STATISTICAL ANALYSIS PLAN

Study 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**
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Transaminase
ATC	Anatomic-therapeutic-chemical
BLOCF	Baseline Observation Carried Forward
BMI	Body Mass Index
CD-LD	Carbidopa-Levodopa
[redacted]	
CMH	Cochran-Mantel-Haenszel
CR	Controlled Release
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
ET	Early termination
GCSI	Gastroparesis Cardinal Symptom Index
IR	Immediate Release
ITT	Intent-to-Treat
LD	Levodopa
LLC	Limited Liability Company
LOCF	Last Observation Carried Forward
MAO-B	Monoamine oxidase B
MAR	Missing At Random
MDS-UPDRS	Movement Disorder Society version of the Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
NCS	Not Clinically Significant
[redacted]	
PD	Parkinson Disease
[redacted]	
PGI-C	Patient Global Impression of Change
[redacted]	
PMM	Pattern-Mixture Model
PT	Preferred Term
RBC	Red Blood Cells

ReML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
WBC	White Blood Cells
WHO	World Health Organization

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-B16-02. This SAP is based on the study protocol amendment 4 dated 28Sep2018. The SAP will be finalized before database lock. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1 Study Objectives

The objective of this study is to evaluate the safety and efficacy of IPX203 in comparison to IR CD-LD in the treatment of CD-LD experienced subjects with Parkinson's disease (PD) who have motor fluctuations.

1.2 Study Design

This is a multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group study. Subjects will continue to take permitted 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. A "stable dosing regimen" means no change in dose or in dosing frequency. Within 4 weeks following the Screening visit, eligible subjects will complete their PD Diaries on each of the 3 consecutive days immediately prior to Visit 1.

Following Visit 1, qualified subjects will enter a 3-week, open-label IR CD-LD treatment period allowing for dose adjustment. During the IR CD-LD dose adjustment period, the initial dosing regimen of IR CD-LD will be the same as the subject's stable prestudy regimen unless the subject is taking a single daily bedtime dose of CR CD-LD, in which case, the CR CD-LD dose will be discontinued and substituted with a 1:1 milligram-equivalent dose of IR CD-LD. A "bedtime dose" is defined as the last daytime dose of CD-LD taken within 1 hour of onset of the subject's normal nighttime sleep period. The dosing regimen of IR CD-LD may be adjusted during the dose adjustment period to minimize "Off" time without causing troublesome dyskinesia. The doses and regimens of the subject's other non-CD-LD Parkinson's disease medications (dopamine agonists, MAO-B inhibitors, amantadine, anticholinergics) should remain stable throughout this study. Any adjustments to the IR CD-LD dosing regimen will be done in consultation with the Investigator or qualified site personnel and will be recorded. The subject must be on a stable dosing regimen (no change in dose or in dosing frequency) of IR CD-LD for at least 5 days prior to returning for Visit 2. Rescue with additional or modified doses of concomitant PD medications or with use of CD-LD products other than the dispensed study medications is not permitted and will trigger discontinuation from the study. Subjects will complete their 3-day PD Diaries on each of the 3 consecutive days immediately prior to Visit 1.

Following completion of the IR CD-LD dose adjustment period, subjects will begin a 4-week open-label period for conversion to IPX203. The initial dosing regimen of IPX203 during the conversion period will be based on the subject's dosing regimen of IR CD-LD at the end of the dose adjustment period (Visit 2) selecting the most frequent dose according to Table 1. A 25-100 mg dose of IR CD-LD converts to a 70-280 mg CD-LD dose of IPX203 but with a longer duration of effect. It is recommended that IPX203 be dosed approximately every 8 hours with the exception that subjects who are currently receiving a total daily dose of less than 125-500 mg IR CD-LD at the end of the dose adjustment period will be initially administered IPX203 every 12 hours. The dosing interval may be reduced to approximately every 8 hours if the subject does not

achieve an acceptable duration of effect. The dosing regimen of IPX203 may be adjusted during the dose conversion period to achieve the optimal balance of efficacy and tolerability (minimize "Off" time without causing troublesome dyskinesia or other dopaminergic side effects). Any adjustments to the IPX203 dosing regimen will be recorded. Rescue with additional or modified doses of concomitant PD medications or with use of CD-LD products other than the dispensed study medications is not permitted and will trigger discontinuation from the study. Subjects will return to the clinic in two weeks for Visit 3 followed by Visit 4 two weeks later. The subject must be on a stable dosing regimen of IPX203 (no change in dose or in dosing frequency) for at least 5 days prior to returning for Visit 4. Subjects will also be instructed to complete their 3-day PD Diaries on each of the 3 consecutive days immediately prior to Visit 4.

The study staff will call the subjects frequently (approximately every 1 to 3 days) during the IR CD-LD dose adjustment and IPX203 dose conversion periods. The calls are to ensure timely and appropriate dosing adjustments and to ensure that the subject is able to follow and adhere to the dosing instructions. The contacts may be less frequent after initial dose adjustments have been made. Any changes in the dosing regimen will be in consultation with the Investigator or qualified site personnel and will be documented.

Subjects who successfully complete the IPX203 dose conversion period will be randomized, stratified by center, in a 1:1 ratio at Visit 4 into one of two parallel treatment arms of IPX203 (with matching IR CD-LD placebo) or IR CD-LD (with matching IPX203 placebo). The subjects will undergo 13 weeks of double-blind, double-dummy maintenance therapy with the stable dosing regimen established at the end of Week 3 (Visit 2) for IR CD-LD and at the end of Week 7 (Visit 4) for IPX203. Subjects will return to the clinic for 3 visits (Visits 5, 6, and 7) and will be instructed to complete their 3-day PD Diaries on 3 consecutive days immediately prior to each of the 3 visits. Rescue with additional or modified doses of concomitant PD medications or use of CD-LD products other than the dispensed study medication is not permitted and will trigger discontinuation from the study.

Figure 1 Study Flowchart

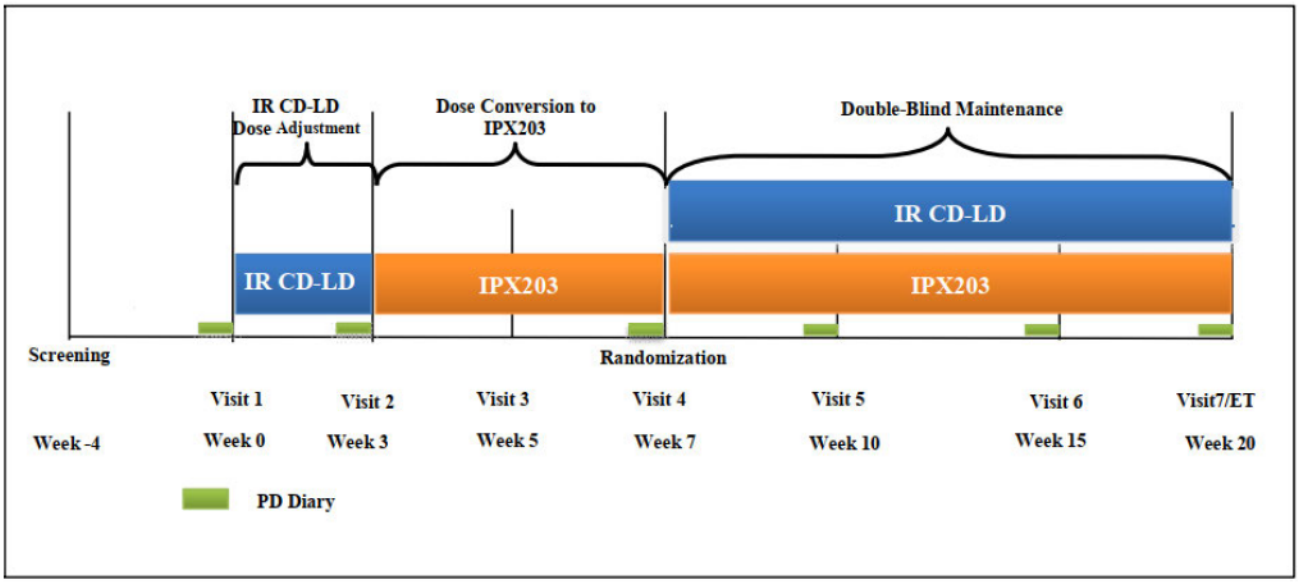


Table 1 Recommended Starting IPX203 LD Dosing Regimen Based on the Dosing Regimen of IR CD-LD at the End of the Dose Adjustment Period

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

[a] Subjects who are on a total daily dose of less than 125-500 mg CD-LD from IR CD-LD should be advised to initially take IPX203 every 12 hours. The dosing interval may be reduced to approximately every 8 hours if the subject does not achieve an acceptable duration of effect.

1.3 Sample Size and Power

Assuming a difference of 1 hour between IPX203 and IR CD-LD in "Good on" time and a standard deviation of the treatment differences to be 3.0 hours, a sample size of 210 subjects per arm will be needed to ensure at least 90% power at a 0.05 significance level.

