Day 15, all assessments, regardless of whether they were done before or after redose, will be used in analyses. If there is a missing assessment, half of the missing time will be assigned to the previous value and half of the missing time will be assigned to next value. If next value does not exist, then assign the entire missing time to the previous value (LOCF).

2.4.1.3. Imputation Method for the Movement Disorder Society Version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

- Imputation of missing individual questions:

  For each assessment time point, if results are missing for a particular part of the MDS-UPDRS questionnaire, the missing items are assigned the average value of the other items in that part. The numbers of missing items allowed for imputation are as follows (Goetz 2015).

  – For Part I (13 questions), up to 1 result is imputed,

  – For Part II (13 questions), up to 2 results are imputed,

  – For Part III (33 questions), up to 7 results are imputed,

  – For Part IV (6 questions), no imputation is done.

  If the number of missing items in each part is more than the above, the entire assessment for that part will be excluded from the analysis.

- Results included in predose average calculations:
  Predose average values are the mean of the results at time points -1, -0.5, and 0 hours.

- Imputation of results for particular time points for Day 1:

  – Prior to or equal to time of rescue medication:

    o If actual results exist before and after the missing time point, calculate the average of the results at time points just prior and immediately after the missing value. Assign the missing value to that average.

    o If actual results only exist prior to the missing time point then assign the missing value to the last actual result available (LOCF).

  – Following rescue medication:

    o Missing values at time points following rescue medication were assigned the predose average value. Actual values observed at time points following rescue medication are not used in analysis. Instead, values are assigned the predose average value and are used in analysis.

- Imputation method prior to or equal to time of rescue medication for Day 1 also applies to all time points for Day 15.

- Postdose averages are the mean of the results from hour 1 to hour 8 for Day 1 and hour 1 to hour 10 for Day 15. Postdose average for Day 1 includes actual results prior to or equal to rescue time, imputed results prior to or equal to rescue time when actual results are missing, and imputed results following rescue.

2.4.1.4. Imputation Method for Missing Vitals and Electrocardiogram (ECG)

- If Vitals and ECG measurements expected at End of Study are missing, they will be imputed using the last actual postdose result available.

2.4.2. Outliers

All data will be included in the data analysis. No sensitivity analysis will be conducted with respect to any potential outliers.

2.5. Data Handling Conventions and Transformations

Selected by-subject listings will be presented for all subjects in the Randomized analysis set and Screened but Not Treated analysis set and sorted by subject ID number, treatment period, and study day (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order by preferred terms (for AEs) or medication verbatim (for concomitant medications) within subject.

Concentrations of LD and CD at predose that are below the limit of quantification (BLQ) will be listed as BLQ of the respective analyte. For analyses at predose, BLQ values are set to zero. For analyses at postdose, they are considered as missing. Any predose or postdose concentrations that were deemed "Not Reportable" by the Analytical Lab are excluded from the PK analysis. Plasma concentrations after rescue medication for Day 1 will not be included in the calculation of Day 1 PK parameters.

2.6. Definitions of Baseline and Study Day

2.6.1. Definition of Baseline

For diary data and Kinesia360 data, baseline is defined as the average of 3 diary/kinesia days before Visit 1.

For pharmacodynamics data and safety, baseline is defined as the last value before dosing.

For certain MDS-UPDRS analyses, predose values will also be used for assessing of change. Predose value is defined as the average of the results at time points -1 hour, -0.5 hours, and Predose (0 hour).

2.6.2. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

3. SUBJECT DISPOSITION

3.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each investigator for the screened, randomized, completed, and early terminated subjects.

A summary of subject disposition will be provided by treatment group and period. This summary will present the number of subjects who received treatment, discontinued treatment and the reasons for early discontinuation. The summary will be based on the randomized analysis set.

3.2. Extent of Prestudy Drug Exposure and Study Drug Exposure

3.2.1. Prestudy Levodopa Dosing

Duration of prestudy levodopa dosing will be summarized for the Screened, Randomized, Completers, and Early Terminated subjects. Frequencies (< 3, 3 to < 6, 6 to < 9, 9 to < 12, ≥ 12 years) and descriptive statistics will be presented.

Total daily dose of prestudy levodopa will be summarized for the Screened, Randomized, Completers, and Early Terminated subjects. Frequencies of IR CD-LD, CR CD-LD, and total LD (< 400, 400 to < 800, 800 to < 1200, 1200 to < 1600, and ≥ 1600 mg) and descriptive statistics will be presented.

Frequencies and durations of current IR CD-LD, CR CD-LD dosing, and the first morning IR CD-LD dose prestudy will also be summarized for the Screened, Randomized, Completers, and Early Terminated subjects.

3.2.2. Study Drug Exposure

3.2.2.1. Study Drug Exposure at Study Site

The distribution of levodopa dose administered at the study site on Day 1 and Day 15 will be summarized by dose (Dose 1, 2, 3, and 4) between the two treatment groups using descriptive statistics (N, mean, SD, median, min, max). Categorical summaries (<= 100 mg, 101 to 150 mg, 151 to 200 mg, 201 to 400 mg, 401 to 600 mg, 601 to 800 mg, > 800 mg) will also be tabulated by dose for Day 1 and Day 15.

The distribution of time to rescue (Day 1) will be provided along with categories: < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, and ≥ 8 hours. The proportion of subjects who required rescue between the two treatment groups will also be summarized.

A Cox regression model adjusting for period, sequence, and treatment will be used to compare the time to rescue between treatment groups. In this analysis, if a subject does not need rescue, the subject will be censored at the last observation of MDS-UPDRS, vital signs, and PK samples for the particular visit.

Likewise, the distribution of time to redose (Day 15) will be provided along with categories: < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, and ≥ 8 hours. The proportion of subjects who required redose between the two treatment groups will also be summarized.

