SAP Title: An Open-Label Extension Study of the Safety and Clinical Utility of IPX203 in Parkinson's Disease Patients with Motor Fluctuations

Date: December 7, 2021

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16.1.9 Documentation of Statistical Methods

This appendix contains the following document:

Statistical Analysis Plan Final dated December 07, 2021

STATISTICAL ANALYSIS PLAN

Study Title:	**An Open-Label Extension Study of the Safety and Clinical Utility of IPX203 in Parkinson's Disease Patients with Motor Fluctuations**
Name of Test Drug:	IPX203
Protocol Number:	IPX203-B16-03
Protocol Version (Date):	Original Protocol, 25 April 2018 Amendment 1, 22 June 2018 Amendment 2, 26 November 2018
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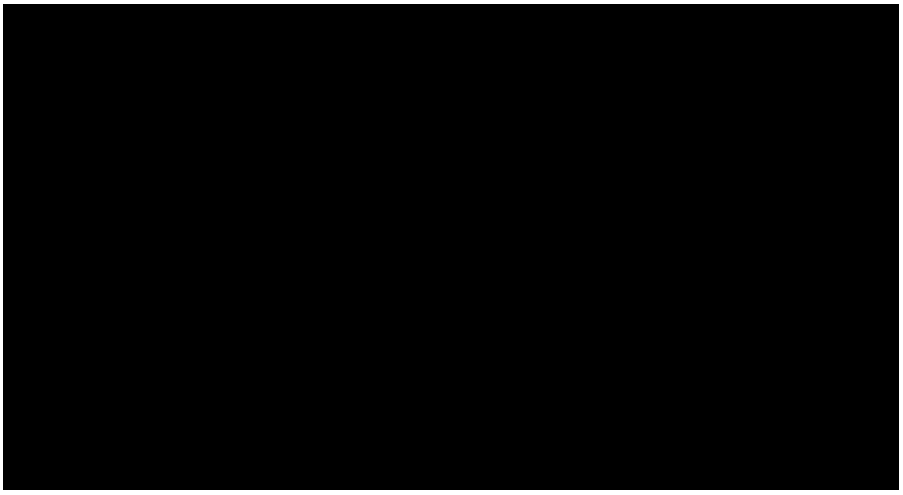

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomic-therapeutic-chemical
BMI	Body Mass Index
CD-LD	Carbidopa-Levodopa
CGI-S	Clinical Global Impression of Severity
CR	Controlled Release
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
eCRF	Electronic Case Report Form
EMSQ	Early Morning Symptoms Questionnaire
EOS	End of Study
GCSI	Gastroparesis Cardinal Symptom Index
HIPAA	Health Insurance Portability and Accountability Act
IR	Immediate Release
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
LD	Levodopa
LLC	Limited Liability Company
MAO-B	Monoamine oxidase B
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
NCS	Not Clinically Significant
NMSS	Non-Motor Symptom Assessment Scale
PAS	Parkinson Anxiety Scale
PD	Parkinson Disease
PDQ-39	Parkinson's Disease Questionnaire-39
PDSS-2	Parkinson's Disease Sleep Scale-2
PGI-S	Patient Global Impression of Severity
PT	Preferred Term
RBC	Red Blood Cells
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
TSA	Treatment Satisfaction Assessment
US	United States
WBC	White Blood Cells

WHO	World Health Organization
ZBI-12	12-Item Zarit Burden Interview (ZBI-12)

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-B16-03. This SAP is based on the study protocol amendment 2 dated 26November2018. 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 long-term safety and clinical utility of IPX203 in the treatment of subjects with advanced Parkinson's disease (PD) who have motor fluctuations.