Assuming approximately an 18% pre-randomization drop-out, approximately 510 subjects would need to be enrolled to randomize 420 subjects.

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. The statistical analyses will be performed by Quartesian LLC, with approval of the Sponsor, using SAS Version 9.4 (or higher).

All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by subject and visit/time point where appropriate. The summary tables will be stratified by, or have columns corresponding to, treatment groups in the randomized double-blind treatment period, i.e. IPX203 and IR CD-LD. Analyses of safety may also have a column for subjects who were not randomized.

The total number of subjects in the treatment group (N) under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. Number of subjects with missing values will also be displayed, but only if non-zero. The minimum and

maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be displayed. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise specified.

In by-visit summaries, only data collected on scheduled visits/timepoints will be summarized. Data from unscheduled assessments will be included in listings and may be used in determination of baseline if applicable.

Relative days will be calculated relative to date of the first study drug dose in the Dose Adjustment period. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first study drug dose:

Relative Day = Date of Assessment – Date of First Study Drug Dose +1.

For assessment before the day of first study drug dose:

Relative Day = Date of Assessment – Date of First Study Drug Dose.

All dates will be displayed in DDMMMYYYY format.

2.1 Definitions of Baseline

There will be two types of baseline defined, study entry baseline and double-blind baseline.

Study entry baseline is defined as the last assessment obtained prior to the first dose of the study drug (IR CD-LD) in the Dose Adjustment period.

Double-blind baseline is generally defined as the last assessment obtained prior to the first dose of the randomized study drug in the double-blind treatment period. For the PD Diary-derived endpoints, double-blind baseline will be derived from the PD Diary collected at Visit 4 (randomization visit).

Unless otherwise specified, “baseline” will refer to the double-blind baseline.

Efficacy endpoints will be summarized relatively to the double-blind baseline. Some select endpoints may be summarized also relative to the study entry baseline, as detailed in section 4.6 of this SAP. Safety parameters will be summarized relative to the study entry baseline, unless otherwise specified.

2.2 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.

2.2.1 Safety Analysis Set

The Safety Analysis set will include all subjects who were treated with any study drug (IPX203 or IR CD-LD).

2.2.2 Randomized Analysis Set

The Randomized Analysis set will include all subjects who were randomized.

2.2.3 Intent-to-Treat Analysis Set

The Intent-to-treat Analysis Set (ITT) will include all subjects who were randomized and treated with any study drug and have a baseline and at least one post-baseline efficacy assessment (using double-blind baseline, as defined in section 2.1).

2.2.4 Modified Intent-to-Treat Analysis Set

The Modified Intent-to-treat Analysis (mITT) Set will include all subjects who were randomized and treated and have a valid baseline PD Diary and at least one valid post-randomization PD Diary (using double-blind PD Diary baseline, as defined in section 2.1). This analysis set will be used for the primary analysis and key secondary analyses.

2.2.5 Completers Analysis Set

The Completers Analysis Set will include all subjects who were randomized and treated and completed the study, attended their Visit 7 no earlier than 18 weeks after Visit 1 and no earlier than 11 weeks after Visit 4, and have valid PD Diaries at the double-blind baseline (Visit 4) and at Visit 7.

2.2.6 Per-Protocol Analysis Set

The Per-Protocol Analysis Set will include all subjects in the mITT set who do not have any major protocol deviations of the following categories:

1. Subject did not meet eligibility criterion but was enrolled in the study
2. Subject met withdrawal criteria but was not withdrawn
3. The site dispensed the incorrect IP bottle and/or kit to the subject
4. IP was not dispensed/administered as per protocol
5. Prohibited medications administered/taken
6. Washout of required Meds
7. Treated and not Randomized
8. Dose Adjustment period extended by more than 50% (i.e. longer than 31 days)
9. IPX203 Conversion period extended by more than 50% (i.e. longer than 42 days).

See section 3.5 for more information on protocol deviations. This analysis set will be used for the sensitivity analysis of the primary and key secondary endpoints.

2.3 Randomization and Blinding

At Visit 4, subjects will be randomized, stratified by center, in a 1:1 ratio into one of two double-blind parallel treatment arms of IPX203 (and matching IR CD-LD placebo) or IR CD-LD (and matching IPX203 placebo).

2.4 Examination of Subject Subgroups

The primary, key secondary endpoints, as well as overall summary of adverse events, will be examined for the following subgroups.

- Age: < 65, ≥ 65 years old at study entry
- Sex: Males, Females
- Race: Caucasians, non-Caucasians

Additionally, the following subgroups may be examined:

- 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:
  - Amantadine
  - selective MAOB inhibitors
  - anticholinergic PD medications
  - dopamine agonists
  - 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

3 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

3.1 Subject Enrollment and Disposition

Subject disposition prior to randomization will be presented for the overall subject population without breakdown by treatment group and will include the number of subjects screened, screen failed, enrolled in the study, number and percentage of subjects who entered the Dose Adjustment period, discontinued during this period (with breakdown by reason for discontinuation), entered the IPX203 Conversion period and discontinued during this period (with breakdown by reason for discontinuation). Percentages will be based on the number of enrolled subjects (except for reasons for discontinuations, for which the percentage will be

based on the number of subjects discontinued in period).

Subject disposition after the randomization will be presented by treatment group and overall and will include the number of subjects that were randomized, number and percentage of subjects who were treated in the double-blind period, included in the Safety, ITT, mITT and Completers analysis sets, completed the study and prematurely discontinued from the study after randomization (with the breakdown by the primary reason for discontinuation). Percentages will be based on the number of randomized subjects in each treatment group, except percentages for the reasons for discontinuation, which will be based on the number of subjects who discontinued early.

In the summary of reasons for discontinuation a separate line will be provided for discontinuations related to COVID-19 pandemic.

An overall summary of the number of subjects in each analysis set by site will be created.

All disposition information will be listed. Additionally, a listing of subjects who discontinued from the study prematurely will be created, including date of discontinuation and primary reason. Also a listing of enrollment details will provide the date of informed consent and inclusion/exclusion criteria not met, if any.

3.2 Demographics and Baseline Characteristics

Demographic characteristics will include:

- age at Screening
- sex
- race
- ethnicity

Baseline physical characteristics will include:

- height at study entry baseline
- weight at study entry baseline
- BMI at study entry baseline

Baseline disease characteristics include

- MDS-UPDRS Parts I, II, III, and IV total scores at study entry baseline, both in “On” and “Off” states
- Hoehn and Yahr stage (at “On” state)
- MoCA score at Screening as continuous variable and categorized as < 24, 24 to < 26, 26 to < 28, 28 to < 30, 30
- Age of onset of PD as continuous variable and categorized as < 65or ≥ 65 years.

Descriptive statistics will be presented for continuous variables. Frequency counts and

percentage will be presented for categorical variables. Height will be reported in centimeters, weight in kilograms and BMI in kg/m^2.

Age will be derived from Informed Consent Date and Date of Birth as the number of whole years between those two dates.

These analyses will be performed for the Safety, ITT and mITT analysis sets. The summaries will be presented for the two treatment group and total; the summary for the Safety analysis set will also include a separate column for the subjects who were not randomized.

The summary of demographic and baseline characteristics will also be presented for subjects who discontinued during the Dose Adjustment period, IPX203 Conversion period and Double-Blind period, by period.

All demographic parameters and baseline characteristics will be presented in the by-subject listings.

3.3 Pre-study Levodopa Dosing

The following characteristics of pre-study levodopa dosing will be summarized for the Safety, ITT and mITT analysis sets:

- Duration of pre-study levodopa (total, IR and CR) dosing in years, as continuous variable and categorized as < 3, 3 to < 6, 6 to < 9, 9 to < 12, ≥ 12 years.
- Total daily dose of pre-study levodopa (total, IR and CR) in mg, as continuous variable and categorized as < 400, 400 to < 800, 800 to < 1200, 1200 to < 1600, 1600 to <=2400, and >2400 mg
- Frequency of CD-LD dosing
- First morning dose of IR CD-LD (in mg)

The summaries will be presented for the two treatment group and total; the summary for the Safety analysis set will also include a separate column for the subjects who were not randomized.

All information will be listed.

3.4 Study Drug Exposure

Average daily dose and total dose of LD received by subjects, as well as average daily dosing frequency will be summarized descriptively for the Dose Adjustment period, IPX203 Conversion period and Double-Blind treatment period (by treatment group).

Average daily dose will also by summarized categorically, categorized as < 400, 400 to < 800, 800 to < 1200, 1200 to < 1600, 1600 to <= 2400mg, and >2400mg.

Treatment duration (calculated as Date of Last Dose – Date of First Dose + 1) will be summarized descriptively by treatment group for the Double-Blind treatment period.