A Cox regression model adjusting for period, sequence, and treatment will be used to compare the time to redose between treatment groups. In this analysis, if a subject does not need redose, the subject will be censored at the last observation of MDS-UPDRS, vital signs, and PK samples for the particular visit.

In the analyses of time to rescue (Day 1) and time to redose (Day 15), if an in-clinic dose is taken beyond the last assessment (8 hours for Visit 1 and 10 hours for Visit 2), then this in-clinic dose is not considered a rescue dose (Day 1) or redose (Day 15).

3.2.2.2. Study Drug Dosing Diary

The actual first morning dose at stable dosing versus the recommended first morning dose will be cross-tabulated for IPX203. The recommended first morning dose is based on Table 1.

The actual stable dosing regimen versus the recommended dosing regimen will also be cross-tabulated for IPX203. The recommended dosing regimen is based on Table 1 and Table 2. The amount of adjustment (in mg) will also be summarized for each dose comparing the actual dose versus the recommended dose for IPX203.

The actual dosing is based on the 3-day dosing diary before Day 15 visit of each treatment period where the subjects are expected to be on stable dosing. If there is a deviation from the stable dosing over the 3-day before Day 15 visit, the mode of the three days will be used.

The distribution and summary of levodopa dosing frequency based on the dosing diary will be provided. The number and percentage of subjects with 2, 3, 4, 5, 6, and > 6 doses/day will be tabulated for each treatment group. The average number of doses/day will be compared between the two treatment groups using a mixed effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. The degrees of freedom for the denominator will be estimated using the Kenward-Roger method. The "AR(1)" within subject covariance structure will be employed. If convergence is an issue, a "Variance Components" covariance structure will be employed.

Average daytime dosing interval and nighttime dosing interval will be summarized based on the dosing diary and compared between the two treatment groups using a mixed effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. The degrees of freedom for the denominator will be estimated using the Kenward-Roger method. The "AR(1)" within subject covariance structure will be employed. If convergence is an issue, a "Variance Components" covariance structure will be employed. The dosing interval between Dose 1 and Dose 2 will also be compared in a similar manner. For other dosing intervals (between Dose 2 and Dose 3, Dose 3 and Dose 4, etc.), only descriptive summaries will be provided.

The final total daily LD dose for IPX203 and IR CD-LD and the ratio of LD of IPX203/IR CD-LD will be summarized descriptively.

3.2.2.3. Dosing Adjustment

The number of titration steps to stable dosing will be summarized descriptively as well as categorically (0, 1 to 2, 3 to 4, 5 to 6, and > 6 steps).

The number of days to stable dosing will be summarized descriptively as well as categorically (0, 1 to 2 days, 3 to 4 days, 5 to 6 days, 7 to 9 days, and > 9 days).

3.3. Protocol Deviations

Protocol deviations, such as subjects who did not meet eligibility criteria at study entry and those occurring after subjects entered the study, are documented during routine monitoring. Details of protocol deviations for each study site will be provided by the Clinical Operations Group to the Statistics and Data Management Group prior to database finalization. These protocol deviations will be listed.

4. BASELINE CHARACTERISTICS

4.1. Demographics

Subject demographic variables (age, sex, race, and ethnicity) will be summarized for the Screened, Randomized, Completers, and Early Terminated subjects using descriptive statistics. Age at baseline is calculated in years at screening date.

A by-subject demographic listing, including the prestudy treatment LD dose in mg (first morning dose, most frequent afternoon/evening dose, and total daily dose), will be provided by subject ID number in ascending order.

4.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), and body mass index (BMI; in kg/m^2). These baseline characteristics will be summarized for the Screened, Randomized, Completers, and Early Terminated subjects using descriptive statistics for both continuous and categorical variables.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order, along with the demographic information.

4.3. Parkinson's Disease Characteristics and Measures

PD characteristics and measures will be summarized for Screened, Randomized, Completers, and Early Terminated subjects.

Age at onset of PD diagnosis will be summarized using continuous descriptive statistics (N, mean, SD, median, min, max) as well as frequencies and percentages of subjects with onset age between < 55, 55 to < 65, 65 to < 75, and ≥ 75 years.

Duration of PD will be summarized using continuous descriptive statistics (N, mean, SD, median, min, max) as well as frequencies and percentages of subjects with PD duration < 2, 2 to < 5, 5 to < 10, 10 to < 15, 15 to < 20, ≥ 20 years.

Descriptive statistics as well as frequencies and percentages of subjects with Hoehn and Yahr PD stages (in "On" state) I, II, III, IV and Montreal Cognitive Assessment (MoCA) (in "On" state) (< 24, 24 to < 26, 26 to < 28, 28 to < 30, 30) will be provided.

Descriptive statistics of MDS-UPDRS scores in the "On" state (Parts I, II, III, IV, II + III, total score) and the "Off" state (Part III) will be provided.

The total "Off" time, "On" time without dyskinesia, "On" time with nontroublesome dyskinesia, "On" time with troublesome dyskinesia, and time asleep will be summarized based on the subjects' diaries for the Randomized, Completers, and Early Terminated subjects. The total "On" time without troublesome dyskinesia (ie, "Good on" time = total "On" time without dyskinesia plus "On" time with nontroublesome dyskinesia) will also be summarized.

4.4. Medical History and Physical Findings

Summaries of clinically significant medical history and abnormal physical findings at baseline will be provided for all Screened, Randomized, Completers, and Early Terminated subjects.

5. EFFICACY AND PHARMACODYNAMIC ANALYSES

For all primary and secondary endpoints analyses using mixed-effect analysis of variance (ANOVA) or analysis of covariance (ANCOVA), the degrees of freedom for the denominator will be estimated using the Kenward-Roger method. The within subject covariance structure will be "AR(1)." If convergence is an issue, a "Variance Components" covariance structure will be employed.