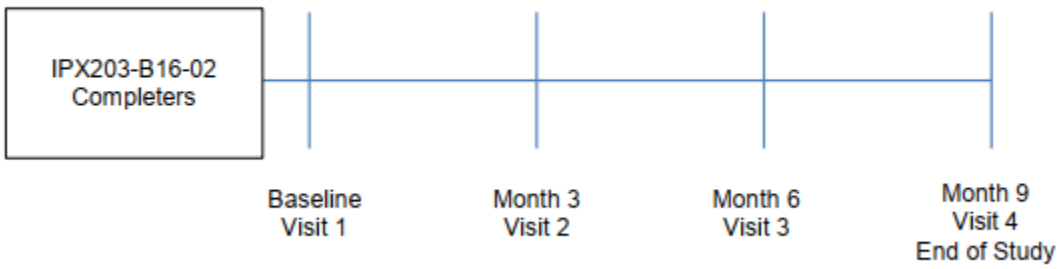
1.2 Study Design

Subjects who have successfully completed Study IPX203-B16-02 (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) may be offered the opportunity to enroll in this 9-month, multicenter open-label study. The study consists of a baseline visit (Visit 1) followed by 3 visits (Visits 2 to 4) spaced at approximately 3-month intervals. For subjects who successfully complete Study IPX203-B16-02, the baseline visit (Visit 1) of this study will occur coincident with the End of Study (EOS) Visit 7 of the preceding study, (with an allowed window of + 7 days). After providing written informed consent (and signing Health Insurance Portability and Accountability Act [HIPAA] authorization for subjects at United States [US] sites only), confirmation of eligibility and baseline procedures will be performed. Subjects will be initially started on the final IPX203 dosing regimen that was determined during the IPX203 dose conversion period of Study IPX203-B16-02. Investigators are permitted to adjust the dosing regimen of IPX203 during this study to achieve the optimal balance of efficacy and safety and any changes will be recorded.

Subjects may continue to take their non-LD-containing PD concomitant medications (including dopamine agonists, amantadine, and selective monoamine oxidase-B (MAO-B) inhibitors [safinamide, rasagiline and selegiline]) during the study. Changes in doses or in dosing regimens of all non-CD-LD PD medications and/or the addition of new non-CD-LD PD medications will be captured. Supplemental CD and benserazide, apomorphine, and the addition of catechol-O-methyltransferase (COMT) inhibitors (eg, entacapone, opicapone, and tolcapone) can be initiated during the study.

Adverse events, supine and standing orthostatic vital signs, and concomitant medications will be evaluated throughout the course of the study. Electrocardiograms (ECGs), clinical laboratory tests, physical examinations, and the Columbia-Suicide Severity Rating Scale (C-SSRS) will also be performed. The following clinical utility measures will be assessed: Patient Global Impression of Severity (PGI-S), Clinician Global Impression of Severity (CGI-S), Treatment Satisfaction Assessment (TSA), Parkinson's Disease Sleep Scale-2 (PDSS-2), the 39-item Parkinson's Disease Questionnaire (PDQ-39), Parkinson Anxiety Scale (PAS), Non-Motor Symptom assessment scale (NMSS) for Parkinson's disease, Gastroparesis Cardinal Symptom Index (GCSI), The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I to IV, 12-Item Zarit Burden Interview (ZBI-12), and Early Morning Symptoms Questionnaire (EMSQ). Visit 4 is the end of study (EOS).

Figure 1 Study Flowchart



1.3 Sample Size and Power

This study is an open-label study in PD subjects. All subjects who successfully complete IPX203-B16-02 are eligible to enroll in this study; it was originally estimated that approximately 300 subjects would be enrolled, but a larger number could be enrolled.

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.

Subjects will be assigned to treatment group defined by the treatment the subject received in the double-blind phase of the previous study IPX203-B16-02 (IPX203 or IR CD-LD).

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. Total group will also be presented.

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.

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 open-label study drug dose in the study IPX203-B16-03. 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

Baseline is defined as the last assessment obtained prior to the first dose of the open-label drug in the study IPX203-B16-03.

The study eCRF does not explicitly capture when the subject took the first open-label study drug dose. It will be assumed that this dose is taken on the day of Visit 1 after all study assessments.

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 the open-label study drug in the study.

The study eCRF does not explicitly capture if a subject took the open-label study drug. It will be assumed that a subject took the open-label study drug if and only if study drug was dispensed to the subject at one of the study visits.

2.2.2 Intent-to-Treat Analysis Set

The Intent-to-treat Analysis Set (ITT) will include all subjects who were treated with the open-label study drug in the study and have at least one post-baseline clinical utility assessment.

2.3 Visit Windows

Generally data will be analyzed by nominal visit when the data was collected. However, if a subject does not have a particular data point for a certain scheduled visit, but instead has it for an

unscheduled visit that occurred within +/-14 days window of the planned date of the scheduled visit, then the data from the unscheduled visit will be used in place of the missing scheduled visit. This will apply to both the clinical utility and safety data.

