IPX203 (CARBIDOPA-LEVODOPA) EXTENDED RELEASE

IPX203-B16-01

A RANDOMIZED, MULTIPLE DOSE STUDY TO ASSESS THE PHARMACOKINETICS AND PHARMACODYNAMICS OF IPX203 IN SUBJECTS WITH ADVANCED PARKINSON'S DISEASE

SPONSOR

Impax Laboratories, Inc.,

acting through its Impax Specialty Pharma division (Impax)

30831 Huntwood Ave.

Hayward, CA 94544

Original Protocol, August 8, 2016

Amendment 1, September 1, 2016

Amendment 2, October 5, 2016

SIGNATURE PAGE

Reviewed and approved by:

10/5/2016	
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10/5/2016	
Weiru Hong, MS Senior CRA, Clinical Operations	Date
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	Oct 05, 2016
Aravind Mittur, PhD Director, Clinical Pharmacology	Date

INVESTIGATOR'S AGREEMENT

Protocol No.: IPX203-B16-01

Protocol Title: A Randomized, Multiple Dose Study to Assess the Pharmacokinetics and Pharmacodynamics of IPX203 in Subjects with Advanced Parkinson's Disease

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements of International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and the appropriate regulatory authority.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this clinical study. I will discuss this material with them to ensure that they are fully informed regarding the study medication, the conduct of the study, and the obligations of confidentiality.

_____ _____

Principal Investigator's signature Date

_____

Principal Investigator's printed name

STUDY CONTACT INFORMATION

Changes in Impax study personnel listed on this page do not require a protocol amendment.

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1. SYNOPSIS

Name of Sponsor/Company: Impax Laboratories, Inc. acting through its Impax Specialty Pharma division (Impax)

Name of Investigational Product: IPX203 (carbidopa-levodopa) Extended-Release Capsules

Name of Active Ingredient: carbidopa (CD), levodopa (LD)

Protocol Title: A Randomized, Multiple Dose Study to Assess the Pharmacokinetics and Pharmacodynamics of IPX203 in Subjects with Advanced Parkinson's Disease

Protocol No.: IPX203-B16-01

Study center(s): Multicenter

Phase of Development: Phase 2

Study Duration: Approximately 8 weeks including Screening

Objectives:

Primary: To compare the pharmacokinetics (PK) of single and multiple doses of IPX203 with immediate release (IR) CD-LD in subjects with advanced Parkinson's disease (PD).

Secondary:

- To compare the pharmacodynamics of single and multiple doses of IPX203 with IR CD-LD
- To compare the efficacy of IPX203 with IR CD-LD following multiple doses
- To evaluate the safety of IPX203.

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

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

Within 2 weeks following Screening, eligible subjects will complete their PD and Dosing diaries, and will wear the Kinesia 360 sensor bands on the more affected side at home immediately after waking on each of the 3 days prior to Visit 1. Subjects will be instructed to take their last dose of CD-LD no later than 10:00 PM on the evening prior to Visits 1 and 3. The first morning dose of study medication will be administered at the study site. The "first morning dose" is defined as the subject's first LD dose upon awakening for the day immediately following the subject's usual nocturnal sleep period intended to achieve an "on"

state. On Day 1 of the IR CD-LD treatment period, subjects will start with a single dose of their usual prestudy first morning IR CD-LD dose. On Day 1 of the IPX203 treatment period, subjects will start with a single dose of IPX203 based on their usual prestudy first morning IR CD-LD dose. Pharmacokinetic and pharmacodynamic measures will be assessed in the clinic for up to 8 hours postdose during Visits 1 and 3. If subject experiences an "off" state for ≥ 3 consecutive hours after dosing, the subject may receive rescue medication, (by taking an additional dose of study medication for that period). PK blood sampling and pharmacodynamic assessments will be continued throughout the 8-hour PK/pharmacodynamic study period including in those subjects who receive rescue medication.

Day 1 (Visits 1 and 3) blood samples (6 mL) for PK analysis will be collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, and 8 hours postdose.

The following pharmacodynamic measures will be conducted during Visits 1 and 3 by qualified clinical staff who are blinded to dosing:

- Assessment of Subject's Motor State ("on" and "off," and state of dyskinesia) at –1, –0.5, 0, and at half-hourly intervals postdose for up to 8 hours.
- MDS-UPDRS Part III (Motor Examination) at predose and hourly for up to 8 hours postdose.

Following the completion of Visits 1 and 3, subjects will be discharged from the clinic and instructed to take their assigned study drug at home for the remainder of Day 1 through Day 14 of each treatment period and return to the clinic on Day 15 (of each treatment period) for Visits 2 and 4.

During the IR CD-LD treatment period, the initial dosing regimen of IR CD-LD will be the same as the subject's stable prestudy regimen unless they were taking a single daily bedtime dose of CR CD-LD, either alone or in combination with IR CD-LD, in which case, the CR CD-LD dose will be discontinued and substituted with a 1:1 milligram-equivalent IR CD-LD dose. A "bedtime dose" is defined as a dose of CR CD-LD taken within 1 hour of the subject's normal nighttime sleep period. During the IPX203 treatment period, the initial doses of IPX203 will be based on the subject's prestudy stable LD regimen and the initial response to IPX203. The typical dosing regimen for IPX203 will be three times a day, dosed approximately every 7 to 8 hours. Some subjects may require more or less frequent dosing to optimize therapeutic effect (minimize "off" time without causing troublesome dyskinesia or other dopaminergic side effects).