5.1. Primary Endpoint

The primary efficacy parameter for this study is the average percent "Off" time during waking hours based on subject PD diaries collected at the end of each treatment period. For each day it will be calculated as the number of half-hour intervals in which "Off" is checked. The average percent "Off" time will be defined as the average of percent "Off" time (total "Off" time divided by the total time not "asleep," (ie, waking hours) per day) from the subject PD diaries completed for the 3 days immediately prior to the visit.

The primary endpoint will be analyzed using a mixed-effect analysis of variance (ANOVA) model which will include treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect.

Analyses will be done for the Completers analysis sets as defined in Section 2.1. Data from the early terminated subject will be listed.

5.2. Secondary Endpoints

For secondary endpoints, the Completers analysis set will be used. Data from the early terminated subject will be listed.

5.2.1. Secondary Endpoints Based on PD Diaries

5.2.1.1. Average "Off" Time

From the subject PD diaries, the number of half-hour intervals marked "Off" will be calculated. The difference between the two treatments will be evaluated using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "Off" time will also be categorized into intervals: 0 hours, > 0 to < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, and ≥ 8 hours, and will be summarized across the treatments.

5.2.1.2. Average "On" Time with No Troublesome Dyskinesia ("Good On")

From the subject PD diaries, the sum of the number of half-hour intervals marked "on without dyskinesia" and "on with nontroublesome dyskinesia" will be calculated. The difference between the averages of "Good on" time between the two treatments will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "Good on" time will also be categorized into intervals: < 4 hours, 4 to < 6 hours, 6 to < 8 hours, 8 to < 10 hours, 10 to < 12 hours, 12 to < 14 hours, and ≥ 14 hours and will be summarized across the treatments.

5.2.1.3. Average "On" Time without Dyskinesia

From the subject PD diaries, the sum of the number of half-hour intervals marked "on without dyskinesia" will be calculated. The difference between the averages of total time "On" time without dyskinesia between the two treatments will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "On" time without dyskinesia will also be categorized into intervals: < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, 8 to < 10 hours, 10 to < 12 hours, and ≥ 12 hours and will be summarized across the treatments.

5.2.1.4. Average "On" Time with Nontroublesome Dyskinesia

From the subject PD diaries, the sum of the number of half-hour intervals marked "on with nontroublesome dyskinesia" will be calculated. The difference between the averages of total time "On" time with nontroublesome dyskinesia between the two treatments will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "On" time with nontroublesome dyskinesia will also be categorized into intervals: 0 hours, 0 to < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, 8 to < 10 hours, and ≥ 10 hours and will be summarized across the treatments.

5.2.1.5. Average "On" Time with Troublesome Dyskinesia

From the subject PD diaries, the sum of the number of half-hour intervals marked "On with troublesome dyskinesia" will be calculated. The difference between the averages of total time "On" time with troublesome dyskinesia between the two treatments will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "On" time with troublesome dyskinesia will also be categorized into intervals: 0 hours, > 0 to < 1 hour, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, and ≥ 4 hours and will be summarized across the treatments.

5.2.1.6. Average Asleep Time

From the subject PD diaries, the sum of the number of half-hour intervals marked "asleep" will be calculated. The difference between the averages of total time "asleep" between the two treatments will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "asleep" time will also be categorized into intervals: < 5 hours, 5 to < 7.5 hours, 7.5 to < 9 hours, 9 to < 11 hours, and ≥ 11 hours and will be summarized across the treatments.

5.2.1.7. Average "Off" Time Normalized for 16 Waking Hours

The average "Off" time normalized for 16 waking hours is calculated by taking the proportion of "Off" time during the waking hours multiplied by 16 hours. The difference between the two groups will be summarized. The treatment difference will be evaluated using a mixed model with treatment, period, and sequence as fixed effects and subject within sequence as random effect. In addition, the "Off" time normalized to 16 waking hours will be tabulated using categories 0 hours, > 0 to < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, and ≥ 8 hours.

5.2.1.8. Average Total "Good On" Time Normalized for 16 Waking Hours

The average "Good on" time normalized for 16 waking hours is calculated by taking the proportion of "Good on" time during the waking hours multiplied by 16 hours. The difference between the two groups will be summarized. The treatment difference will be evaluated using a mixed model with treatment, period, and sequence as fixed effects and subject within sequence as random effect. In addition, the "Good On" time normalized to 16 waking hours will be tabulated using categories < 4 hours, 4 to < 6 hours, 6 to < 8 hours, 8 to < 10 hours, 10 to < 12 hours, and ≥ 12 hours.

5.2.1.9. Proportion of Subjects with a Reduction in "Off" Time of at Least 0.5, 1, 1.5, 2, 3, and 4 Hours

Proportion of subjects with a reduction in "Off" time from baseline by at least 0.5, 1, 1.5, 2, 3, and 4 hours will be tabulated between the two treatment groups and compared using Fisher's Exact test. Baseline is defined as an average of "Off" hours from the 3 days of the PD Diary prior to Visit 1 Day 1.

5.2.1.10. "On" and "Off" State in First 30 Minutes upon Awakening from Nocturnal Sleep

The proportions of subjects with 0 days, 1 day, 2 days, and 3 days in "On" and in "Off" states in the first 30 minutes upon awakening from nocturnal sleep will be summarized by treatment groups and compared using Fisher's Exact test. Subjects will be classified into waking up in "On" state, "Off" state, or "Non-classifiable."

Awakening from nocturnal sleep is defined as having at least one "asleep" status post-midnight and 3 consecutive hours of non-asleep after 3:00 AM and after the post-midnight "asleep" episode. For those who don't meet the above 3 consecutive hours of non-asleep after 3:00 AM, they will be considered a non-classifiable outcome. Likewise, for those who don't have any "asleep" status between 12:00 AM and 3:00 AM, the subjects will be considered non-classifiable.