The number of titration steps to stable dosing and the number of days to stable dosing will be summarized descriptively for IR CD-LD in the Dose Adjustment period and for IPX203 in the IPX203 Conversion period for subjects who achieve stable dosing. The number of steps will also be categorized as 0, 1 to 2, 3 to 4, 5 to 6, and > 6 steps and the number of days as 0, 1 to 2 days,

3 to 4 days, 5 to 6 days, 7 to 9 days, and > 9 days, and both parameters will be summarized categorically.

Number and percentages of subjects who do not achieve stable dosing will be summarized separately.

Summaries for the Dose Adjustment period and IPX203 Conversion period will be done on the Safety analysis set. Summaries for the Double-Blind treatment period will be done for all subjects treated in this period and for the ITT population.

Total daily dose of levodopa, the number of daily doses and the most frequently used dose will be summarized descriptively at the following timepoints:

- Start of Dose Adjustment period (pre-study regimen of IR CD-LD)
- End of Dose Adjustment period (stable regimen of IR CD-LD)
- Start of IPX203 Conversion period (starting IPX203 regimen)
- End of IPX203 Conversion period (stable IPX203 regimen)

This analysis will be done for the Randomized Analysis Set.

The ratio of the stable IPX203 total daily dose to IR CD-LD total daily dose as well as the ratio of the stable IPX203 most frequent dose to IR CD-LD most frequent dose will be summarized descriptively by the range of IR CD-LD total daily dose and overall. The same ranges will be used as for the summary of the average daily dose: < 400, 400 to < 800, 800 to < 1200, 1200 to < 1600, 1600 to <= 2400 mg, and >2400 mg.

The protocol recommends the starting IPX203 regimen based on the most frequently used IR CD-LD dose in the stable IR CD-LD regimen after the Dose Adjustment period. The relationship of the most frequently used IR CD-LD dose in the stable IR CD-LD regimen to the starting IPX203 regimen and to the stable IPX203 regimen (after IPX203 Conversion) will be explored. The most frequently used IR CD-LD dose in the stable IR CD-LD regimen will be categorized in terms of LD dose: 100, >100-150, >150-200 and >200 mg. For each category the number and percentage of subjects with each starting IPX203 regimen and each stable IPX203 regimen will be presented. The percentages will be based on the number of subjects within each category of most frequent IR CD-LD dose.

The relationship between then stable IR CD-LD total daily dose and stable IPX203 total daily dose will also be presented graphically. A scatter plot will be created with X-axis representing the stable IR CD-LD total daily dose and Y-axis representing stable IPX203 total daily dose.

These analyses will be done for the Randomized Analysis Set.

3.5 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 and throughout the study. The process for the management of protocol deviations is defined in the Protocol Deviation and Non-compliance Management Plan. Details of protocol deviations for each study site are documented and reviewed regularly, and 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. Deviations related to COVID-19 will be

identified in the listing.

3.6 Medical History

Medical history will be summarized by MedDRA System Organ Class and Preferred Term. Each subject will be counted once within each applicable Preferred Term and System Organ Class. This summary will be performed for the Safety analysis set by treatment group and for subjects who were not randomized, as well as for all subjects overall.

All medical history information will be listed.

4 EFFICACY ANALYSES

4.1 Imputation of missing data

4.1.1 Imputation Method for PD Diary Data

For all endpoints based on the PD Diaries the following imputation of missing diary entries will be applied.

A PD Diary is valid if at least 1 day of diary data is available using the rules defined below.

Imputation of missing data for subject PD diaries will be required if the PD diary is not completed for a full day (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:

- For subjects with more than 1 day of diary data, the following rules will apply:
  - If more than 4 half-hour time intervals are missing, then that particular day will not be included in the analysis. The missing data will be handled in the MMRM model.
  - 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 2, 3 or 4 half-hour time intervals are missing, 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 or not available, 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 are missing across all days, then the approach will be to split the individual missing half-hour intervals into 2 periods, with the first half-interval being imputed with data from the immediate previous non-missing time period and the second half-interval being imputed with the next

non-missing time interval. If the missing period starts with the very first or ends with the very last interval of the diary, then the entire missing period will be imputed with the data from the immediate adjacent non-missing interval.

- For subjects with only 1 day of diary data (instead of 3 day), the following rules will apply:
  - If more than 4 half-hour time intervals are missing, then that particular day will not be included in the analysis. The missing data will be handled in the MMRM model.
  - If a one-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 2, 3, or 4 consecutive half-hour intervals are missing, then the approach will be to split the individual missing half-hour intervals into 2 periods, with the first half-interval being imputed with data from the immediate previous non-missing time period and the second half-interval being imputed with the next non-missing time interval. If the missing period starts with the very first or end with the very last interval of the diary, then the entire missing period will be imputed with the data from the immediate adjacent non-missing interval.

4.1.2 Missing Data for MDS-UPDRS

For all endpoints based in MDS-UPDRS questionnaire the following imputation of missing responses will be used.

If the MDS-UPDRS are missing for the particular visit, the missing data will be handled via the MMRM model.

If component questions are missing for a particular part of the MDS-UPDRS questionnaire, the missing items are assigned the average value for other items in that part as follows:

- For Part I (13 questions): up to 1 missing question will be imputed using the average value of the remaining 12 questions.
- For Part II (13 questions): up to 2 missing questions will be imputed using the average value of the remaining 11 questions.
- For Part III (33 questions): up to 7 missing questions will be imputed using the average value of the remaining 26 questions.
- For Part IV (6 questions): no imputation is done.

If more component questions are missing than above for a particular part of the MDS-UPDRS questionnaire, the entire questionnaire and the affected part will not be included in the analysis for that particular assessment. Missing data will be handled in a fashion similar to PD Diary data using the MMRM model.

4.1.3 Missing Data for Global Assessments (PGI-C, [redacted]

For all endpoints based on PGI-C, [redacted] global assessments the following imputation rules will be applied.

For subjects with missing PGI-C or [redacted] for a particular visit, the data will be imputed as non-responders (i.e., not being "much improved" or "very much improved").

[redacted]

4.1.4 Handling of Missing Visit Data

An MMRM approach will be used to handle missing visit data for continuous endpoints. MMRM analysis will use all available valid visit data, including subjects with some missing visit data, in order to arrive at an estimate of the mean treatment effect.

4.2 Visit Windows for Efficacy Analyses

It is anticipated that a number of subjects in this study might attend their visits out of schedule due to COVID-19 pandemic and a number of unscheduled visits might be added.

Efficacy assessments collected at unscheduled visits will be mapped to scheduled visits if the following conditions hold:

- The unscheduled visit falls into appropriate visit window for a scheduled visit
- It occurs no later than the subject's Visit 7/ET if one exists
- No corresponding scheduled visit exists at all or within the appropriate window. If the scheduled visit exists, but is out of window, the out-of-window scheduled visit will be treated as unscheduled and will be replaced by the in-window unscheduled visit for analysis.

The following windows will be used:

Visit	Window in days after Visit 4
5	21 +/- 3 days
6	56 +/- 3 days
7	91 +/- 3 days

In addition, if the subject's last visit (by date) is unscheduled and there is no scheduled Visit 7/ET, the last unscheduled visit will be mapped to Visit 7/ET.

4.3 Center Pooling Algorithm

In all analysis models where pooled center is a factor, pooled center will be determined as follows.

1. Sort centers from each country from smallest to largest based on the number of subjects in the modified intent-to-treat analysis set (mITT).
2. Centers that have less than 5 mITT subjects in total or do not have at least one mITT subject per treatment group will be pooled with the smallest among the other centers in

the same country until the combined center (namely, pseudo-center) has more than 5 mITT subjects and at least one mITT subject per treatment group.

3. If after pooling within the same country, the pseudo-center still has less than 5 mITT subjects or still has zero subjects in one of the treatment group, that pseudo-center will be pooled with the smallest other center in the same geographical region (Western Europe, Eastern Europe, North America).
4. If after pooling within the same geographical region, the pseudo-center still has less than 5 mITT subjects or still has zero subjects in one of the treatment group, that pseudocenter will be pooled with the smallest other center in any region.

The process continues until all pooled pseudo-centers have at least 5 mITT subjects and at least one mITT subject per treatment group. These pooled centers will be used in analyses that adjust for pooled centers.

4.4 Primary Endpoint

The primary efficacy endpoint is the mean change from baseline in "Good on" time in hours per day, averaged over the PD Diary days, at the end of the double-blind therapy (Visit 7 or early termination).

4.4.1 Calculation of the primary endpoint

"Good on" time is derived from the 3-day PD Diaries completed prior to Visits 4, 5, 6 and 7 or early termination, respectively. Subjects will also complete PD Diaries prior to Visits 1 and 2, but these will not be used in the calculation of the primary endpoint.

When more than one states are checked at a particular time point in the PD Diary, the worse result is selected as the final reported outcome. The selection order (from the worst to the best) is defined below:

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

If any half-hour interval in the PD Diary has a missing response, the algorithm in the section 4.1.1 will be used to impute missing values.

A PD Diary is valid if at least 1 full day (from 6:00 am to 6:00 am the next day) of diary data is available after the imputations mentioned above. For visits with no valid PD Diary "Good on" time will not be derived (and missing value will be handled by the MMRM procedure).