During Days 1 through 9 of both treatment periods, investigators may adjust each subject's study medication regimen if necessary to optimize efficacy and safety. Site staff should follow-up on the subject's status (dosing, response and adverse events) every 1-3 days by telephone.

On Days 10 through 14 of each treatment period, subjects should be on a stable dosing regimen. Subjects may 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. Subjects will complete their Dosing and PD Diaries and wear the Kinesia 360 sensor bands on the more affected side at home immediately after waking in the morning on each of the 3 days prior to Visits 2 and 4 (Days 12-14 of each treatment period).

For the Day 15 clinic visits, the subjects will be instructed to withhold their study medication

for at least 5 hours before arriving at the study site. The first morning dose of study medication will be administered at the study site. This first morning dose and subsequent doses administered in the clinic will be the same as the dosing regimen recorded in the dosing diary for Days 12-14 of the current treatment period.

Pharmacokinetic and pharmacodynamic measures will then be assessed in the clinic for up to 10 hours postdose during Visits 2 and 4. PK blood sampling and pharmacodynamic assessments will be continued throughout the 10-hour PK/pharmacodynamic study period.

Day 15 (Visits 2 and 4) blood samples (6 mL) for PK analysis will be collected predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours postdose.

The following pharmacodynamic measures will be conducted during Visits 2 and 4 by qualified clinical staff who are blinded to dosing:

- Assessment of Subject's Motor State ("on" and "off," and state of dyskinesia) at –1, –0.5, 0, and half-hourly intervals postdose for up to 10 hours.
- MDS-UPDRS Parts I, II, and IV will be assessed at predose
- MDS-UPDRS Part III (Motor Examination) will be assessed at predose and hourly for up to 10 hours postdose.

When the subject leaves the clinic after Visit 2 for wash-out and after Visit 4 (end of treatment period 2), he/she will revert to his/her prestudy dosing regimen.

Number of subjects (planned): Approximately 30 subjects will be randomized to complete 26.

Diagnosis and main criteria for inclusion:

- Male or female subjects diagnosed with idiopathic PD at age ≥40 years who are currently being chronically treated with stable regimens of CD-LD but experiencing motor complications. Idiopathic PD is defined by United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria.
- Hoehn and Yahr Stages 2, 3, or 4 (part of MDS-UPDRS Part III)
- Montreal Cognitive Assessment (MoCA) score ≥24 at Screening Visit in the "on" state.
- For the 4 weeks prior to Screening, the subject experiences daily "wearing-off" episodes with periods of bradykinesia and rigidity, and experiences an "off" state upon awakening on most mornings by history.
- At Visit 1, review of the 3-day PD diary confirms the following: that the subject is able to properly complete the diary with valid entries; and that the subject has an average of at least 2.5 hours per day of "off" time during the waking hours over the 3 days with at least 1.5 hours "off" time on each day. Inability to properly complete the diary is indicated when more than 1 day of the diary is not returned or when more than 2 hours (4 half-hour periods) of one 24-hour diary day are missing.
- Responsive to CD-LD therapy and currently being treated on a stable regimen with CD-LD for at least 4 weeks prior to Visit 1 and:
  - requires 100 to 250 mg (in units of 50 mg) of IR CD-LD for the morning dose
  - requires a total daily dose of at least 400 mg of IR CD-LD
  - takes a maximum total daily dose of 1800 mg LD, comprising IR CD-LD alone or

IR CD-LD in combination with a single daily bedtime dose of CR CD-LD.
  - has a dosing frequency of 4 to 9 times daily of CD-LD
  - typically experiences an "on" response with the first dose of IR CD-LD of the day (by subject history)
  - By history, efficacy of the first morning dose of IR CD-LD lasts less than 4 hours, typically wearing "off" prior to the next dose; or subject takes the second dose of PD medications prior to 4 hours to avoid an "off."
- Has not used doses of controlled-release (CR) CD-LD apart from a single daily bedtime dose for at least 4 weeks prior to Visit 1.
- Has not used any doses of Rytary for the past 4 weeks prior to Visit 1.
- At Screening, the MDS-UPDRS Part III total score in the "off" state is:
  - at least 20 units
  - at least 25% or 10 units greater than in the "on" state
- **Exclusions:**
  - History of medical conditions or of a prior surgical procedure that would interfere with LD absorption, such as gastrectomy or proximal small-bowel resection.
  - Liver enzyme values ≥2.5 times the upper limit of normal; or history of severe hepatic impairment; or serum creatinine level ≥1.75 times the upper limit of normal; or requires dialysis at the time of Screening.
  - History of drug or alcohol abuse within the 12 months prior to Screening.
  - Received within 4 weeks of Visit 1 or planning to take during participation in the clinical study: any doses of a controlled-release (CR) LD apart from a single bedtime dose or any doses of Rytary, additional CD (eg, Lodosyn) or benserazide (eg, Serazide), or catechol-O-methyl transferase inhibitors (entacapone or tolcapone) or medications containing these inhibitors (Stalevo). Received within 4 weeks of Visit 1 or planning to take during participation in the clinical study: nonselective MAO inhibitors, apomorphine, or dopaminergic blocking agents including antiemetics.
  - History of psychosis within the past 10 years. Mild PD-associated illusions are not exclusionary provided that they do not occur more than once per week and the subject does not lose insight
  - Treatment with any dopamine antagonist antipsychotics within the last 2 years.
  - Based on clinical assessment, subject does not adequately comprehend the terminology needed to complete the PD diary.

Investigational product, dosage and mode of administration: IPX203 (carbidopa-levodopa) Extended-Release capsules, containing 180 mg and 270 mg of LD, for oral administration.