2.4 Early Termination Visits

Early termination visits and Visits 4 are collected in the study database as a single Visit/ET visit. For the purposes of by-visit summaries two separate visits will be presented:

- Visit 4 (identified as Visit 4/ET from the study database for subjects who completed the study)
- Visit 4/ET (i.e. all visits collected as Visit 4/ET in the study database)

3 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

3.1 Subject Enrollment and Disposition

The number of subjects that were enrolled, number and percentage of subjects who were included in the Safety and ITT analysis sets, completed the study and prematurely discontinued from the study (with the breakdown by the primary reason for discontinuation) will be presented by treatment group and overall. Percentages will be based on the number of enrolled 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 the 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. 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 the date of informed consent
- sex
- race
- ethnicity

Baseline physical characteristics will include:

- height at study IPX203-B16-02 screening
- weight at baseline
- BMI at baseline (note that height will not be collected during study IPX203-B16-03. Height will be taken from the previous study and BMI will be calculated using that height measurement and this study baseline weight)

Baseline disease characteristics include

- MDS-UPDRS Parts I, II, III, and IV total scores at baseline
- Hoehn and Yahr stage
- 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 and ITT analysis sets. The summaries will be presented for the two treatment group and total.

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

3.3 Study Drug Exposure

Overall summary of study drug exposure will include descriptive summary by treatment group of the following parameters:

- Average total daily dose of IPX203 – defined as the total IPX203 dose taken over the course of the study divided by the treatment duration in days
- Average daily dosing frequency – defined as the total number of administrations over the course of the study divided by the treatment duration in days
- Treatment duration – defined as [the date of last dose] – [the date of first dose] + 1.

IPX203 dosing regimen will be recorded at each visit. Frequency of daily dose administration (number of administrations per day), total daily dose of IPX203 (in mg) and most frequently used dose (mg) and their changes from the starting (Visit 1) regimen will be summarized by visit and treatment group. If more than one dose is used most frequently, the higher dose will be selected as the most frequent dose.

Total daily dose will also by summarized categorically, categorized as < 400, 400 to < 1000, 1000 to < 1400, 1400 to < 1800, 1800 to <= 2400, and >2400 mg.

Changes in total daily dose and daily dosing frequency will be analyzed for the following time periods: Visit 1 to Visit 2, Visit 2 to Visit 3, Visit 3 to Visit 4, Visit 1 to Visit 3 and Visit 1 to Visit 4. For each period subjects will be categorized into one of the following categories:

- No change in total daily dose
- Total daily dose modified, but returned to the same level (e.g. an increase followed by a decrease by the same value)
- Total daily dose increased during the period
- Total daily dose decreased during the period

Separately subjects' changes in daily dosing frequency will be categorized in a similar way.

Number and percentage of subjects in each of these categories will be presented for each time period.

Similar comparison of both total daily dose and daily dosing frequency will be made for the subject's stable IPX203 regimen in study IPX203-B16-03 vs. the starting (Visit 1) regimen in this study.

For subjects who changed their total dose or number of daily doses the number of steps during the time period will be categorized as 1, 2, 3, 4 or >4 and also be summarized.

For each time period Visit 1 to Visit 2, Visit 2 to Visit 3,Visit 3 to Visit 4, Visit 1 to Visit 3 and Visit 1 to Visit 4 the number and percentage of subjects with no change on their treatment regimen and with any change in their regimen will be provided. Number of changes will be summarized descriptively for each time period. Regimen changes include changes in dosing frequency or the dose taken at any administration and will be derived from the IPX203 Dose Adjustment Log CRF.

These summaries will be done on the Safety analysis set.

3.4 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.

3.5 Medical History

Medical history changes since the study IPX203-B16-02 screening will be recorded at Visit 1. Adverse Events that were recorded in study IPX203-B16-02 that have a stop date prior to or equal to Visit 1 Date of study IPX203-B16-03, will be recorded as medical history in this study. For the purposes of analysis medical history collected at IPX203-B16-02 screening will be pooled with the new entries collected at Visit 1 of study IPX203-B16-03 and resolved adverse events from study IPX203-B16-02.

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, as well as for all subjects overall.

All medical history information will be listed.

4 CLINICAL UTILITY ANALYSES

4.1 Imputation of missing data

Generally, missing data will not be imputed and data will be summarized as observed. Imputations will be performed for partially missing MDS-UPDRS responses as detailed in the following section.