For each day, "Good on" time is calculated by adding the number of half-hour intervals in which either an "On without dyskinesia" or "On with nontroublesome dyskinesia" is checked. Then the time is averaged across all days with available data in the PD Diary for the given visit.

The baseline will be the "Good on" time from the PD Diary collected prior to Visit 4. Change from baseline at each subsequent visit will be calculated as "Good on" time at that visit minus the baseline "Good on" time.

4.4.2 Analysis of the primary endpoint

"Goon on" time and its change from baseline will be summarized descriptively by post-randomization visit and treatment group.

The primary efficacy endpoint will be analyzed using a mixed model for repeated measures (MMRM). The model will include baseline (Visit 4) "Good on" time as a covariate, treatment (IPX203 or IR CD-LD) and visit (5, 6 or 7/ET) as fixed effects, pooled center (see section 4.3) as random effect and a treatment-by-visit interaction. The model will employ an unstructured within subject covariance matrix and a restricted maximum likelihood (ReML) estimation method. The degree-of-freedom of the denominator will be estimated using the Kenward-Roger method. The primary analysis set will be the modified intent-to-treat (mITT) as defined in Section 2.2.4. See appendix 9.2.1 for SAS code samples.

If the model fails to converge with the unstructured covariance matrix, a simpler covariance matrix will be employed in the order of 1) heterogeneous Toeplitz [SAS PROC MIXED type =TOEPH], 2) heterogeneous autoregressive of order 1 [type = ARH(1)], 3) heterogeneous compound symmetry [type = CSH], 4) Toeplitz [type = TOEP], 5) autoregressive of order 1 [type = AR(1)], 6) compound symmetry [type = CS]. The first covariance structure that does not have a convergence problem will be the one used for the primary analysis.

LS Mean estimates for each treatment group at Visit 7/early termination will be produced from the MMRM model, along with their standard errors (SE) and 95% confidence interval. LS Mean difference between the IPX203 and IR CD-LD treatments will also be estimated along with its SE and 95% confidence interval. P-value for the hypothesis of no treatment difference will be provided.

Mean (+/- SE) "Good on" time will also be plotted by visit and by treatment group.

4.5 Analysis of the Key Secondary Endpoints

Analysis of the key secondary endpoints will be performed on the mITT population.

4.5.1 Change from baseline in "Off" time at the end of double-blind treatment period (Visit 7 or early termination)

This secondary endpoint will be calculated similar to the primary endpoint, summing the time period checked as "Off". It will analyzed in the same manner as the primary endpoint.

4.5.2 Proportion of subjects with either "much improved" or "very much improved" in PGI-C scores at the end of double-blind treatment period (Visit 7 or early termination)

The patient will compare his/her condition from the start of the study on a 7-point scale ranging from "Very much worse" (1) to "Very much improved" (7) at the time of the assessment.

This assessment will be performed at Visits 5, 6 and 7 (or early termination).

The number and percentage of subjects with each PGI-C response will be displayed by visit (starting with Visit 5) and treatment group. The number and percentage of subjects with either "much improved" or "very much improved" response will also be provided, with imputations for missing data as described in the section 4.1.3.

Cochran-Mantel-Haenszel (CMH) test stratified by the pooled center will be used to compare the

proportion of subjects with either "much improved" or "very much improved" response at the end of the double-blind therapy (Visit 7 or early termination) between the two treatment groups; p-value for the hypothesis of equal proportions will be shown. Percent difference between the IPX203 and IR CD-LD groups will be shown with its 95% confidence interval. See appendix 9.2.2 for SAS code details.

4.5.3 Change from baseline in the MDS-UPDRS Part III at the end of double-blind treatment period (Visit 7 or early termination)

MDS-UPDRS will be administered at Screening visit (in "On" and "Off" states) and Visits 1, 2, 4, 5, 6 and 7 (or early termination) (in any state).

Part III total score will be derived as the sum of the answers for all questions in this part of the questionnaire. Missing data will be imputed as described in the section 4.1.2.

Double-blind baseline, as defined in section 2.1 will be used for all visits after Visit 4. Change from baseline will be calculated as the result at the visit minus the baseline value.

Change from baseline in MDS-UPDRS Part III score will be analyzed in the same manner as the primary endpoint, as described in the section 4.4.2.

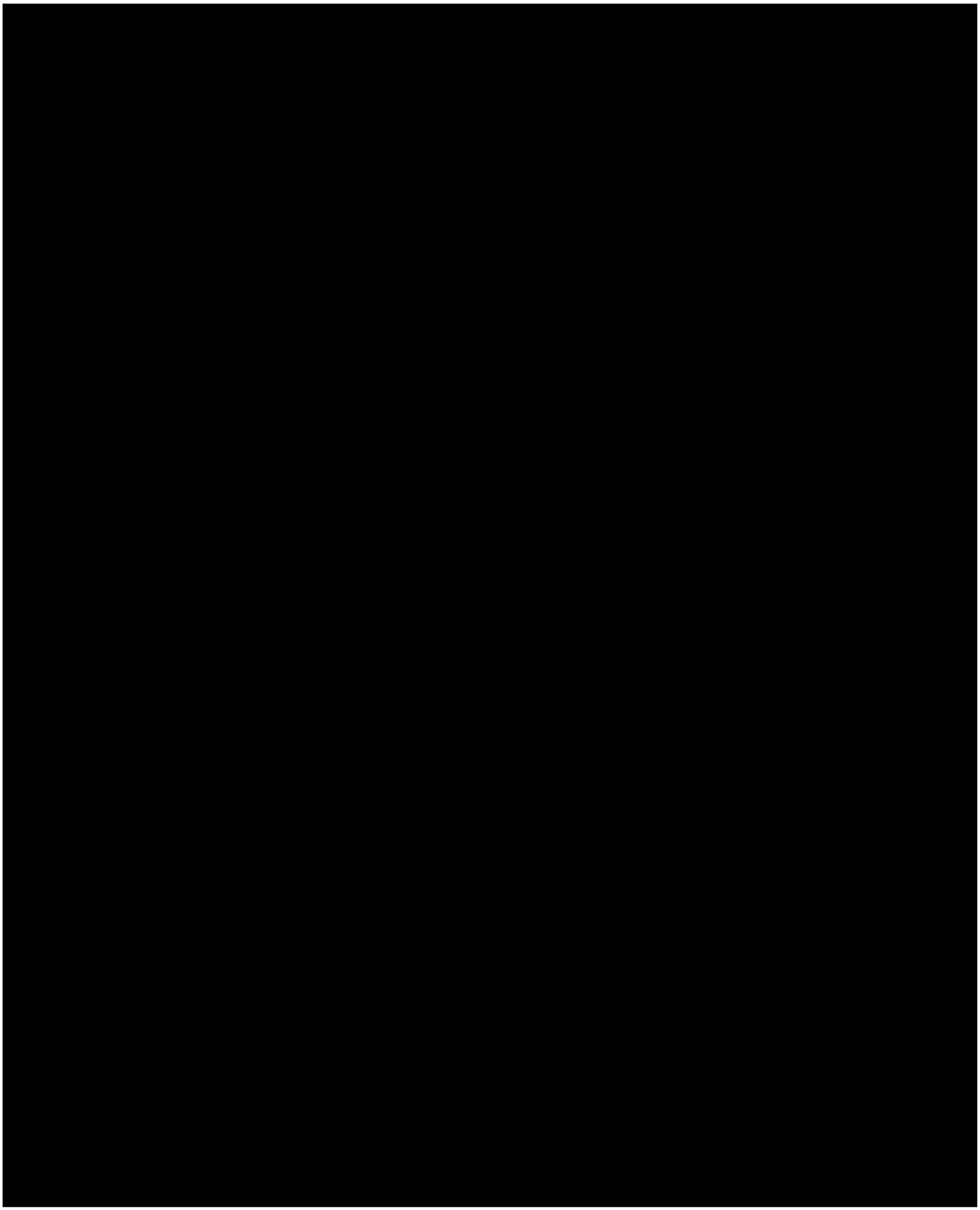
4.5.4 Change from baseline in the sum of MDS-UPDRS Part II and III at the end of double-blind treatment period (Visit 7 or early termination)