Reference therapy, dosage and mode of administration: Immediate-release carbidopa-levodopa (IR CD-LD) tablet containing 100 mg of LD for oral administration.

Criteria for evaluation:

Efficacy:

- Primary: Percent "off" time during waking hours, based on subject PD diaries for the last

3 days collected at the end of each treatment period

- Secondary:
  - Subject PD diaries for the last 3 days collected at the end of each treatment period:
    - Average of (1) total "off" time (2) total "on" time with no troublesome dyskinesia [good on] (3) total "on" time with no dyskinesia (4) total "on" time with troublesome dyskinesia (5) total "on" time with non-troublesome dyskinesia (6) total time asleep
    - Proportion of subjects with an improvement of at least 0.5, 1, 1.5, 2, and 3 hours from baseline in the total "off" time based on PD Diaries
    - Proportion of subjects in "off" state within the first 30 minutes of awakening for the day immediately following the subject's usual nocturnal sleep period.
    - Average total "off" time and total "on" time with no troublesome dyskinesia normalized for 16 waking hours
  - Change in the dyskinesia, mobility, and tremor measures obtained using the Kinesia 360
  - MDS-UPDRS collected predose on Day 15 of each treatment period – Average of
    - total MDS-UPDRS score for the sum of Parts I to IV
    - total scores for each of the 4 parts of the MDS-UPDRS
    - total MDS-UPDRS score for the sum of Parts II and III

Pharmacodynamics:

- Subject Motor Assessment - Day 1 and Day 15 of each treatment period
  - average of (1) total off time (2) total "on" time with no troublesome dyskinesia [good on] (3) total "on" time with no dyskinesia (4) total "on" time with troublesome dyskinesia (5) total "on" time with non-troublesome dyskinesia (6) total time asleep,
  - proportion of subjects who are "off" and proportion of subjects "on" without troublesome dyskinesia will be presented at each time point
- MDS-UPDRS Part III - Day 1 and Day 15 of each treatment period
  - average of change in MDS-UPDRS Part III score from Day 1 predose value at each time point
  - average of the area under the curve (AUC) of change in MDS-UPDRS Part III motor score value from predose value on Day 1
  - average duration of effect estimated using the time point at which an improvement of at least (1) 4 points (2) 7 points (3) 13 points in the MDS-UPDRS Part III score from predose value on Day 1 is first observed and continuing until the time point at which the improvement is no longer observed.
  - Individual and average of change in sum of questions 4 through 8 and question 14 MDS-UPDRS Part III score from Day 1 predose value at each time point to assess bradykinesia.

Pharmacokinetics (Visits 1 – 4):
The following PK parameters will be calculated from the CD and LD plasma concentration-time profiles after each treatment:

- fluctuation index (Visits 2 and 4)
- accumulation (Visits 2 and 4)
- observed maximum plasma concentration (C_{max}) and time to maximum concentration (T_{max}) on Day 1
- area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}), and from time zero to infinity ($AUC_{0-\infty}$) on Day 1
- apparent elimination half-life ($t_{1/2}$) on Day 1
- bioavailability of IPX203 relative to IR CD-LD on Day 1
- time to 50% C_{max} of LD on Day 1
- duration > 50% C_{max} of LD on Day 1.

Safety:

- electrocardiograms (ECGs), clinical laboratory tests, physical examinations, C-SSRS, and vital signs
- adverse events and concomitant medications evaluated throughout the course of the study.

Statistical methods:

Pharmacokinetics:

Descriptive statistics will be presented by treatment group for the PK parameters for IR CD-LD and IPX203. Following natural logarithm transformation, analyses of variance (ANOVA) will be performed on CD and LD AUC and C_{max} normalized for dose. Additionally, duration of LD plasma concentration above 50% of C_{max} values will be analyzed using ANOVA. Comparisons will be performed using a mixed-effect ANOVA model that includes treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect for the following treatments: IPX203 versus IR CD-LD.

Efficacy:

- Descriptive statistics and frequency distributions will be displayed for all endpoints
- Primary: The primary efficacy parameter for this study will be the average percent "off" time during waking hours based on subject PD diaries collected at the end of each treatment period. For each day it will be calculated as the number of half-hour intervals in which "off" is checked. The average percent "off" time will be defined as the average of percent "off" time (total "off" time divided by the total time not "asleep" (ie, waking hours) from the subject PD diaries completed for the 3 days immediately prior to the visit. The difference between the average percent "off" time between treatments will be analyzed using a standard mixed-model analysis of variance at a 0.05 level of significance. This model will include the fixed-effect factors of treatment, and period and the random-effect inter- and intra-subject factors.
- Secondary: The continuous efficacy endpoints will be evaluated for differences between treatments using a standard mixed-model analysis of variance at a 0.05 level of significance. This model will include the fixed-effect factors of treatment, sequence and period and the random-effect inter- and intra-subject factors. The categorical endpoints will be analyzed using generalized estimating equations methods. The model will include treatment and period. All comparisons of secondary endpoint will be tested at 5% significance level without any multiplicity correction.

Pharmacodynamics:

- Descriptive statistics and frequency distributions will be displayed for all pharmacodynamic endpoints.
- The continuous endpoints will be evaluated for differences between treatments using a standard mixed-model analysis of variance at a 0.05 level of significance. This model will include the fixed-effect factors of treatment, sequence and period and the random-effect inter- and intra-subject factors. The categorical endpoints will be analyzed using generalized estimating equations methods. The model will include treatment and period. All comparisons of secondary endpoint will be tested at 5% significance level without any multiplicity correction.