4.1.1 Missing Data for MDS-UPDRS

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

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.

4.2 Analysis of the Clinical Utility Endpoints

Analysis of the clinical utility endpoints will be performed on the ITT population.

4.2.1 MDS-UPDRS

MDS-UPDRS will be administered at all scheduled visits 1-4.

The Total MDS-UPDRS and each of its components (Parts I through IV), and Parts II and III combined, as well as the changes from baseline in these scores, will be summarized by visit and treatment group, as well as for both treatment groups combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

4.2.2 PGI-S and CGI-S

The patients will rate the severity of their disease on a 7-point PGI-S scale ranging from “1: Normal, not at all ill” to “7: Extremely severely ill” at every visit.

Similarly, clinician’s global impression of severity will be rated on a 7-point CGI-S scale ranging from “1: Normal, not at all ill” to “7: Among the most extremely ill of subjects” at every visit.

PGI-S and CGI-S scores as well as their changes from baseline will be summarized descriptively by visit and treatment group, as well as for both treatment groups combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

Number and percentage of subjects with each score will also be summarized by visit and treatment group. Additionally number of subjects having PGI-S >= 4, CGI-S >= 4 or PGI-S >= 5, CGI-S >= 5 will be tabulated. Summary of study entry baseline of study IPX203-B16-02 will also be included.

4.2.3 PDQ-39 total score and individual domain scores

Parkinson's Disease Questionnaire-39 (PDQ-39) is a self-reported questionnaire. Using the 39 items, 8 domains are defined: mobility (Questions 1-10), activities of daily living (ADL) (Questions 11-16), emotional well-being (Questions 17-22), stigma (Questions 23-26), social support (Questions 27-29), cognition (Questions 30-33), communication (Questions 34-36) and bodily discomfort (Questions 37-39).

PDQ-39 will be administered at all scheduled visits 1-4.

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

All scores and their changes from baseline will be summarized descriptively by visit and treatment group, as well as both treatment group combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

4.2.4 PAS total score and individual domains

Parkinson Anxiety Scale (PAS) is a 12-item patient or observer rated questionnaire with 3 domains: persistent anxiety (Questions A.1-A.5), episodic anxiety (Questions B.1-B.4) and avoidance anxiety (Questions C.1-C.3).

PAS will be administered at all scheduled visits 1-4.

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

All scores and their changes from baseline will be summarized descriptively by visit and treatment group, as well as both treatment group combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

4.2.5 NMSS total score and individual domains

Non-Motor Symptom assessment scale for Parkinson's Disease (NMSS) is a 30-item investigator rated questionnaire. The NMSS contains 9 domains: cardiovascular (Questions 1, 2), sleep/fatigue (Questions 3-6), mood/cognition (Questions 7-12), perceptual problems (Questions 13-15), attention/memory (Questions 16-18), gastrointestinal (Questions 19-21), urinary (Questions 22-24), sexual function (Questions 25, 26), and miscellaneous (Questions 27-30).

NMSS will be administered at all scheduled visits 1-4.

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

All scores and their changes from baseline will be summarized descriptively by visit and treatment group, as well as both treatment group combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

4.2.6 PDSS-2 total score and individual domains

Parkinson's Disease Sleep Scale-2 (PDSS-2) is 15-item self-reported questionnaire. Three

domains are defined: disturbed sleep (Questions 1-3, 8, 14), motor symptoms at night (Questions 4-6, 12, 13), PD symptoms at night (Questions 7, 9-11, 15).

PDSS-2 will be administered at all scheduled visits 1-4.

Total scores will be calculated for the entire questionnaire and each domain. Additionally sum of questions 9, 10, 11, 12, and 13 will be calculated. If at least one question is not answered then the total score and the affected domain score will not be calculated.

All scores and their changes from baseline will be summarized descriptively by visit and treatment group, as well as both treatment group combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

4.2.7 TSA

Treatment Satisfaction Assessment will be administered at visits 2-4. The subjects will rate their satisfaction with their PD treatment on a 7-point scale ranging from "1: Very much dissatisfied" to "7: Very much satisfied".

TSA scores will be summarized descriptively by visit and treatment group, as well as for both treatment groups combined.