For the Diary Day -3, because diary starts at 6:00 AM, the consideration of "3 consecutive hours of non-asleep" will start at 6:00 AM. Thus, for Diary Day -3, awakening from nocturnal sleep is defined as having 3 consecutive hours of non-asleep after 6:00 AM.

5.2.1.11. Clinical Fluctuations

From the subject PD diaries, clinical fluctuation is defined as a change from "On" to "Off" state or "Off" to "On" state over the 3-day PD Diaries. The number of clinical fluctuations per day

will be the number of clinical fluctuations over the 3-day PD Diaries divided by 3. The difference between the numbers of fluctuations between the two treatments will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

If there is a missing or invalid diary data for the middle day of the 3 days, a continuation from Day -3 to Day -1 is not assumed. Instead, two additional fluctuations are assumed (one fluctuation goes from end of Day -3 to Day -2 and one fluctuation goes from end of Day -2 to Day -1).

If there is a missing diary day(s) and the remaining diary days are contiguous, the clinical fluctuations will be calculated out of the remaining day(s).

The number of clinical fluctuations will also be tabulated using categories < 2, 2 to < 4, 4 to < 6, 6 to < 8, 8 to < 10, and ≥ 10 and will be summarized between the two treatments.

5.2.1.12. Duration of "Good On"

The average duration of "Good on" is the sum of all "Good on" durations over 3 days divided by the number of "Good on" episodes during those 3 days. The average duration of "Good on" will be summarized and compared between the two treatment groups using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

If there is a missing or invalid diary day(s), then the duration of "Good on" will be calculated out of the remaining day(s).

The average duration of "Good on" will also be tabulated between two treatment groups using categories 0 to < 2 hours, 2 to < 4 hours, 4 to < 6 hours, 6 to < 8 hours, and ≥ 8 hours.

5.2.2. Secondary Endpoints Based on the Assessment of Subject Motor State

For the Day 1 and Day 15 in-clinic visits, the blinded rater determined the subject's motor state hourly using the scale "Off", "On" without dyskinesia, "On" with nontroublesome dyskinesia, "On" with troublesome dyskinesia, and Asleep. On Day 1, assessments were performed at every half an hour interval from 1 hour predose to 8 hours postdose. On Day 15, assessments were performed at every half an hour interval from 1 hour predose to 10 hours postdose. The assessment of the subject's motor state is summarized as follows for Day 1 and Day 15 separately. Summaries will be based on Completers analysis set. Data from the early terminated subject will be listed.

5.2.2.1. "Off" Time

The number of half-hour intervals marked "Off" will be calculated. The difference between the two treatments will be evaluated using a mixed-effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "Off" time will also be categorized into intervals: 0 hours, > 0 to < 2 hours, 2 to < 4 hours, 4 to < 6 hours, and ≥ 6 hours, and will be summarized across the treatments.

In addition, the proportion of subjects in "Off" state at each time point will also be presented. Comparisons between two treatments will be done via Fisher's exact test.

5.2.2.2. "Good On" Time

The number of half-hour intervals marked with either "On" without dyskinesia or "On" with nontroublesome dyskinesia will be calculated. The difference between the two treatments will be evaluated using a mixed-effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "Good on" time will also be categorized into intervals: < 2 hours, 2 to < 3 hours, 3 to < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, and ≥ 7 hours for Day 1, and < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, 7 to < 8 hours, 8 to < 9 hours, ≥ 9 hours for Day 15, and will be summarized across the treatments.

In addition, the proportion of subjects in "Good on" state at each time point will also be presented. Comparisons between two treatments will be done via Fisher's exact test.

5.2.2.3. "On" Time without Dyskinesia

The number of half-hour intervals marked with "On" without dyskinesia will be calculated. The difference between the two treatments will be evaluated using a mixed-effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "On" time without dyskinesia will also be categorized into intervals: 0 hours, > 0 to < 1 hours, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, 4 to < 5 hours, 5 to < 6 hours, and ≥ 6 hours for Day 1, and < 3 hours, 3 to < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, 7 to < 8 hours, 8 to < 9 hours, and ≥ 9 hours for Day 15, and will be summarized across the treatments.

5.2.2.4. "On" Time with Nontroublesome Dyskinesia

The number of half-hour intervals marked with "On" with nontroublesome dyskinesia will be calculated. The difference between the two treatments will be evaluated using a mixed-effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "On" time with nontroublesome dyskinesia will also be categorized into intervals: 0 hours, > 0 to < 1 hours, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, and ≥ 7 hours for Day 1, and < 1 hours, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, and ≥ 7 hours for Day 15, and will be summarized across the treatments.

5.2.2.5. "On" Time with Troublesome Dyskinesia

The number of half-hour intervals marked with "On" with troublesome dyskinesia will be calculated. The difference between the two treatments will be evaluated using a mixed-effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total "On" time with troublesome dyskinesia will also be categorized into intervals: < 1 hours, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, and ≥ 4 hours for Day 1, and < 1 hours, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, ≥ 4 hours for Day 15, and will be summarized across the treatments.

5.2.2.6. "Asleep" Time

The number of half-hour intervals marked with "Asleep" will be calculated. The difference between the two treatments will be evaluated using a mixed-effect ANOVA model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

The total time "Asleep" will also be categorized into intervals: 0 hours, > 0 to < 1 hours, 1 to < 2 hours, 2 to < 3 hours, and 3 to < 4 hours and will be summarized across the treatments.

5.2.2.7. Time from First Dose to First Morning "On" and "Good On" State after Dosing on Day 1 and Day 15

The average time to first morning "On" state after first dosing in clinic on Day 1 and Day 15 will be summarized and compared between the two treatment groups using a mixed-effect model with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect. If a subject doesn't achieve an "On" state before redose, then the subject will be censored at the second dose. If a subject doesn't have the second dose in clinic or if the second dose is beyond the 8 hours on Day 1 or 10 hours on Day 15, then the time to first morning "On" is censored at the 8 hour for Day 1 and 10 hour for Day 15.