Safety:

Quantitative data for safety will be summarized using descriptive statistics. Qualitative safety data will be summarized by count per category and number and percentage of subjects where appropriate.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AADC	aromatic amino acid decarboxylase
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the curve
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last measurable concentration
AUC_{0-inf} or $AUC_{0-\infty}$	area under the plasma concentration time curve from time 0 to time infinity
CD	Carbidopa
CR	controlled release
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
ENTA	Entacapone
ER	extended release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IR	immediate release

Abbreviation or Specialist Term	Explanation
IRB	institutional review board
LD	Levodopa
MDS-UPDRS	Movement Disorders Society version of the Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
PK	pharmacokinetic (adjective) pharmacokinetics (singular noun)
PI	principal investigator
SAE	serious adverse event
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
$t_{1/2}$	apparent elimination half-life

4. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the extrapyramidal nervous system. Levodopa (LD) used in combination with carbidopa (CD) is considered the gold standard for the symptomatic treatment of PD. LD is a dopamine precursor converted to dopamine by aromatic amino acid decarboxylase (AADC). Carbidopa is an AADC inhibitor that does not cross the blood-brain barrier. When used in combination with LD, CD increases the plasma half-life of LD from 50 minutes to 1.5 hours. Carbidopa inhibits the conversion of LD into dopamine in the periphery, thereby reducing the peripheral side-effects caused by dopamine and increasing the amount of LD available for transport into the brain. The administration of CD with LD reduces the dose of LD required to produce a dopaminergic response by about 75 percent (Sinemet prescribing information, Appendix A).

Due to its proven efficacy, LD is prescribed eventually to most subjects with PD. However, long-term use of LD is associated with certain complications, including "wearing off" or "end-of-dose effect," where symptom control decreases resulting in the drug effects to wear off sooner. As the disease progresses further, motor complications, namely dyskinesias and motor "on/off" fluctuations, develop in about 50% of the patients after 5 years of treatment (Fahn 1999). Such motor complications can be a significant source of disability and their management is a major unmet need in the treatment of PD.

Mechanisms underlying motor complications involving dyskinesias and "on/off" fluctuations in PD are unclear. The pulsatile nature of standard orally administered LD is thought to contribute to the appearance of motor complications. Chronic intermittent pulsatile stimulation of the dopamine receptors that are under tonic control contributes to the development of dyskinesia in PD animal models as compared to animals treated with continuous infusion (Juncos 1989, Engber 1989, Blanchet 1995). In addition, unreliable absorption of LD potentially due to erratic gastric empting and variable in vivo dissolution of LD products is thought to contribute to the delay or inadequate response after oral dosing with standard CD-LD products (Melamed 1986, Kurlan 1988, Stocchi 1994). These findings suggest that motor complications in patients with PD may be less likely to develop with continuous dopaminergic stimulation.

Intraduodenal infusion of LD has been shown to significantly reduce motor complications and to reduce "off" time. The findings of infusion studies in PD patients indicate that the maintenance of stable plasma LD concentrations and the avoidance of low trough levels are effective in reducing "off" hours, increasing "on" hours without disabling dyskinesia, and reducing the severity of dyskinesia versus standard oral LD formulations (Mizuno 2007, Nilsson 2001, Nyholm 2005, Stocchi 2005). These findings provide a strong rationale for the development of an extended release (ER) oral formulation that delivers a constant LD plasma concentration in order to optimize relief of PD symptoms, and to minimize "off" time and dyskinesia.

IPX203 is an investigational product containing CD-LD that is being developed by Impax Laboratories, Inc. through its Impax Specialty Pharma division (Impax). The primary objective of the IPX203 program is to develop an extended release product that can attain therapeutic LD plasma concentrations rapidly and maintain constant LD plasma concentrations for a longer duration than currently approved products with minimal peak to trough fluctuations. IPX203 is designed to be dosed approximately every 8 hours, three times a day based on the plasma LD

concentration time profile observed in healthy subjects (Study IPX203-B14-01) and in subjects with advanced PD (Study IPX203-B14-02).

Study IPX203-B14-02 characterized the PK and pharmacodynamics of IPX203 following a single dose in subjects with advanced PD versus IR CD-LD and Rytary. Twenty-six (26) subjects have been randomized. Preliminary results are based on data available as of August 4, 2016. At the time of this cutoff, one subject had discontinued study early due to subject withdrawal. Administration of IPX203 yielded an initial increase in LD plasma concentrations that was similar to both IR and Rytary but maintained LD concentrations longer than Rytary. IPX203 provided a longer duration of effect compared with IR CD-LD and Rytary, including "Good On Time" based on the Assessment of Subject's Motor State and on several of the MDS-UPDRS-III improvement thresholds. In this ongoing single dose study, 5 (19.2%, 5/26) subjects have reported adverse events. Two subjects (8%, 2/25) reported 3 treatment-related AEs after treatment with IPX203 compared with 4 subjects (16.7%, 4/24) who reported treatment-related AEs after treatment with IR CD-LD. To date, no subjects in this study have reported serious or severe AEs, or have discontinued from the study because of AEs, irrespective of treatment.

Study IPX203-B16-01 is designed to assess the single- and multiple-dose PK, pharmacodynamics, efficacy and safety of IPX203.

5. TRIAL OBJECTIVES

5.1. Primary Objective

- To compare the pharmacokinetics (PK) of single and multiple doses of IPX203 with immediate release (IR) CD-LD in subjects with advanced Parkinson's disease (PD).