Number and percentage of subjects with each score will also be summarized by visit and treatment group. Also, the number and percentage of subjects with scores 5-7 (satisfied) vs. scores 1-4 (dissatisfied or neutral) will be tabulated.

4.2.8 ZBI-12

The 12-Item Zarit Burden Interview (ZBI-12) is used to assess the perceived burden of caregivers who provide assistance to patients with long-term progressive neurological disorders, including PD. The questionnaire consist of 12 questions, each answered on a scale from "0: Never" to "4: Nearly always".

The ZBI-12 should be completed by the same caregiver during each scheduled visit.

Total score will be calculated by summing up the responses to all questions. If at least one question is not answered then the total score will not be calculated.

The total score and its change from baseline will be summarized descriptively by visit and treatment group, as well as for both treatment group combined.

Additionally the total score will be classified as follows:

- 0-10: no to mild burden
- >10-20: mild to moderate burden
- >20: high burden

Number and percentage of subjects at each category will be tabulated by visit and treatment group.

4.2.9 EMSQ

The EMSQ is a 3-question, subject-rated questionnaire that is used to assess whether a subject is experiencing any of 10 early morning PD symptoms by answering questions about prevalence

(Question 1), severity (Question 2), and response to the first morning dose of PD medications (Question 3). Study site staff will complete this questionnaire by questioning subjects during each scheduled visit.

For each symptom, number and percentage of subjects with each frequency and severity will be tabulated by visit and treatment group, as well as for both treatment groups combined. Whether the symptom improves after taking the first morning dose of the study drug will be similarly summarized. Summary of study entry baseline of study IPX203-B16-02 will also be included.

Total severity score will be calculated as the sum of severities across all 10 symptoms (None = 0, Mild = 1, Moderate = 2, Severe = 3). If the severity score is missing for at least one symptom, then the total severity score will not be calculated. The total severity score and its change from baseline will be summarized descriptively by visit and treatment group, as well as for both treatment group combined. Summary of study entry baseline of study IPX203-B16-02 will also be included.

5 SAFETY ANALYSES

Safety analyses will be performed on 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 not be summarized at that visit.

5.1 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, unless otherwise specified. An AE will be considered as treatment-emergent if the date of onset is on or after the date of the first open-label study drug administration in the study IPX203-B16-03 and no later than 1 day after the last study drug dose in the study. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the first open-label 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 open-label study drug and no later than 1 day after the last study drug dose.

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 will only be counted once for that preferred term. Similarly, if a subject experiences multiple AEs within the same system organ class, that subject will be counted only once in that system organ class. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class 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 will be selected for displays in summary tables.

An overall summary will include, 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.

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 overall:

- 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.

TEAEs will also be presented by SOC, PT, treatment group and one of the following subgroups of AEs:

- Total daily dose on the day of AE onset, categorized as < 400, 400 to < 1000, 1000 to < 1400, 1400 to < 1800, 1800 to <= 2400, and >2400 mg
- Daily dosing frequency on the day of AE onset (2, 3, 4, etc. times a day)
- Time to first onset, defined as the study day of the first onset of AE of the given SOC or PT for the subject, categorized as <= 7 days, >7 to 30 days, >30 to 90 days, >90 to 180 days, and >180 days.
- Time period. In this analysis each AE will be assigned to all (possibly several) time periods as in the previous paragraph during which the AE was active (i.e. after onset and prior to resolution).

TEAEs will also be presented by SOC, PT, treatment group and one of the following subgroups of subjects:

- Age: < 65, ≥ 65 years old at Visit 1
- Sex: Males, Females
- Race: Caucasians, non-Caucasians
- Region: North America or Europe
- PD duration at Visit 1: <8 years or ≥8 years
- 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

Additional summaries of non-treatment-emergent AEs that started in the previous study IPX203-B16-02 will be provided:

- AEs that started in study IPX203-B16-02 and resolved in the current study vs. those that did not resolve, by SOC, PT and treatment at the onset of AE (IPX203 or IR CD-LD and both treatments together)
- AEs that started in study IPX203-B16-02 and ended in the current study vs. are ongoing at the end of the current study by SOC, PT and treatment at the onset of AE (IPX203 or IR CD-LD and both treatments together)

For this analysis AE will be defined as resolved if its outcome is recorded as "Recovered/Resolved" or "Recovered/Resolved with Sequelae" in the eCRF. All other AEs will be considered not resolved.