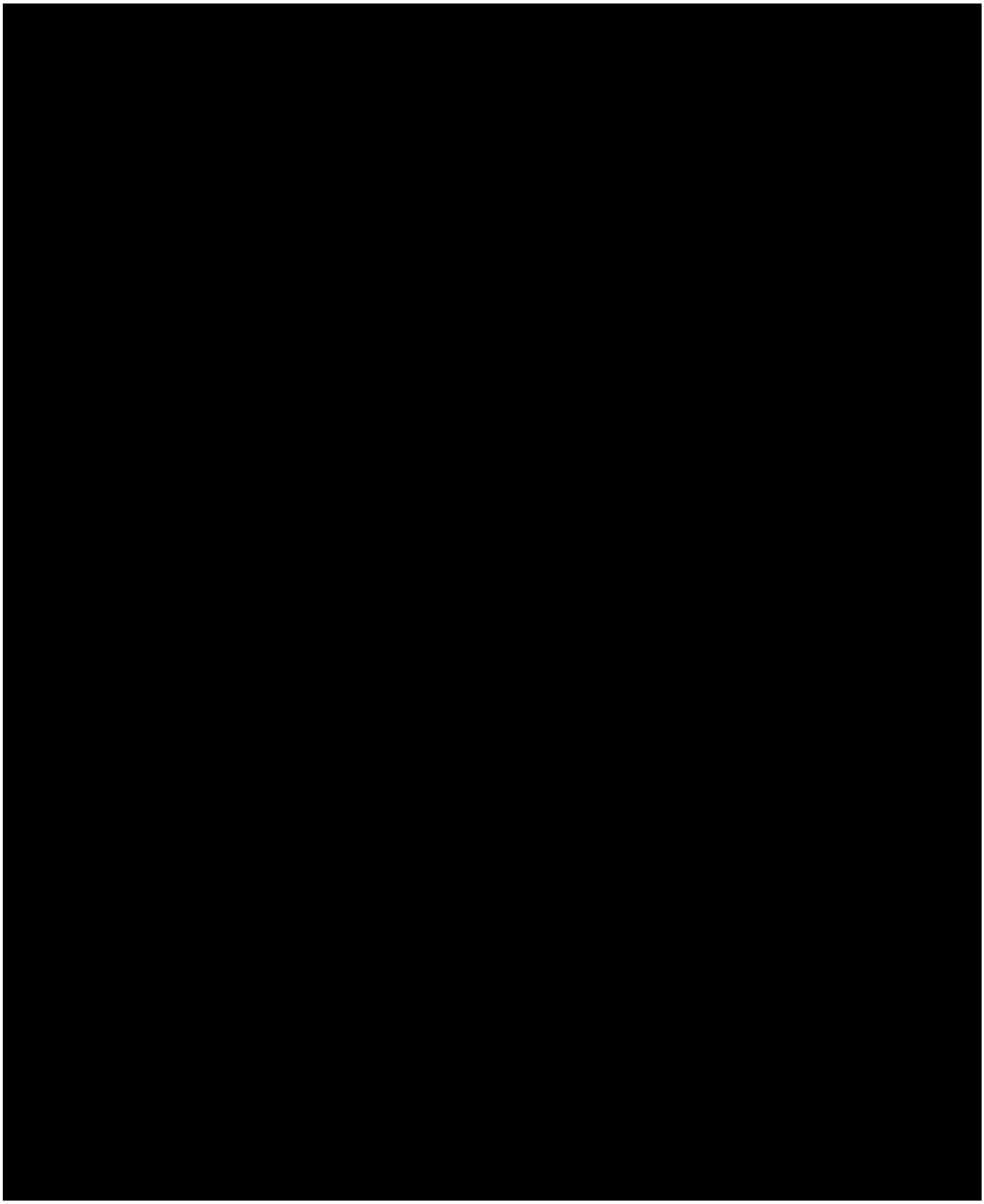
This endpoint will be calculated as the sum of all answers in Parts II and III of the MDS-UPDRS questionnaire. It will be analyzed in the same manner as MDS-UPDRS Part III.

4.6 Additional Endpoints

In general, continuous endpoints will be summarized by standard descriptive statistics (mean, standard deviation, median, minimum, and maximum) by visit (starting with Visit 4) and treatment group. Categorical endpoints will be summarized by frequencies and percentages. Double-blind baseline will be used. For some endpoints study entry baseline will also be used, as specified in the subsections below.

These analyses will be performed on the mITT population (for endpoints related to PD diary) or ITT population (for endpoints not related to the PD diary) as appropriate.





[redacted]

[redacted]

4.7 Sensitivity Analyses

Sensitivity analyses will be performed with respect to the primary efficacy endpoint and continuous key secondary endpoints ("Off" time, MDS-UPDRS Part III, and MDS-UPDRS Parts II and III combined) as follows.

4.7.1 Assessing Assumptions of the Mixed Model for Repeated Measures (MMRM)

The normality and homoscedasticity assumptions will be examined through residual analyses. The residuals from the primary analysis models will be tested for normality using Shapiro-Wilk statistic. The assumption of homoscedasticity (homogeneity of variance) will be tested for outcomes from Visit 7/early termination using a one-way ANOVA model with the factor of treatment with Levene's test. See Appendices 9.2.3 and 9.2.4 for SAS code samples.

If either of the tests is significant at the 0.05 level, the following non-parametric analyses will be performed.

I. Nonparametric Wilcoxon Rank Sum test will be performed to compare the two treatment groups at Visit 7, with missing data imputed by the last observation carried forward (LOCF) method (that is, the latest available result obtained post-randomization will be carried forward to impute the missing Visit 7 result).

II. Multiple imputation rank based analysis: instead of missing data imputed by the LOCF method, in this analysis, missing data at Visit 7 will be imputed multiple times to create 50 complete datasets. The multiple imputation procedure is described in Section 4.7.8 (part of the pattern-mixture model), using $f = 0\%$. The Wilcoxon Rank Sum test will be performed on each of the 50 datasets. The results are then combined using Rubin's rule via SAS PROC MIANALYZE.

See appendices 9.2.5 and 9.2.9 for SAS code samples.

Missing at Random (MAR) assumption will be evaluated as discussed in Section 4.7.8.

4.7.2 Complete Case Analysis

The primary endpoint will be analyzed using an ANCOVA model with "Good on" time at double-blind baseline as a covariate, pooled center and treatment as factors. The analysis will be performed on the Completers Analysis Set.

Similar to the primary analysis, LS Mean estimates for each treatment group will be produced from the ANCOVA model, along with their standard errors (SE) and 95% confidence interval. LS Mean difference between the IPX203 and IR CD-LD treatments will also be estimated along with its SE and 95% confidence interval. P-value for the hypothesis of no treatment difference will be provided. See appendix 9.2.6 for SAS code samples.

4.7.3 Single LOCF/BLOCF Imputation

The primary efficacy endpoint will be analyzed using an ANCOVA model with "Good on" time at double-blind baseline as a covariate, pooled center and treatment as factors. Missing data will

be imputed by the LOCF and baseline observation carried forward (BLOCF) methods:

- In the LOCF method the latest available result obtained post-randomization will be carried forward to impute the missing Visit 7 result
- In the BLOCF method missing Visit 7 "Good on" time will be replaced with the baseline result, in other words, change from baseline will be imputed as zero.

These analyses will be performed on the mITT population. See appendix 9.2.6 for SAS code samples.

4.7.4 Site as Fixed Effect

The primary efficacy endpoint will be summarized with the MMRM model similar to the primary analysis, except pooled site will be used as a fixed effect rather than random. See appendix 9.2.7 for SAS code.

4.7.5 Region Effect

The primary efficacy endpoint will be summarized with the MMRM model similar to the primary analysis, except geographic region (North America or Europe) will be used as a fixed effect instead of pooled site as random effect. See appendix 9.2.7 for SAS code, replacing pooled site with region.

4.7.6 Per-Protocol Analysis

The analysis of the primary and key secondary endpoints will be repeated on the Per-Protocol Analysis Set.

4.7.7 Exclusion of Late Visit 7

Primary analysis of the primary endpoint will be repeated excluding out-of-window Visit 7 assessments. In this analysis PD Diaries collected for Visit 7 will be excluded from analysis if the first day in the diary is more than 3 days later than planned, i.e. more than 91 days after randomization.

4.7.8 Pattern-Mixture Model

If an overall dropout rate post-randomization is > 15%, pattern-mixture models (PMM) will be employed to assess the robustness of the results under the missing not at random (MNAR) assumption. The pattern for PMM is defined by patients' last visit with an observed primary efficacy endpoint and the reason for dropout.

Multiple imputations with mixed missing data mechanism (MNAR for a missing data pattern and MAR for others) will be used to investigate the robustness of the primary result. Four specific data patterns will be examined:

1. Dropout at Visit 5 and reason = Lack of efficacy in IPX203 treatment arm,
2. Dropout at Visit 5 and reason = Lack of efficacy or adverse events in IPX203 treatment arm,
3. Dropout at Visit 6 and reason = Lack of efficacy in IPX203 treatment arm,
4. Dropout at Visit 6 and reason = Lack of efficacy or adverse events in IPX203

treatment arm.

The patter-mixture analysis will be performed separately for each of the patterns above.