The average time to first morning "On" state will also be tabulated using categories 0 hours, > 0 to < 1 hour, 1 to < 2 hours, 2 to < 3 hours, 3 to < 4 hours, and ≥ 4 hours and will be summarized between two treatments.

Similar analyses will be performed for "Good on" state.

5.2.3. Secondary Endpoints Based on MDS-UPDRS

5.2.3.1. Predose MDS-UPDRS

For this analysis, "Baseline" is defined as values at Screening.

The predose MDS-UPDRS and change from baseline in predose MDS-UPDRS Parts I, II, III, IV, II+III, and Total will be summarized and compared between the two treatment groups using a mixed-effect model with treatment, period, sequence as fixed effects, baseline as a covariate, and subject-within-sequence as random effect. Baseline values for all parts were assessed in "On" state.

For predose MDS-UPDRS Part III, "Off" state score at baseline was also assessed. The predose MDS-UPDRS and change from baseline in predose MDS-UPDRS Part III using "Off" state baseline values will also be summarized similarly.

5.2.3.2. MDS-UPDRS Part III

The MDS-UPDRS Part III on Day 1 and Day 15 will be summarized at each time point (predose to 8 hours on Day 1; predose to 10 hours on Day 15).

At predose on Day 1, the two treatments will be compared via a mixed-model ANOVA with treatment, period, and sequence as fixed effects and subject-within-sequence as random effect.

For postdose on Day 1 and for all time points on Day 15, the two treatments will be compared via a mixed-model analysis of covariance (ANCOVA) with treatment, period, sequence as fixed effects, baseline (Day 1 predose) as covariate, and subject-within-sequence as random effect.

The postdose average MDS-UPDRS Part III for Day 1 and Day 15 will also be summarized and compared between the two treatment groups using an ANCOVA model similar to above.

5.2.3.3. Mean Change in MDS-UPDRS Part III

The change from predose in MDS-UPDRS Part III over time on Day 1 will be summarized between two treatments and compared via a mixed-model ANCOVA with treatment, period, and sequence as fixed effects, baseline (Day 1 predose) as covariate, and subject-within-sequence as random effect.

The change from Day 1 predose in MDS-UPDRS Part III over time on Day 15 will be summarized between two treatments and compared via a mixed-model ANCOVA with treatment, period, and sequence as fixed effects, baseline (Day 1 predose) as covariate, and subject-within-sequence as random effect.

The postdose average of the change from Day 1 predose in MDS-UPDRS Part III for Day 1 and Day 15 will also be summarized and compared between the two treatment groups using an ANCOVA model similar to above.

5.2.3.4. Duration of Effect of at Least 4, 7, and 13 Units Improvement from Day 1 Predose MDS-UPDRS Part III

The duration of having at least 4, 7, and 13 units improvement from Day 1 predose MDS-UPDRS Part III on Day 1 and Day 15 will be will be summarized between two treatments and compared via a mixed-model ANOVA with treatment, period, sequence as fixed effects, and subject-within-sequence as random effect.

To determine the duration of effect, the midway point between two adjacent time points will be used. For example, if a subject does not have 4 units of improvement from the predose MDS-UPDRS Part III assessment at the 1-hour postdose assessment, but has an improvement at the 2-hour post dose assessment, and loses the 4-unit improvement at the 3-hour assessment, the duration of effect will be considered as 1 hour using the interpolated time value.

The duration of having at least 4, 7, and 13 units improvement will also be categorically summarized using categories : < 2 hours, 2 to < 3 hours, 3 to < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, and ≥ 7 hours for Day 1, and < 4 hours, 4 to < 5 hours, 5 to < 6 hours, 6 to < 7 hours, 7 to < 8 hours, 8 to < 9 hours, ≥ 9 hours for Day 15.

5.2.3.5. Proportions of Subjects with at Least 4, 7, and 13 Units Improvement from Day 1 Predose MDS-UPDRS Part III Over Time

The proportions of subjects with at least 4, 7, and 13 units improvement from Day 1 predose MDS-UPDRS Part III will be summarized over time for Day 1 and Day 15. Comparisons between the two treatments will be done based on Fisher's exact test.

5.2.3.6. MDS-UPDRS Part III, Sum of Questions 4 through 8 and 14

Questions 4 through 8 and 14 assess the bradykinesia of subjects. For questions 4 through 8, assessments were performed on both left and right side. The left side score will be added to the right side score before analyses.

To assess bradykinesia, the change from Day 1 predose in the sum of questions 4 through 8 and 14 in the MDS-UPDRS Part III over time on Day 1 will be summarized between two treatments and compared via a mixed-model ANCOVA with treatment, period, sequence as fixed effects, baseline (Day 1 predose) as covariate, and subject-within-sequence as random effect.

The change from Day 1 predose in the sum of questions 4 through 8 and 14 in the MDS-UPDRS Part III over time on Day 15 will be summarized between two treatments and compared via a mixed-model ANCOVA with treatment, period, sequence as fixed effects, baseline (Day 1 predose) as covariate, and subject-within-sequence as random effect.

The postdose average of the change from Day 1 predose in the sum of questions 4 through 8 and 14 in the MDS-UPDRS Part III for Day 1 and Day 15 will also be summarized and compared between the two treatment groups using an ANCOVA model similar to above.

Similar analyses will be performed for individual questions 4, 5, 6, 7, 8, and 14.

5.2.3.7. MDS-UPDRS Part IV

Individual components of the MDS-UPDRS Part IV and the change from Screening in individual components of MDS-UPDRS Part IV will be summarized and compared between the two treatment groups using a mixed-effect ANCOVA with treatment, period, sequence as fixed effects, baseline as a covariate, and subject-within-sequence as random effect.