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.

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.

5.2 Laboratory Evaluations

The following laboratory tests will be performed at all scheduled visits 1-4:

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 pregnancy test will be performed at Visit 1 only.

For hematology, chemistry and urinalysis actual values and changes from baseline will be summarized descriptively by visit and treatment group, as well as both treatment group combined.

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 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 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.

5.3 Vital Signs

Vital signs will be collected at all scheduled visits. Blood pressure, heart rate and respiratory rate will be collected at all visits, temperature at Visits 1 and 4 only. Blood pressure and heart rate will be recorded at two positions: supine and standing.

Weight will also be measured at all scheduled visits.

Vital signs (including weight) and their changes from baseline will be summarized descriptively by visit, position and treatment group, as well as for both treatment groups combined.

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.

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

All vital signs will be listed.

5.4 Electrocardiogram

ECG will be performed at all scheduled visits 1-4. 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 baseline by visit and treatment group as well as for both treatment groups combined.

Rhythm assessment and overall interpretation will be summarized categorically by visit and treatment group, as well as both treatment group combined.

Shifts in overall interpretation from 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, as well as both treatment group combined.

All results will be listed.

5.5 Physical Examination

Physical examination will be performed at Visit 1 and 4. 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, as well as both treatment group combined.

All results will be listed.

5.6 C-SSRS

Columba Suicide Severity Rating Scale ("Since Last Visit" version) will be administered at each scheduled visit.

Suicidal ideation will be defined as "yes" answer to any one of the five suicidal ideation questions (Question 1-5) on the C-SSRS.

Suicidal behavior will be defined as "yes" answer to any one of the 5 suicidal behavior questions (Actual attempt, Interrupted attempt, Preparatory Acts or Behavior, Suicidal behavior, Completed suicide) on the C-SSRS.

Number and percentage of subjects with any suicidal ideation and/or any suicidal behavior will be presented by visit and treatment group, as well as for both treatment groups combined.

Time from 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 baseline, but report it during the study).

All results will be listed.

5.7 GCSI

Gastroparesis Cardinal Symptom Index (GCSI) questionnaire will be administered at Visits 1 and 4. 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 baseline will be summarized descriptively by visit and treatment group as well as for both treatment groups combined.

All results will be listed.

5.8 Concomitant Medications

Concomitant medications are defined as medications taken while a subject took the open-label study drug, i.e. medications with stop date on or after the date of the first administration of the open-label study drug or those that are ongoing.

Concomitant medications will be coded using WHO Drug Dictionary version March 2019.

Use of concomitant medications will be summarized by ATC class (the highest available level), preferred name and treatment group, as well as for both treatment groups combined. 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 as well as for both treatment groups combined.

All 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 can be delayed, canceled or conducted remotely. To account for these circumstances the following changes were implemented in analysis:

1. All measurements for the following scales that were done remotely due to COVID-19 will be included in the analysis as if they were done at a face-to-face visit:
   - C-SSRS (Columbia Suicide Severity Rating Scale)
   - NMSS (Non-Motor Symptom Assessment Scale for Parkinson's Disease
   - PAS (Parkinson Anxiety Scale)
   - PDQ-39 (39-item Parkinson Disease Questionnaire
   - PDSS-2 (Parkinson's Disease Sleep Scale-2)
   - PGI-S (Patient Global Impression of Severity)
   - GCSI (Gastroparesis Cardinal Symptom Index)
   - TSA (treatment Satisfaction Assessment)
   - ZBI-12 (12-item Zarit Burden Interview)
   - EMSQ (Early Morning Symptoms Questionnaire)
   - MDS-UPDRS parts I, II, and IV
2. Remote measurements, due to COVID-19, of the following scales will be excluded from all analyses:
   - MDS-UPDRS Part III
   - CGI-S (Clinical Global Impression of Severity)
3. Samples for laboratory tests and ECG that were done outside of regular visits, due to COVID-19, will be included in the analysis and mapped to the closest protocol defined visit (section 2.3).
4. Subjects who discontinued for reasons related to COVID-19 pandemic will be summarized separately in the disposition tables (section x)
5. Adverse events in subjects with COVID-19 will be summarized separately (section 5.1)

6. Protocol deviations related to COVID-19 will be identified in the listing (section 3.4)

7 Changes From Protocol-Specified Analyses

The protocol envisioned summarizing AEs, vital signs and ECG across the entire IPX203 exposure including information from the open-label extension and the prior IPX203-B16-02 study into which the subjects were enrolled. It was decided to postpone such analyses until an Integrated Summary of Safety (ISS) is prepared. Such analyses will not be done as part of this SAP.