For each pattern, the missing values will be imputed 50 times (multiple imputation) under the assumption that the distribution of the missing values is the same as that of the observed values. The PMM then investigates the departure from the MAR assumption by progressively decreasing the outcome (the "penalty") for those on IPX203 arm who fall into an assumed MNAR pattern above. For the dropout subjects on IPX203 arm that fall into one of the patterns above, the "penalty" is obtained by subtracting the imputed missing data after dropout by a factor *f*, with *f* ranges 0% to 100% , with the increment by 5%, of the treatment difference seen in the primary model. This process continues until the conclusion from the primary analysis is overturned (a tipping point). In other words, if the dropout subject is from IPX203 arm and the dropout pattern falls into one of the 4 patterns above, then the subject's imputed value will be adjusted downward by a factor *f*, where *f* goes from 0% to 100% of the treatment difference seen in the primary model. Note that if 0% is used, the analysis is essentially multiple imputations under MAR assumption. On the other hand, if 100% is used, then the analysis is essentially a "jump to reference" where outcome on IPX203 arm is assumed to be the same as outcome on IR CD-LD. After imputations, the dataset will be analyzed using an MMRM model similar to the primary analysis model. The results will then be combined using the Rubin's rule via SAS PROC MIANALYZE.

The procedure will be carried out in SAS as described in appendix 9.2.8.

If in the MMRM analysis a covariance structure other than Unstructured is selected due to convergence issues, the same structure should be used for all imputations. In other words, if a covariance structure results in convergence problems for at least one of the multiple imputations, the next structure from the list specified in section 4.4.2 should be tried until a structure is found that converges for all imputations.

4.8 Subgroup analyses

The primary and key secondary endpoints will be summarized for the subgroups identified in section 2.4. The same analysis methods as the primary and key secondary endpoints will be applied, unless the sample size in one of the subgroups becomes too small to hinder the statistical analysis. In that case, no inferential statistics will be provided for such a subgroup.

4.9 Multiplicity Adjustments

The primary endpoint and 5 key/important secondary endpoints will be tested in a sequential hierarchical order as follows.

1. The primary endpoint, the mean change from baseline in "Good on" time (hours per day), will be 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), will be 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, will be 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, will be 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 will be tested next at a 0.05 level of significance.
6. If statistical significance is demonstrated, then the important secondary endpoint, being "on" upon awakening will be tested next at a 0.05 level of significance.

For the other efficacy endpoints, no adjustment will be made.

5 SAFETY ANALYSES

Safety analyses will be performed on the Safety Analysis Set and Randomized Analysis Set. The analysis on the Safety Analysis Set will include a separate column for subjects who were not randomized.

For safety parameters that are collected by visit and have their first post-study-entry-baseline assessment after randomization, study entry baseline values will be summarized for the Safety Analysis Set and all post-randomization values will be summarized for the Randomized Analysis Set.

For safety parameters that are collected at visits after the study entry baseline, but prior to randomization, their values will be summarized for the Safety Analysis Set.

No imputation will be performed for missing safety data. In by-visit summaries, if a subject does not have a value collected at a given visit, this subject will be summarized at that visit. Data from the Early Termination visits will not be used in the by-visit summaries, but will be listed and may participate in the selection of the last post-baseline assessment if applicable.

5.1 Visit Windows for Safety Assessments

Samples for laboratory tests and ECGs are scheduled to be collected at Visits 1, 5 and 7/ET, However, if at the time of Visit 4 it is anticipated that the subject would not be able to travel to the site due to COVID-19 related restrictions, these assessments can be collected at Visit 4. If these assessments were not collected at Visit 4 or Visit 5, they can be collected at Visit 6. Therefore for subjects who do not have laboratory or ECG parameters collected under Visit 5, assessments collected under Visit 4, Visit 6 or Unscheduled visit will be mapped to Visit 5 for analysis under the following circumstances

1. Subject completed the study or discontinued later than 18 days after Visit 4 (i.e. after the start of the window for Visit 5)
2. The assessment was performed at Visit 4, Visit 6 or at Unscheduled visits that occurred after Visit 4 and no later than day 59 after Visit 4 (end of visit window for Visit 6).
3. The Unscheduled assessment occurred no later than the subject's Visit 7/ET if one exists.

5.2 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 22.0 AE coding system for purposes of summarization.

Only Treatment Emergent Adverse Events (TEAE) will be used for the summary analysis. An AE will be considered as treatment-emergent if the date of onset is on or after the first study drug administration date (IR CD-LD in the Dose Adjustment period) and no later than 1 day after the last dose of the study drug (IR CD-LD or IPX203). AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the first study drug administration date. If the AE start date is partially missing, the AE will be considered treatment-emergent, unless the month and year (when available) rule out the possibility that the event occurred post start of the study drug no later than 1 day after the last dose of the study drug.

All AEs will be assigned to study periods for the purposes of the tabulations:

Dose Adjustment Period: All TEAEs with onset that meets these criteria:

- on or after the date of the first IR CD-LD administration in the Dose Adjustment period
- If the subject proceeds into IPX203 Conversion period, then prior to the first dose of IPX203 in the IPX203 Conversion period. Otherwise, up to 1 day after the last study drug dose

IPX203 Conversion Period: All TEAEs with onset that meets these criteria:

- on or after the date of the first IPX203 administration in the IPX203 Conversion period
- If the subject proceeds into Double-blind period, then prior to the first dose of the randomized drug in the Double-blind period. Otherwise, up to 1 day after the last study drug dose

Double-Blind Period: All TEAEs with onset that meets these criteria:

- on or after the date of the first randomized drug administration in the Double-blind period
- up to 1 day after the last study drug dose

For the purposes of assigning TEAEs to study periods partial onset dates will be imputed as the latest possible date compatible with the known partial information; thus in case of ambiguity TEAEs will be assigned to the later period.

A TEAE is defined as treatment-related if it is recorded as “possibly related” or “related” to the study medication on the eCRF. AEs recorded as “not related” or “unlikely related” will be considered not related. In case the relatedness was not assessed, the most conservative result (related) will be chosen for the analysis.

In summaries of TEAEs a subject experiencing the same AE (with the same preferred term) multiple times within the same study period will only be counted once for that preferred term and study period. Similarly, if a subject experiences multiple AEs within the same system organ class in the same study period, that subject will be counted only once in that system organ class for that study period. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class and study period will be used. Similarly, when summarizing AEs by relationship to study drug, only the most related occurrence within the preferred term or system organ class and study period will be selected for displays in summary tables.

AEs will be summarized by study period, and for the Double-Blind period also by treatment

group.

An overall summary will include, by study period and by treatment group and overall, the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- TEAE leading to discontinuation of the study drug
- TEAE leading to death.

This overall summary will also be presented for subgroups of subjects identified in section 2.4.

The following TEAE frequency tables will be prepared summarizing the overall number of TEAEs, the number and percentage of subjects reporting at least one TEAE by MedDRA System Organ Class (SOC) and preferred term (PT), by treatment group and by study period:

- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- AEs leading to discontinuation of the study medication
- TEAEs in subjects with COVID-19
- TEAEs by severity
- TEAEs by relationship to study drug.

The summaries by SOC and PT will be ordered alphabetically by SOC and PT.

Additionally number and percentage of subjects with TEAE will be presented by preferred term only in the descending order of total frequency. Proportion of subjects experiencing TEAEs that occur in at least 5% of subjects in either treatment group will be compared between these groups using Fisher's exact test.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, severity, outcome, action taken and causal relationship to the study drug.

5.3 Laboratory Evaluations

The following laboratory tests will be performed at Screening, Visit 5 and Visit 7/Early Termination:

HEMATOLOGY: hemoglobin, hematocrit, red blood cell count, white blood cell count, % neutrophils,

% lymphocytes, % monocytes, % basophils, % eosinophils, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute basophils, absolute eosinophils, platelet count

CHEMISTRY: sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, albumin, total protein, uric acid, total bilirubin, direct

bilirubin, indirect bilirubin, alkaline phosphatase, alanine aminotransferase, (ALT, SGPT), aspartate aminotransferase (AST, SGOT), creatine phosphokinase, lactate dehydrogenase

URINALYSIS: pH, specific gravity, blood, glucose, ketones, microscopic exam (RBC and WBC, only when indicated), leukocyte esterase, protein

Urine drug test (for amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidines, benzodiazepines), urine pregnancy test and alcohol breath test will be performed at screening.

For hematology, chemistry and urinalysis baseline values will be summarized for the Safety Analysis Set. Actual values and changes from baseline will be summarized descriptively by visit and treatment group for the Randomized Analysis Set. Study entry baseline will be used.

Additionally, numeric hematology, chemistry and urinalysis results will be classified as Low (below the reference range), Normal (within the reference range) or High (above the reference range). Categorical Urinalysis results will be classified as Normal or Abnormal. Shifts among these categories between study entry baseline and last available post-baseline assessment will be provided.

All results will be listed.

Additionally, subject listings will be provided for the following occurrences during any period of the trial.

1. Liver enzyme (ALT or AST) values ≥ 2.5 times the upper limit of normal;
2. Serum creatinine level ≥ 1.75 times the upper limit of normal.

For subjects/tests that meet the above criteria at least once during the study, results from all available visits will be shown.