5.2.4. Secondary Endpoints Based on Kinesia 360

For Kinesia 360 data, summaries will be based on the Kinesia 360 completers analysis set. Data from the early terminated subject will be listed.

5.2.4.1. Tremor

The distribution of tremor will be summarized and compared between the two treatments using a mixed model ANOVA with treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. Summaries will include the total wear time, proportion of subjects with at least one tremor detected, total wear time with tremor detected, and the percent of wear time with tremor detected.

5.2.4.2. Dyskinesia

The distribution of dyskinesia will be summarized and compared between the two treatments using a mixed model ANOVA with treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. Summaries will include the total wear time, proportion of subjects with at least one dyskinesia detected, total wear time with dyskinesia detected, and the percent of wear time with dyskinesia detected.

5.2.4.3. Mobility

The distribution of mobility measures based on Kinesia 360 device will be summarized and compared between the two treatments using a mixed model ANOVA with treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. Summaries will include the total wear time, total time rest as a percent of the wear time, total time active (non-gait) as a percent of wear time, total time gait as a percent of wear time, total active time as a percent of wear time, percent arm swing during gait, wear time steps, and wear time steps normalized for wear time (steps/hour).

5.3. Changes From Protocol-Specified Efficacy Analyses

The following efficacy endpoints were added to fully characterize the efficacy and pharmacodynamics of IPX203:

- Clinical fluctuations
- Time to first morning "On" state after first dosing
- Duration of "Good on"
- Proportion of subjects who are "On" in first 30 minutes upon awakening
- Proportion of subjects with a 4-hour reduction in "Off" time from Baseline

The protocol states that for efficacy, a subject will be considered a completer if the subject receives treatments in both periods and has at least 2 days of evaluable PD diary data for each period. The "at least 2 days" in the definition above has been revised to "at least 1 day" per FDA feedback on the Phase 3 protocol (IPX203-B16-02).

The protocol states that categorical pharmacodynamics endpoints will be analyzed using generalized estimating equations methods. The model will include treatment and period. Due to small sample sizes and sparse data, this has been changed to Fisher's Exact test to simplify the analyses.

6. SAFETY ANALYSES

6.1. Adverse Events and Deaths

6.1.1. Adverse Event Dictionary

Reported AEs will be coded to standard terms using a standard dictionary (Medical Dictionary for Regulatory Activities [MedDRA]) Version 20 or latest version at the time of the database finalization.

6.1.2. Adverse Event Severity

Severity of adverse events will be determined by the investigator as mild, moderate, or severe. AEs with missing severity will be queried to resolution.

6.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related," "Possibly Related," or "Unlikely Related" on the AE CRF to the question of "Relationship to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. AEs with missing relationship to study drug will be queried to resolution.

6.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Drug Safety database before data finalization.

6.1.5. Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAE) are defined as events with an onset date on or after the study drug start date, up to and including 1 day after the last dose of study drug in each treatment period. A worsening of previous illnesses or experience from baseline while on study drug is also considered a TEAE. Otherwise the experience is defined as prior to treatment if it begins before the first dose of study drug; washout if it occurs more than 1 day after the last dose of the first period, but prior to the first dose of the second period; or post treatment if it occurs more than 1 day after the last dose of study medication. An AE with a missing start date is considered a TEAE unless the stop date is non-missing and is prior to the first administration of study medication.

6.1.6. Summaries of Adverse Events and Deaths

TEAEs will be summarized based on the Randomized analysis set. All TEAEs will be summarized by body system, and by preferred terms within a body system, by severity, and by relation to study medication. Each AE (based on preferred terminology) is counted only once for a given subject within a specified treatment or study period. If the same AE occurred on multiple occasions, the highest severity and least complimentary relationship was assumed. If two or more AEs were reported as a unit, the individual terms will be reported as separate AEs.

The incidence of treatment-emergent AEs, as well as, SAEs will be summarized.

6.1.7. Additional Analysis of Adverse Events

Summaries of the Columbia-Suicide Severity Rating Scale (C-SSRS) (suicidal ideation and suicidal behavior) will be provided for subjects in the Randomized analysis set. Individual responses will be listed.

6.2. Laboratory Evaluations

Laboratory data are collected at Screening and at End of Study for this study. Laboratory data collected will be summarized using the Randomized analysis set. The analysis will be based on values reported in conventional units.

A by-subject listing for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, chemistry, urinalysis, and urine drug test, alcohol breath test, and pregnancy test. Values falling outside the normal reference range and/or having a clinical significance (with "clinical significance" determined by the investigator) will be flagged in the data listings, as appropriate.

A listing of normal ranges of laboratory test results will also be provided.

No formal statistical testing is planned.

6.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be provided for Screening and End of Study time points for each laboratory test specified in the study protocol. The proportion of subjects with Low (below the lower limit of normal range), Normal (within the limit of normal range), High (above the upper limit of normal range) will be presented.

6.2.2. Shifts Relative to the Baseline Value

Shift tables will be presented by showing changes in results from screening value (low, normal, and high) to the end of study for hematology, blood chemistry, and urinalysis.

6.2.3. Other Laboratory Results

Because all subjects were either surgically sterile or post-menopausal, a summary of urine pregnancy test results will not be summarized.

Positive alcohol breath test and urine drug screen at Screening will be provided.

6.3. Vital Signs

Descriptive statistics of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature will be provided at Screening, during Day 1 and Day 15 of each treatment period, and at End of Study. The change from baseline at hours 2, 4, and 8 on Day 1, and to hours 2, 4, and 10 on Day 15 of each treatment period will be summarized similarly.

Baseline is defined as the predose assessment at Visit 1 for vital signs analyses. The change from Baseline at the End of Study (Study Exit Visit) in systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature will be summarized for Randomized Subjects. In addition, the change from supine to standing in blood pressure and heart rate will also be summarized.