5.2. Secondary Objectives

- To compare the pharmacodynamics of single and multiple doses of IPX203 with IR CD-LD
- To compare the efficacy of IPX203 with IR CD-LD following multiple doses
- To evaluate the safety of IPX203.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

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

As shown in Figure 1, this study will consist of 4 study visits after Screening: Day 1 of each treatment period (Visits 1 and 3), and Day 15 of each treatment period (Visits 2 and 4). Study Exit procedures are done at the end of Visit 4 or within 3 days of Visit 4, or during an early withdrawal. Between treatment periods, subjects will return to their prestudy PD medication regimen during the 1-week (± 2 days) washout period. Subjects may continue to take allowed non-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.

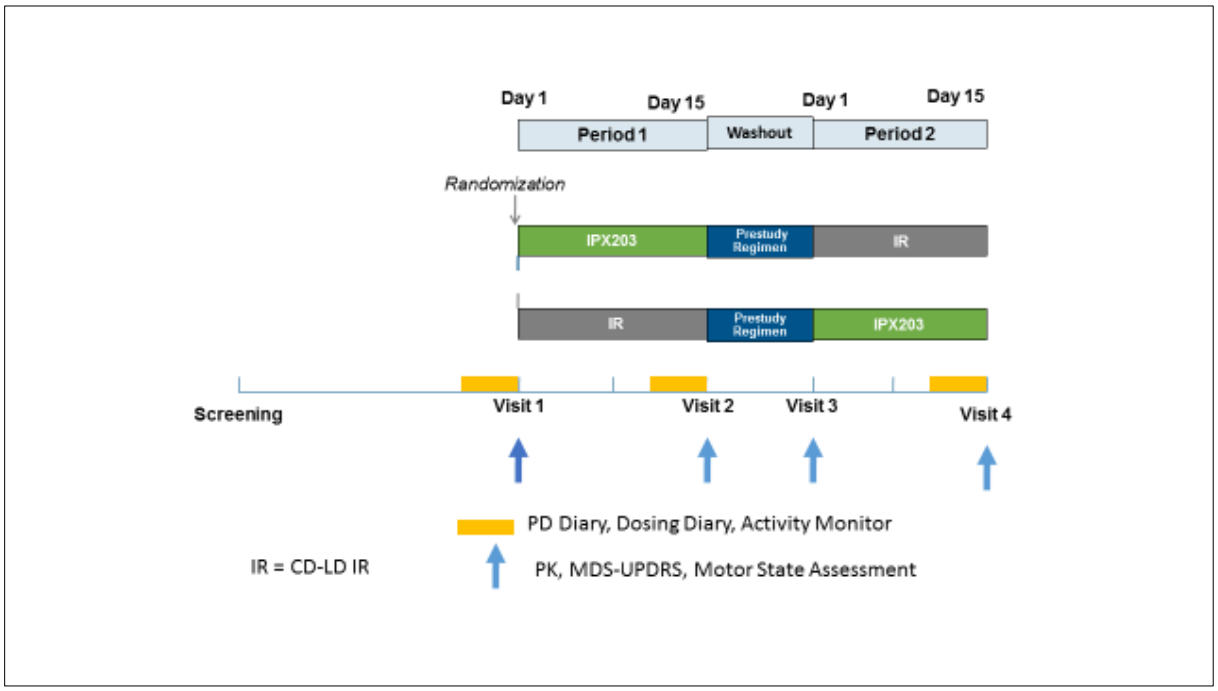
Within 2 weeks following Screening, eligible subjects will complete their PD and Dosing diaries, and will wear the Kinesia 360 sensor bands on the more affected side at home immediately after waking on each of the 3 days prior to Visit 1. Subjects will be instructed to take their last dose of CD-LD no later than 10:00 PM on the evening prior to Visits 1 and 3. The first morning dose of study medication will be administered at the study site. On Day 1 of the IR CD-LD treatment period, subjects will start with a single dose of their usual prestudy first morning IR CD-LD dose. On Day 1 of the IPX203 treatment period, subjects will start with a single dose of IPX203 based on their usual prestudy first morning IR CD-LD dose according to the guidance provided in Table 3. During each treatment period subjects will dose for 15 days with study medication. During the IR CD-LD treatment period, the initial dosing regimen of IR CD-LD will be the same as the subject's stable prestudy regimen unless they were taking a single daily bedtime dose of CR CD-LD, either alone or in combination with IR CD-LD, in which case, the CR CD-LD dose will be discontinued and substituted with a 1:1 milligram-equivalent IR CD-LD dose. A "bedtime dose" is defined as a dose of CR CD-LD taken within 1 hour of the subject's normal nighttime sleep period. During the IPX203 treatment period, subjects are assigned their initial IPX203 dosing regimen according to the guidance provided in Table 4 (see Section 6.4.2), which is based on each individual's prestudy IR CD-LD morning dose and daily dosing regimen. The typical dosing regimen for IPX203 will be three times a day, dosed approximately every 7 to 8 hours. Some subjects may require more or less frequent dosing to optimize therapeutic effect (minimize "off" time without causing troublesome dyskinesia or other dopaminergic side effects). Nighttime dosing of study medication is allowed as needed with the exception of the evening prior to Day 15 (withhold dosing for at least 5 hours before arriving at the site) of each treatment period. Subjects may continue to take allowed non-CD-LD based PD medications throughout the study if documented in their prestudy regimen and if dosing regimens have been stable for at least 4 weeks prior to Visit 1.

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

Pharmacokinetic and pharmacodynamic measures are assessed in the clinic for up to 8 hours postdose on Day 1 of each treatment period (Visits 1 and 3), and for up to 10 hours on Day 15 of

each treatment period (Visits 2 and 4). Additionally, subjects will complete the PD and Dosing diaries, and use the Kinesia 360 sensor bands on the ankle and wrist of their more affected side immediately after waking on each of the 3 days prior to Visits 1, 2, and 4.