5.4 Vital Signs

Vital signs will be collected at all visits. Blood pressure, heart rate and respiratory rate will be collected at all visits, temperature at Screening and Visit 7/Early termination only. Blood pressure and heart rate will be recorded at two positions: supine and standing. At Visits 1 and 4, orthostatic vital signs (blood pressure and heart rate) will be performed in triplicate, each set separated by at least 15 minutes from the previous set. These triplicate assessments will be averaged and the average will be used in analysis.

Weight will be measured at Screening, Visit 5 and Visit 7/Early Termination.

Vital signs (including weight) and their changes from study entry baseline will be summarized descriptively by visit, position and treatment group (including "Not randomized" group for visits prior to Visit 4).

Vital signs will also be classified as follows:

- Systolic blood pressure: < 90 mmHg, 90 to < 140 mmHg, and ≥ 140 mmHg.
- Diastolic blood pressure: < 60 mmHg, 60 to < 90 mmHg, and ≥ 90 mmHg.
- Heart rate: < 60 beats/min, 60 to < 100 beats/min, and ≥ 100 beats/min.
- Respiratory rate: < 9 breaths/min, 9 to < 20 breaths/min, ≥ 20 breaths/min.

- Body temperature < 36.5ºC, 36.5ºC to < 37.5ºC, 37.5ºC to< 38.5ºC, and ≥ 38.5 ºC

Subjects will be summarized with counts and percentages by these categories.

Orthostatic hypotension is defined as a systolic blood pressure decrease of ≥ 20 mmHg or a diastolic blood pressure decrease of ≥ 10 mmHg within 3 minutes of standing. At visits when orthostatic vital signs are performed at triplicate, a subject will be defined as having orthostatic hypotension if it occurred between any pair of the supine and standing measurements.

Number and percentage of subjects with orthostatic hypotension will be presented by treatment group and visit, as well as at least after the study entry baseline.

All vital signs will be listed.

5.5 Electrocardiogram

ECG will be performed at Screening, Visit 5 and Visit7/Early termination. The following parameters will be recorded: Ventricular Rate (beats/min), PR Interval (msec), QRS Duration (msec), QT Interval (msec), RR Interval (msec), Rhythm Assessment (Normal Sinus Rhythm VR 60-100 bpm, Sinus Bradycardia VR less than 60 bpm, Sinus Tachycardia VR greater than 100 bpm or Other) and Overall Interpretation (Normal, Abnormal Not Clinically Significant (NCS) or Abnormal Clinically Significant (CS)).

QT Interval corrected using Fridericia's formula (QTcF) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{(\frac{RR}{1000})}}$$

Ventricular rate and ECG intervals will be summarized descriptively with their changes from study entry baseline by visit and treatment group for the Randomized Analysis Set. Study baseline values will also be summarized for the Safety Analysis Set.

Rhythm assessment and overall interpretation will be summarized categorically by visit and treatment group.

Shifts in overall interpretation from study entry baseline to the last available post-baseline assessment will be tabulated.

Additionally, ECG parameters will be classified as follows:

Parameter	Categories of value	Categories of change from baseline
Ventricular rate	< 60 beats/min, 60 to 100 beats/min, and > 100 beats/min	< -10 beats/min, -10 to < 0 beats/min, 0 to < 10 beats/min, and ≥ 10 beats/min.
PR Interval	< 120 msec, 120 to 200 msec, and > 200 msec	< -1 msec, -1 to 5 msec, and ≥ 5 msec
QRS Interval	< 60 msec, 60 to 100 msec, and > 100 msec	< 0 msec, 0 to < 3 msec, and ≥ 3 msec
QT Interval	< 200 msec, 200 to 430 msec, >430 to 450 msec, > 450 to 500 msec, and > 500 msec	< 30 msec, 30 to < 60 msec, and ≥ 60 msec

RR Interval	< 600 msec, 600 to 1000 msec, and > 1000 msec	< -33 msec, - 33 to < 12 msec, and ≥ 12 msec
QTcF Interval	< 200 msec, 200 to 430 msec, > 430 to 450 msec, > 450 to 500 msec, and > 500 msec	< 30 msec, 30 to < 60 msec, and ≥ 60 msec

Subjects will be summarized by number and percentage in each of the categories above by visit and treatment group.

All results will be listed.

5.6 Physical Examination

Physical examination will be performed at Screening and Visit 7/Early Termination. The following body systems will be examined: Gastrointestinal; Reproductive/Breast; Cardiovascular; Endocrine; General Appearance; Head, Eyes, Ears, Nose, Throat; Musculoskeletal; Neurologic; Peripheral Vascular; Psychiatric; Genitourinary/Renal; Respiratory; Dermatologic. Each system will be classified as Normal, Abnormal Not Clinically Significant (NCS) or Abnormal Clinically Significant (CS).

Number and percentage of subjects with each assessment result will be tabulated by body system, visit and treatment group for the Randomized Analysis Set. Study Baseline Values will also be summarized for the Safety Analysis Set.

All results will be listed.

5.7 C-SSRS

Columba Suicide Severity Rating Scale will be administered at each visit. Baseline/Screening version will be administered at the screening visit and Since Last Visit version at all subsequent visits.

Number and proportion of subjects with any suicidal ideation or and any suicidal behavior will be presented by visit and treatment group.

Time from study entry baseline to the first appearance of suicidal ideation or suicidal behavior will be summarized descriptively for those subjects who develop suicidal ideation or suicidal behavior during the study (i.e. do not have suicidal ideation or suicidal behavior at study entry baseline, but report it during the study).

All results will be listed.

5.8 GCSI

Gastroparesis Cardinal Symptom Index (GCSI) questionnaire will be administered at Visit 1 and Visit 7/Early Termination. GCSI contains 3 subscales: post-prandial fullness/early satiety (questions 4-7), nausea/vomiting (questions 1-3) and bloating (questions 8-9).

Total scores will be calculated for the entire questionnaire and each subscale. If at least one question is not answered then the total score and the affected subscale score will not be calculated.

Individual question scores, total score and subscale total scores as well as their changes from the study entry baseline will be summarized descriptively by visit and treatment group for the Randomized Analysis Set. Study entry baseline values will also be summarized for the Safety

Population.

All results will be listed.

5.9 Prior and Concomitant Medications

Prior medications are defined as medications taken prior to the study and stopped before the first dose of the study drug (IR CD-LD in the Dose Adjustment period). Concomitant medications are defined as medications taken while a subject took study drug, i.e. medications with stop date on or after the date of the first administration of the study drug or those that are ongoing.

Prior and concomitant medications will be coded using WHO Drug Dictionary version March 2019.

Use of prior and concomitant medications will be separately summarized by ATC class (the highest available level), preferred name, treatment group and study period (Dose Adjustment, IPX203 Conversion and Double-Blind treatment). A medication will be assigned to all periods during which it was taken at least once. A subject reporting the same medication more than once will be counted only once for that medication name; similarly, a subject reporting several medications in an ATC class will be counted once for that class. The summary will be ordered alphabetically by ATC class and preferred name.

Concomitant medications will also be grouped into various anti-PD medication classes:

- Amantadine
- selective MAO-B inhibitors
- anticholinergic PD medications
- dopamine agonists
- others

as well as antidepressants, sleep aids, and others.

Frequencies and percentages of subjects taking these classes of medications as well as each medication preferred name under the class will be summarized by treatment group and study period.

All prior and concomitant medications will be listed.

6 COVID-19 considerations for analyses

As the study will be partly conducted during the COVID-19 pandemic, a number of visits were delayed, cancelled or conducted remotely. To account for these circumstances the following changes were implemented in analysis:

1. A new sensitivity analysis will be conducted excluding the PD Diaries collected at Visit 7/ET that occurred later than planned (section 4.7.7)
2. Subjects with Dose Adjustment and IPX203 Conversion periods extended by more than 50% of the planned time will be excluded from the Per Protocol population (section 2.2.6)
3. Samples for laboratory tests and ECG for Visit 5 can be collected at Visits 4 or 6 (section 5.1)

4. Subjects who discontinued for reasons related to COVID-19 pandemic will be summarized separately in the disposition tables (section 3.1)
5. Adverse events in subjects with COVID-19 will be summarized separately (section 5.2).
6. Protocol deviations related to COVID-19 will be identified in the listing (section 3.5)

7 Changes From Protocol-Specified Analyses

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

8 REFERENCES

Study protocol: 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, Amendment 4, September 28, 2018.