Systolic blood pressure will also be tabulated for subjects with < 90 mmHg, 90 to < 140 mmHg, and ≥ 140 mmHg.

Diastolic blood pressure will also be tabulated for subjects with < 60 mmHg, 60 to < 90 mmHg, and ≥ 90 mmHg.

Heart rate will also be tabulated for subjects with < 60 beats/min, 60 to < 100 beats/min, and ≥ 100 beats/min.

Respiratory rate will also be tabulated for subjects with < 9 breaths/min, 9 to < 20 breaths/min, ≥ 20 breaths/min.

Body temperature will also be tabulated for subjects with < 36.5ºC, 36.5ºC to < 37.5ºC, 37.5ºC to < 38.5ºC, and ≥ 38.5 ºC.

6.4. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug or prior to taking study drug and continued during the study. Use of concomitant medications will be summarized by reported name using the number and percentage of subjects for each of the Randomized, Completers, and Early Terminated subjects. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by reported term.

Concomitant medications will also be grouped into various anti-PD medication classes (amantadine, anticholinergic, dopamine agonist, monoamine oxidase (MAO) type B inhibitor, CD-LD IR, CD-LD CR, CD-LD extended release (ER), entacapone, carbidopa/levodopa/entacapone (CLE)), as well as antidepressants, sleep aids, and others. Frequencies and percentages of subjects taking these classes of medications as well as each medication under the class will be summarized for Randomized, Completers, and Early Terminated subjects. Prohibited medications will not be included in the summaries.

Summaries will be based on the Randomized Analysis Set. No formal statistical testing is planned.

6.5. Electrocardiogram Results

6.5.1. Investigator Electrocardiogram Assessment

Descriptive statistics of ventricular rate, PR interval, QRS interval, QT interval, and RR interval at Screening will be provided for Screened, Randomized, Completers, and Early Terminated subjects. Descriptive statistics will also be provided during each treatment period at Day 1 and Day 15 for Randomized subjects. For each day, summaries will be provided at predose, at 2 hours postdose, and the change from Day 1 predose values. Summaries will also be provided at

End of Study as well as the change from Baseline. Baseline is the defined as the predose assessment at Visit 1.

Ventricular rate will also be categorized into < 60 beats/min, 60 to 100 beats/min, and > 100 beats/min. The change from Day 1 Predose at hour 2 of each treatment period and the change from Baseline at the End of Study in ventricular rates will also be summarized with the following categories: < -10 beats/min, -10 to < 0 beats/min, 0 to < 10 beats/min, and ≥ 10 beats/min.

PR interval will also be categorized into < 120 msec, 120 to 200 msec, and > 200 msec. The change from Predose at hour 2 of each treatment period and the change from Baseline at the End of Study in PR interval will also be summarized with the following categories: < -1 msec, -1 to 5 msec, and ≥ 5 msec.

QRS interval will also be categorized into < 60 msec, 60 to 100 msec, and > 100 msec. The change from Predose at hour 2 of each treatment period and the change from Baseline at the End of Study in QRS interval will also be summarized with the following categories: < 0 msec, 0 to < 3 msec, and ≥ 3 msec.

QT interval will also be categorized into < 200 msec, 200 to 430 msec, >430 to 450 msec, > 450 to 500 msec, and > 500 msec. The change from Predose at hour 2 of each treatment period and the change from Baseline at the End of Study in QT interval will also be summarized with the following categories: < 30 msec, 30 to < 60 msec, and ≥ 60 msec.

RR interval will also be categorized into < 600 msec, 600 to 1000 msec, and > 1000 msec. The change from Predose at hour 2 of each treatment period and the change from Baseline at the End of Study in ventricular rates will also be summarized with the following categories: < -33 msec, -33 to < 12 msec, and ≥ 12 msec.

6.5.2. Corrected QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

The QTcF interval values at Screening, during each treatment period (predose and at 2 hours postdose), and at Baseline and End of Study will be summarized within the following categories: < 200 msec, 200 to 430 msec, > 430 to 450 msec, > 450 to 500 msec, and > 500 msec.

The change from Predose at hour 2 of each treatment period and the change from Baseline at the End of Study in QTcF interval values obtained during the study will also be summarized within the following categories: < 30 msec, 30 to < 60 msec, and ≥ 60 msec.

6.6. Other Safety Measures

The frequency distribution of abnormal physical findings at baseline and at Study Exit for Randomized subjects will also be tabulated.

6.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

7. PHARMACOKINETIC ANALYSES

7.1. PK Sample Collection

On Day 1 of each treatment period, PK samples will be collected at predose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5 and 8 hours postdose. On Day 15 of each treatment period, PK samples will be collected at predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours.

7.2. PK Analyses

PK over an 8-hour dosing interval (for Day 1) and a 10-hour dosing interval (for Day 15) will be determined. Concentrations of levodopa and carbidopa in plasma will be determined using a validated bioanalytical assay. In summaries and in PK parameter calculations, plasma concentrations with BLQ values at predose will be set to zero, those with BLQ values at postdose time points will be considered missing. Any predose or postdose concentration that was deemed "Not Reportable" by the Analytical Lab was excluded from PK analysis.

7.2.1. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects with PK samples in whom plasma concentrations were available. Levodopa and carbidopa analytes will be evaluated. Concentrations and PK parameters normalized to 280 mg LD (70 mg CD) will also be generated.

The analytes and parameters presented in Table 4 will be used to evaluate the PK objectives of the study.