Figure 1: Study Flow Chart



6.2. Number of Subjects

A sufficient number of subjects will be screened to ensure that approximately 30 subjects are randomized to complete 26 subjects. Subjects who discontinue will not be replaced.

6.3. Treatment Assignment

Investigational product: IPX203 (carbidopa-levodopa) Extended-Release Capsules, containing 180 mg and 270 mg of LD, for oral administration.

Reference therapy: Immediate-release carbidopa-levodopa (IR CD-LD) tablet containing 100 mg of LD, for oral administration.

Subjects will be randomly assigned to one of the treatment sequences to receive IPX203 and IR CD-LD (Table 2).

Table 2: Randomization Schedule for IPX203-B16-01

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

6.4. Dosing and Dose Determination Criteria

IR CD-LD will be supplied as tablets containing 100 mg of LD. IR CD-LD tablets may be split using a pill cutter.

IPX203 will be supplied as capsules containing 180 mg and 270 mg LD. The suggested doses and regimen of IPX203 are intended to provide an onset of effect comparable to the subject's prestudy IR LD regimen and to extend the duration of effect. .

Doses of IPX203 should be based on the subject's prestudy stable LD dose regimen and the response to IPX203. The typical dosing regimen for IPX203 will be three times a day, dosed approximately every 7 to 8 hours. Some subjects may require more or less frequent dosing to optimize therapeutic effect (minimize "off" time without causing troublesome dyskinesia or other dopaminergic side effects).

6.4.1. Day 1 In-Clinic Dosing at Visit 1 and at Visit 3

There are two treatment periods in this study. On Day 1 of the IR CD-LD treatment period, subjects will receive a single dose of their usual prestudy first morning IR CD-LD dose. The "first morning dose" is defined as the subject's first dose upon awakening for the day immediately following the subject's usual nocturnal sleep period intended to achieve an "on" state.

On Day 1 of the IPX203 treatment period, subjects will start with a single dose of IPX203 based on their usual prestudy first morning dose of IR CD-LD as shown in Table 3.

Table 3: Day 1 In-clinic Dosing — First Morning Dose of Study Medication

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

Rescue: Subjects who need rescue during the IR CD-LD treatment will receive a dose of IR CD-LD that corresponds to their typical pretreatment regimen based on the subject's dosing diary. For rescue during the IPX203 treatment, subject will receive a dose of IPX203 that is based on Table 4 in Section 6.4.2.

6.4.2. Study Drug Regimen following First In-Clinic Dose at Visits 1 and 3

The IR CD-LD and IPX203 dosing regimen may be adjusted if needed during the first 9 days of each treatment period to achieve adequate efficacy and safety. The dosing regimen should be stable for the last 5 days of each treatment period (Days 10 – 14).

IR LD Dose Adjustment (Days 1-9):

- During the IR CD-LD treatment period, the initial dosing regimen of IR CD-LD will be the subject's stable prestudy CD-LD regimen.
- If the subject's prestudy regimen included a single daily bedtime dose of CR CD-LD, either alone or in combination with IR CD-LD, the CR CD-LD dose will be discontinued and substituted with a 1:1 milligram-equivalent IR CD-LD dose. A "bedtime dose" is defined as a dose of CR CD-LD taken within 1 hour of the subject's normal nighttime sleep period. For example, a 200-mg daily bedtime dose of CR CD-LD will be replaced with a 200-mg bedtime dose of IR CD-LD.

IPX203 Dose Adjustment (Days 1-9):

Table 4 outlines the suggested initial conversion from a prestudy regimen of CD-LD to an IPX203 regimen. The suggested initial dosing of IPX203 is three times a day, approximately every 7 to 8 hours.

The recommended morning dose of IPX203 is based on Table 3.

To determine the IPX203 regimen of subsequent doses for the day, identify the most frequent prestudy LD dose in milligrams that the subject receives in the afternoon and evening and administer IPX203 according to Table 4.

- If the subject takes different prestudy LD doses with equal frequency, determine the IPX203 dose based on the highest LD dose.
- When determining the most frequent prestudy LD dose for subsequent IPX203 doses, consider all prestudy LD doses taken from noon to bedtime. If the subject takes a bedtime CR CD-LD dose and the subject also takes a dose of IR CD-LD within one hour of the bedtime dose of CR CD-LD, then add the CR and IR LD doses together.

Table 4: Initial IPX203 LD Dosing Regimen Subsequent to IPX203 Morning Dose Based on Prestudy Regimen of LD

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

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

The examples below illustrate the IPX203 dosing regimen.

Example:

Pre-study IR LD Morning Dose (mg)	Most Frequent Pre-study LD Dose (mg) Afternoon and Evening	IPX203 Regimen
100	100	360 mg as the morning dose followed by 270 mg approximately every 7 to 8 hours
200	100	720 mg as the morning dose followed by 270 mg approximately every 7 to 8 hours

- The IPX203 dosing regimen may be adjusted as needed based on the subject's response to the previous day's dosing. Doses of IPX203 may be adjusted in increments of 90 mg to achieve adequate therapeutic effects. The 90 mg adjustments can be achieved by adjusting the number of 180 mg and 270 mg capsules. For example, a 360 mg dose (180 mg × 2 capsules) can be increased by 90 mg (to 450 mg) by administering a 270 mg capsule and a 180 mg capsule.
- If a subject experiences bothersome peak-related or levodopa-related side effects, the doses of IPX203 may be reduced in steps of 90 mg.
- If a subject experiences end-of-dose "off" episodes with the suggested dose regimen or if persistent "off" periods occur during the day,
    - the IPX203 dose may be increased (if the subject does not experience troublesome dyskinesia), or
    - the time between two doses may be decreased, or
    - the dosing frequency may be increased to achieve an adequate therapeutic effect.
- IPX203 should not require dosing more than four times a day. For subjects who require an adjustment from three times a day to a four times a day dosing of IPX203, each individual dose may need to be reduced by 90-180 mg depending on response.