Changes related to the COVID-19 pandemic are summarized in section 6.

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

8 REFERENCES

Study protocol: An Open-Label Extension Study of the Safety and Clinical Utility of IPX203 in Parkinson's Disease Patients with Motor Fluctuations, Amendment 1, June 22, 2018.

9 APPENDICES

9.1 Schedule of events

Table 1 Schedule of Events

	Visit 1 Baseline	9 Months of IPX203 Therapy					
		Study Drug Resupply Months 1-2	Visit 2	Study Drug Resupply Months 4-5	Visit 3	Study Drug Resupply Months 7-8	Visit 4/ Early Termination
Study Month	**0**		**3**		**6**		9
ICF and HIPAA Authorization [b]	X						
Check Inclusion/Exclusion Criteria	X						
Update Medical History	X						
Physical Examination	X						X
Vital Signs [c]	X		X		X		X
Weight	X		X		X		X
C-SSRS [d]	X		X		X		X
Clinical Laboratory Tests [e]	X		X		X		X
Urine Pregnancy Test	X[f]						
ECG	X		X		X		X
MDS-UPDRS Parts I-IV [g]	X		X		X		X
PGI-S [h]	X		X		X		X
CGI-S [i]	X		X		X		X
PDQ-39[j]	X		X		X		X
GCSI [k]	X						X
NMSS [l]	X		X		X		X
PDSS-2[m]	X		X		X		X
PAS [n]	X		X		X		X
TSA [o]			X		X		X
ZBI-12 [p]	X		X		X		X
EMSQ [q]	X		X		X		X
Contact phone calls [r]			X		X		X
Contact IWRS to 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
Concomitant Medications	X		X		X		X

[a] Visit 1 is expected to occur on the same day as the End-of-Study Visit (Visit 7) of Study IPX203-B16-02 but not later than 1 week. After the subject provides consent for this study, carry over and record information from procedures at the End-of-Study Visit of IPX203-B16-02 as the Baseline data for this study.

[b] Subjects enrolled at sites in the United States (US) must sign HIPAA authorization prior to the conduct of any study-specific procedures.

[c] Record vital signs (blood pressure, heart rate, respiratory rate, and temperature [Visit 1 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.

[d] See Appendix B of the protocol.

[e] See Appendix C of the protocol.

[f] This test will be performed at Visit 1 of this study.

[g] See Appendix D of the protocol.

[h] See Appendix E of the protocol.

[i] See Appendix F of the protocol.

[j] See Appendix G of the protocol.

[k] See Appendix H of the protocol.

[l] See Appendix I of the protocol.

[m] See Appendix J of the protocol.

[n] See Appendix K of the protocol.

[o] See Appendix L of the protocol.

[p] See Appendix M of the protocol.

[q] See Appendix N of the protocol.

[r] Contact phone calls for Visits 2 through 4:

- Following Visit 1, contact subjects weekly for the first month and then monthly thereafter between visits to review the subject's medication dosing regimen.
- Instruct subjects to call the study site before making any changes to their IPX203 dosing regimen.
- Update and record concomitant medications and IPX203 dose adjustments.
- Contact subjects 1 day prior to Visits 2 to 4 to remind them to bring back any unused medication and empty medication bottles.

CGI-S = Clinical Global Impression of Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EMSQ = Early Morning Symptoms Questionnaire; GCSI = Gastroparesis Cardinal Symptom Index; HIPAA = Health Insurance Portability and Accountability Act; ICF = informed consent form; IWRS = interactive web response system; PAS = Parkinson Anxiety Scale; PD = Parkinson's disease; PDQ-39 = 39-Item Parkinson's Disease Questionnaire; PDSS-2 = Parkinson's Disease Sleep Scale-2; PGI-S = Patient Global Impression of Severity Scale; MDS-UPDRS = MDS version of Unified Parkinson's Disease Rating Scale; NMSS = Non-Motor Symptom Assessment Scale; TSA = Treatment Satisfaction Assessment; ZBI-12 = 12-Item Zarit Burden Interview