9 APPENDICES

9.1 Schedule of events

Table 2 Schedule of Events

		3 Weeks of IR CD-LD Dose Adjustment	4 Weeks of IPX203 Dose Conversion			13 Weeks of Double-Blind Therapy		
Assessment	**Screening**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 Randomization**	**Visit 5**	**Visit 6**	**Visit 7/Study Exit/Early Termination[b]**
Study Week[a]	**–4**	**0**	**3**	**5**	**7**	**10**	**15**	**20**
ICF & HIPAA Authorization[c]	X							
Contact IWRS	X	X	X	X	X	X	X	X
Randomization					X			
Inclusion/Exclusion	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]		X[e]
C-SSRS[f]	X	X	X	X	X	X	X	X
Clinical Laboratory Tests[g]	X					X		X
Urine Pregnancy Test	X							
Urine Screen for Drug Abuse	X							
Alcohol Breath Test	X							
ECG	X					X		X
MoCA[h]	X							
MDS-UPDRS Parts I-IV	X[i]	X	X		X	X	X	X

PGI-C[j]						X	X	X
[redacted]								
PD Diary Training; Perform Concordance Testing at Screening Only[s]	X	X	X	X	X	X	X	
Dispense PD Diaries[t]	X	X		X	X	X	X	
Review PD Diaries[u]		X	X		X	X	X	X
Reminder phone calls[v,w]	X[v]	X[w]	X[w]	X[w]	X[w]	X	X	X
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

[redacted] C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, GCSI = Gastroparesis Cardinal Symptom Index, HIPAA = Health Insurance Portability and Accountability Act, ICF = informed consent form, IWRS = interactive web response system, MDS-UPDRS = MDS version of Unified Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment, [redacted] PD = Parkinson's disease, [redacted] PGI-C = Patient Global Impression of Change,

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

b Study Exit procedures to be conducted at the end of Visit 7 or during an early termination visit.

c Subjects enrolled at sites in the United States (US) must 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 has been resting supine for at least 5 minutes, then record orthostatic blood pressure and heart rate after subject has been standing for approximately 2 minutes. At Visits 1 and 4, orthostatic vital signs (blood pressure and heart rate) will be performed in triplicate, each set separated by at least 15 minutes from the previous set.

e Weight only.

f C-SSRS: Columbia Suicide Severity Rating Scale. See Appendix O of the protocol.

g See Appendix R of the protocol.

h Montreal Cognitive Assessment in the "On" state: see Appendix D of the protocol.

i At Screening MDS-UPDRS Parts I through IV will be done in both the "On" and "Off" state (see Appendix E) of the protocol.

j See Appendix F of the protocol.

k [redacted]

l

m

n

o See Appendix K of the protocol.

p [redacted]

q

r

s Train at Screening and then as needed at subsequent visits. Perform concordance testing at Screening.

t Dispense PD Diaries at Screening and Visits 1, 3, 4, 5, and 6. Call subjects 4 days prior to Visits 1, 2 and 4-7 to remind them to complete PD Diaries. Subjects record diary information for 3 consecutive days immediately prior to each of the visits (Days -3, -2, and -1). Call subjects 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.

u Review PD Diaries at Visits 1, 2, and 4-7.

v Post-Screening reminder phone call: Notify individuals who successfully complete screening procedures following review of all study entry criteria and clinical laboratory results that they may continue in the study. The interval between Screening and Visit 1 should not exceed 4 weeks.

w Reminder phone calls for Visits 1 through 4: In addition to the calls discussed above, make regular phone calls (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.

9.2 Code Fragments

9.2.1 MMRM Analysis of the Primary Endpoint and Continuous Secondary Endpoints

```
proc mixed data=…;
  class trtpn sitegr1 visitnum usubjid;
  model chg = base trtpn visitnum trtpn*visitnum / ddfm=kr residual
outp=resid;
  repeated visitnum / subject=usubjid type=UN;
  random sitegr1;
  lsmeans trtpn*visitnum / diff;
run;
```

Notes:

4. The input dataset includes one record per subject per visit.
5. Meaning of the variables:
   - TRTPN: treatment group
   - SITEGR1: pooled center
   - VISITNUM: visit number
   - USUBJID: unique subject identifier
   - CHG: value of the endpoint
   - BASE: baseline value of the endpoint
6. If the model does not converge with type=UN, further covariance structure types are to be tried as explained in section 4.4.2.
7. For covariance structures other than UN and CS, an additional statement "random usubjid" needs to be added.
8. OUTP option saves residuals for normality tests (see section 9.2.3).

9.2.2 CMH Test for Categorical Endpoints

```
proc freq data=...;
  tables sitegr1*trtpn*avalc / cmh;
run;
```

Percent difference with 95% confidence interval:

```
proc freq data=...;
  tables trtpn*avalc / riskdiff;
run;
```

Notes:

1. The input dataset includes one record per subject
2. Meaning of the variables:
   - TRTPN: treatment group

- SITEGR1: pooled center
- AVALC: outcome (e.g. Y or N)

9.2.3 Normality Test for Residuals

```
proc univariate data=residuals normal;
  var resid;
run;
```

Notes: input datasets comes from the OUTP option in the main analysis model.

9.2.4 Homogeneity of Variance Test

```
proc glm data=…;
  class trtpn;
  model chg = trtpn;
  means trtpn / hovtest;
run; quit;
```

Notes:

1. The input dataset includes one record per subject from Visit 7/ET only.
2. Meaning of the variables is the same as in section 9.2.1.

9.2.5 Wilcoxon Rank-Sum Test for Sensitivity Analysis

```
proc npar1way wilcoxon data=…;
  class trtpn;
  var chg;
  output out=WilcoxonOut;
run;
```

Notes:

1. Input dataset includes one record per subject from Visit 7 with imputations
2. Meaning of the variables is the same as in section 9.2.1.

9.2.6 ANCOVA Model for Complete Case or Single LOCF/BOCF Imputation Analyses

```
proc mixed data=...;
  class trtpn sitegr1;
  model chg = base trtpn  / ss3;
  random sitegr1;
  lsmeans trtpn / diff;
run;
```

Notes:

1. The input dataset includes one record per subject from Visit 7 only.
2. For the Complete Case analysis only subjects from the Completers Analysis Set are used
3. For the Single LOCF/BOCF imputation analysis CHG at Visit 7 may be imputed if applicable.
4. Meaning of the variables is the same as in section 9.2.1.

9.2.7 Site as Fixed Effect

```
proc mixed data=…;
  class trtpn sitegr1 visitnum usubjid;
  model chg = base trtpn visitnum sitegr1 trtpn*visitnum / ddfm=kr;
  repeated visitnum / subject=usubjid type=UN;
  lsmeans trtpn*visitnum / diff;
run;
```

All notes to the primary analysis (section 9.2.1) are applicable.

9.2.8 Pattern-Mixture Model

The following steps need to be repeated for each of the 4 dropout patterns specified in section 4.7.8.

Step1. Efficacy data needs to be transposed to one record per subject structure with responses from different visits in different variables. In the examples below responses from Visits 5, 6 and 7 are denoted as CHG5, CHG6 and CHG7.

Step 2. Impute intermittent missing values 50 times:

```
proc mi data=.. out=... nimpute=50 seed=2031602;
  var chg5-chg7;
  mcmc chain=multiple impute=monotone;
run;
```

Note: pre-specified seed is necessary to ensure results are repeatable and amenable to validation by double-programming. The value is chosen arbitrarily based on the protocol number.

Step 3. Impute trailing missing data (after discontinuation):

```
proc mi data=... out=... nimpute=1 seed=2031602;
  var trtpn sitegr1 base chg5-chg7;
  class trtpn sitegr1;
  monotone reg(chg5-chg7);
run;
```

Notes:

1. The input dataset is the output from the previous step.
2. The meaning of the variables is the same as in the primary model (section 9.2.1).
3. Missing values are imputed based on regression using the factors from the primary model.

Step 4. Transpose the output dataset back to vertical structure.

Step 5. Penalization. For each subject in the IPX203 treatment group in the current drop-out pattern, for each imputed value after the subject's discontinuation, generate 21 penalized records. For the penalization factor *pf* ranging from 0% to 100% in 5% increments, reduce the endpoint value by *pf* **EFFECT_SIZE*/100%, where *EFFECT_SIZE* is the LS Mean difference between IPX203 and IR CD-LD arms from the primary model (section 9.2.1).

Step 6. Analysis of imputed data. For each of the 50 imputations and 21 penalization factors perform the primary analysis as in section 9.2.1.

Step 7. Combine multiple imputation results for each penalization factor:

```
proc mianalyze parms=…;
   by pf;
   modeleffects trtpn*visitnum;
run;
```

Notes:

1. The input dataset (parms option) is LS Means or LS Means Differences (Diffs) dataset from the primary model from the previous step.

2. *pf* is the penalization factor.

9.2.9 Multiple Imputation Rank-Based Analysis

Steps 1-4 of this process will the same as in the Pattern Mixture Model (section 9.2.8).

Step 5. Analysis of imputed data. For each of the 50 imputations perform the rank-based analysis as in section 9.2.5.

Step 6. In order to combine the multiple imputation results in the next step, add a variable StdErr to the output dataset (WilcoxonOut) from the previous step, equal 1 on all records. This reflects the fact that Wilcoxon statistic has asymptotic standard normal distribution (with mean of 0 and standard deviation of 1) under the null hypothesis of no treatment effect.

Step 7. Combine multiple imputation results:

```
proc mianalyze data=WilcoxonOut;
   modeleffects Z_WIL;
   StdErr StdErr;
run;
```