Dosing of Study Medication on Days 10 – 14

For Days 10-14 subjects should maintain the dosing regimen achieved by Day 9.

Dosing of Study Medication on Day 15

The IR CD-LD and IPX203 dosing regimens during the clinic visit on Day 15 should be the same as the regimens reflected on the last day in the Dosing diary on Days 12-14.

6.5. Dose Adjustment Criteria

As detailed in Section 6.4.2 above, a subject's IR CD-LD and IPX203 dosing regimen may be adjusted for the first 9 days in order to achieve adequate efficacy and safety.

6.6. Criteria for Study Termination

The Sponsor has the right to terminate this study and remove all study material from the study site at any time for medical or administrative reasons. The Sponsor will endeavor to give adequate notice to allow safe withdrawal of subjects from the study.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Each subject must meet all of the following inclusion and exclusion criteria to qualify for enrollment.

7.1. Subject Inclusion Criteria

1. Male or female subjects diagnosed with idiopathic PD at age ≥40 years who are being chronically treated with stable regimens of CD-LD but experiencing motor complications. Idiopathic PD is defined by United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (Appendix B). There are no known secondary causes (eg, vascular, toxin or medication-induced, metabolic, or infectious) for subject's Parkinsonism nor does subject have another neurodegenerative disorder with Parkinsonism symptoms (eg, progressive supranuclear palsy, corticobasal degeneration, multiple-system atrophy).
2. Able to provide written informed consent and willing to sign Health Insurance Portability and Accountability Act (HIPAA) authorization prior to the conduct of any study-specific procedures.
3. Female subjects of childbearing potential must have a negative urine pregnancy test at Screening Visit.
4. Negative urine screen for drugs of abuse and negative alcohol breath test at Screening.
5. Hoehn and Yahr Stages 2, 3, or 4 (part of MDS-UPDRS Part III)
6. Agrees to use a medically acceptable method of contraception throughout the study and for 6 weeks after completing the study. Medically acceptable methods of contraception that may be used by the subject and/or partner include but are not limited to: abstinence, oral contraception, NuvaRing or transdermal systems, diaphragm with vaginal spermicide, intrauterine device, condom and partner using vaginal spermicide, surgical sterilization (6 months), progestin implant or injection, or postmenopausal female (no menstrual period for > 2 years) or vasectomy (>6 months).
7. Montreal Cognitive Assessment (MoCA) score ≥ 24 at Screening Visit in "on" state.
8. For the 4 weeks prior to Screening, the subject experiences daily "wearing-off" episodes with periods of bradykinesia and rigidity, and experiences an "off" state upon awakening on most mornings by history.
9. At Visit 1, review of the 3-day PD diary confirms the following: that the subject is able to properly complete the diary with valid entries; and that the subject has an average of at least 2.5 hours per day of "off" time during the waking hours over the 3 days with at least 1.5 hours "off" time on each day. Inability to properly complete the diary is indicated when more than 1 day of the diary is not returned or when more than 2 hours (4 half-hour periods) of one 24-hour diary day are missing (Appendix H).
10. Responsive to CD-LD therapy and currently being treated on a stable regimen with CD-LD for at least 4 weeks prior to Visit 1 and:

a. requires 100 to 250 mg (in units of 50 mg) of IR CD-LD for the morning dose
b. requires a total daily dose of at least 400 mg of IR CD-LD
c. takes a maximum total daily dose of 1800 mg LD, comprising IR CD-LD alone or IR CD-LD in combination with a single daily bedtime dose of CR CD-LD.
d. has a dosing frequency of 4 to 9 times daily of CD-LD
e. typically experiences an "on" response with the first dose of IR CD-LD of the day (by subject history)
f. by history, efficacy of the first morning dose of IR CD-LD lasts less than 4 hours, typically wearing "off" prior to the next dose; or subject takes the second dose of PD medications prior to 4 hours to avoid an "off."

11. Has not used doses of controlled-release (CR) CD-LD apart from a single daily bedtime dose for at least 4 weeks prior to Visit 1.
12. Has not used any doses of Rytary for the past 4 weeks prior to Visit 1.
13. At Screening, the MDS-UPDRS Part III total score in the "off" state is:
    a. at least 20 units
    b. at least 25% or 10 units greater than in the "on" state
14. At Screening, the subject has predictable "off" periods defined by a score of 1 or 2 on Item #4.5 (Complexity of Motor Fluctuations) of the MDS-UPDRS Part IV B (Motor Fluctuations) (Appendix D).
15. Has a score of ≥ 1 on Item #4.3 (Time Spent in the "off" State) of the MDS-UPDRS Part IV B at Screening (Appendix D).
16. Hemoglobin level must be above the lower limits of the laboratory's normal reference range.
17. Able and willing to comply with the protocol, including completion of diaries and availability for all scheduled study visits and data and blood-sample collection times.