Table 4: Pharmacokinetic Parameters for Each Analyte

Analyte	Study Day	Parameters
Levodopa	1	C_{max}, T_{max}, tau, C_{tau}, AUC_{tau}, AUC_{last}, AUC_{inf}, $AUC_{\%ext}$, $t_{1/2}$, k, AUC_{0-2}, AUC_{2-8}, AUC_{8-inf}, T(430ng/mL), T(1000ng/mL), T(50%C_{max}), Dur(>50%C_{max}), and BA relative to IR CD-LD
Carbidopa	1	C_{max}, T_{max}, tau, C_{tau}, AUC_{tau}, AUC_{last}, AUC_{inf}, $AUC_{\%ext}$, $t_{1/2}$, k, AUC_{0-2}, AUC_{2-8}, AUC_{8-inf}, and BA relative to IR CD-LD
Levodopa	15	C_{max}, T_{max}, tau, C_{tau}, AUC_{tau}, AUC_{last} (equivalent to AUC_{0-10}), C_{avg}, AUC_{0-2}, AUC_{2-10}, T_{max}, T(430ng/mL), T(1000ng/mL), T(50%C_{max}), Dur(>50%C_{max}), fluctuation index, accumulation ratio, and time-invariance ratio
Carbidopa	15	C_{max}, T_{max}, tau, C_{tau}, AUC_{tau}, AUC_{last} (equivalent to AUC_{0-10}), C_{avg}, AUC_{0-2}, AUC_{2-10}, T_{max}, fluctuation index, accumulation ratio, and time-invariance ratio

Individual subject concentration data and individual subject PK parameters for levodopa and carbidopa will be listed and summarized using descriptive statistics by treatment for the Completer analysis sets. Data from the early terminated subject will be included in listings. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, minimum, and maximum) will be presented within treatments for both individual subject concentration data by

time point and individual subject PK parameters. Summaries for all subjects, for subgroups differentiated by dose levels, and for dose-normalized values will be presented. Moreover, the geometric mean, the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

7.2.2. Statistical Analysis Methods

Descriptive statistics (mean, SD, coefficient of variation [CV %], median, minimum, and maximum) will be used to summarize the PK parameters for each treatment group on Day 1 and Day 15. Following natural logarithm transformation, ANOVA model will be performed on AUC and concentration parameters. The model will include treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. ANOVA models on untransformed data will also be performed on AUC and concentration parameters, accumulation ratio, fluctuation index, and time invariance. These analyses will be done on Day 1 and Day 15 and the AUC and concentration parameters will be dose-normalized to the lowest treatment dose of the reference treatment (100 mg).

Plasma PK parameters for LD and CD will be listed by subject and summarized by treatment using descriptive statistics. Noncompartmental methods will be used to estimate T_{max}, C_{max}, $AUC_{s\text{-}t}$, $AUC_{0\text{-}\infty}$, k, and $t_{½}$ for LD and CD (Phoenix WinNonlin version 6.4.0). Descriptive statistics (mean, SD, coefficient of variation, median, minimum, and maximum) will be used to summarize the PK parameters for each treatment group. To assess the bioavailability of IPX203 relative to the IR CD-LD reference treatment, analyses of variance will be performed on natural log transformed AUC and C_{max} values using a mixed-effect model that included treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. In these analyses, all treatments are dose-normalized to the lowest treatment dose of the reference treatment (100 mg of levodopa). Additionally, time for plasma concentrations of LD to reach 50% of its C_{max} and duration of LD plasma concentrations >50% C_{max} will be calculated for both treatments. The extent of LD exposure following the treatments on Day 1 will also be assessed by calculating partial AUC between 0-2 hours, 2-8 hours, and 8 hours extrapolated to infinity to yield values for $AUC_{0\text{-}2}$, $AUC_{2\text{-}8}$ and $AUC_{8\text{–}\infty}$, respectively. On Day 15, partial AUC between 0-2 hours and 2-10 hours ($AUC_{0\text{-}2}$ and $AUC_{2\text{-}10}$, respectively) will be calculated.

The time to 50% C_{max} and duration above 50% C_{max} will be estimated using a linear interpolation between the two adjacent time points.

The Wilcoxon Signed Rank test will be used to compare LD T_{max}, duration above 50% C_{max}, time to reach 430ng/mL, and time to reach 1000ng/mL between treatments on Day 1 and Day 15. Tau will be added to the Day 15 comparison. The Wilcoxon Signed Rank test will also be used to compare CD T_{max} on Day 1, and CD T_{max} and Tau on Day 15.

The mean LD and CD plasma concentration time profiles will be plotted as well as the plasma concentration time profiles for each subject. For both Day 1 and Day 15, mean LD plasma concentration will be plotted based on the first dose only and based on all doses.

7.3. Changes from Protocol-Specified PK Analyses

Additional PK parameters were added to fully elucidate the PK profiles of IPX203. They are $AUC_{(0\text{-}2)}$, $AUC_{2\text{-}8}$, $AUC_{8\text{-}inf}$, $AUC_{\%ext}$, C_{avg}, T(430ng/mL), T(1000ng/mL), tau, and time

invariance parameter. AUC_{0-10} stated in the protocol is replaced by AUC_{last} as the AUC_{0-10} is best represented by AUC_{last}.

The protocol stated that the duration of LD concentration above 50% of C_{max} values would be analyzed using ANOVA based on the protocol. The analysis method has been updated to signed rank test.

The protocol stated that, following natural logarithm transformation, analyses of variance (ANOVA) will be performed on CD and LD AUC and C_{max} adjusted for dose, fluctuation, and accumulation. It was clarified that ANOVA will be performed on the fluctuation index, accumulation index, in addition to log-transformed dose-normalized AUC and C_{max}.

8. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

Phoenix WinNonlin Software Version 6.4.0. Certara, Princeton, NJ, USA

9. REFERENCES

Goetz CG, Luo S, Wang L, Tilley BC, LaPelle NR, Stebbins GT. Handling missing values in the MDS-UPDRS. Mov Disord. 2015 Oct;30(12):1632-8.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997 Sep;53(3):983-97.