7.2. Subject Exclusion Criteria

1. Female subjects who are currently breastfeeding or lactating.
2. Had prior neurosurgical ablation treatment for PD or if such procedure is planned or anticipated during the study period. Previous implantation of a deep brain stimulator (DBS) for the treatment of PD is permitted as long as the DBS settings have been stable for at least 4 weeks prior to Screening and the procedure is not planned during this study or for up to 6 weeks after study participation.
3. Allergic to any excipients of IPX203 (Appendix E).
4. History of medical conditions or of a prior surgical procedure that would interfere with LD absorption, such as gastrectomy or proximal small-bowel resection.
5. History of peptic ulcer disease or upper gastrointestinal hemorrhage within the past 5 years.
6. History of narrow angle glaucoma with intraocular pressures that are elevated despite appropriate medical management.

7. History of seizure or epilepsy and experienced at least 1 seizure during the past 12 months or has not been compliant with medically recommended therapy or visits.
8. History of myocardial infarction with residual atrial, nodal, or ventricular arrhythmias that are not controlled with medical and/or surgical interventions.
9. History of neuroleptic malignant syndrome or of nontraumatic rhabdomyolysis.
10. Liver enzyme values ≥ 2.5 times the upper limit of normal; or history of severe hepatic impairment.
11. Serum creatinine level ≥ 1.75 times the upper limit of normal; or requires dialysis at the time of Screening.
12. Subject with a history of malignant melanoma or with a suspicious undiagnosed skin lesion which in the opinion of the investigator could be melanoma.
13. History of drug or alcohol abuse within the 12 months prior to Screening.
14. Received within 4 weeks of Visit 1 or planning to take during participation in the clinical study: any doses of a controlled-release (CR) LD apart from a single daily bedtime dose or any doses of Rytary, additional CD (eg, Lodosyn) or benserazide (eg, Serazide), or catechol-O-methyl transferase inhibitors (entacapone or tolcapone) or medications containing these inhibitors (Stalevo). Received within 4 weeks of Visit 1 or planning to take during participation in the clinical study: nonselective MAO inhibitors, apomorphine, or dopaminergic blocking agents including antiemetics.
15. History of psychosis within the past 10 years. Mild PD-associated illusions are not exclusionary provided that they do not occur more than once per week and the subject does not lose insight.
16. Treatment with any dopamine antagonist antipsychotics for the purposes of psychosis or bipolar disorder within the last 2 years.
17. Subjects considered IPX066 or Rytary failures for reasons of efficacy or safety.
18. Donated blood or plasma within 6 weeks prior to Visit 1 or planning to donate blood or plasma within 12 weeks after Study Exit.
19. Answered "YES" on Questions 4 or 5 on the Suicidal Ideation subscale of the C-SSRS (Appendix F) at Screening (defined period as 3 months prior to Screening) or evidence of suicidal behavior within 6 months of Screening as measured by the Suicidal Behavior subscale of the C-SSRS.
20. Employees or family members of the Investigator, study site, or Sponsor.
21. Subjects who, in the opinion of the clinical investigator, should not participate in the study.
22. Based on clinical assessment, subject does not adequately comprehend the terminology needed to complete the PD diary.

7.3. Subject Withdrawal Criteria

Site personnel should make every effort to conduct all protocol-specific procedures to complete the study. A subject may be discontinued from the study due to the following reasons:

1. Withdrawal by subject
2. Adverse event (AE)
3. Lack of efficacy
4. Study terminated by Sponsor
5. Protocol deviation
6. Noncompliance with study drug
7. Lost to follow-up
8. Death
9. Other

Subjects who withdraw early from the study will not be replaced.

8. STUDY PROCEDURES

The procedures to be performed at each study visit are described below and summarized in Table 5.

Table 5: Events Schedule for Impax Study IPX203-B16-01

Assessment	Screening	Visit 1 (Day 1)	Visit 2 (Day 15)	7-Day Washout Period	Visit 3 (Day 22)	Visit 4 (Day 36)	Study Exit[a]
Study Week	**–2**	**0**	**2**	**3**	**4**	**5**	
ICF & HIPAA Authorization	X						
Assign Subject ID	X						
Randomization		X					
Inclusion/Exclusion	X	X					
Medical History	X						
Hoehn and Yahr Staging (MDS-UPDRS)	X						
Physical Examination	X						X
Vital Signs[b]	X	X	X		X	X	X
Height and Weight	X						X[c]
C-SSRS[d]	X	X	X		X	X	X
Clinical Laboratory Tests[e]	X						X
Urine Pregnancy Test	X						
Urine Screen for Drug Abuse	X						
Alcohol Breath Test	X						
ECG[f]	X	X	X		X	X	X
MoCA[g]	X						
MDS-UPDRS Parts I, II, and IV[h]	X		X			X	
MDS-UPDRS Part III Motor Examination[i]	X	X	X		X	X	
Assessment of Subject's Motor State[j]		X	X		X	X	
PD Diary, Dosing Diary, Kinesia 360 Training[k]	X	X	X		X		
Dispense PD Diary, Dosing Diary, Kinesia 360[l]	X	X			X		

Assessment	Screening	Visit 1 (Day 1)	Visit 2 (Day 15)	7-Day Washout Period	Visit 3 (Day 22)	Visit 4 (Day 36)	Study Exit[a]
Study Week	**–2**	**0**	**2**	**3**	**4**	**5**	
Review PD and Dosing diaries, Kinesia 360[m]		X	X			X	
PK Sampling[n]		X	X		X	X	
Resume Prestudy Meds/Dosing				X			
Reminder phone calls[l,o,p]	X[o]	X[p]	X[p]		X[p]	X[p]	
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Provide low protein breakfast/and provide snacks and other meals		X	X		X	X	

C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, HIPAA = Health Insurance Portability and Accountability Act, ICF = informed consent form, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease, PK = pharmacokinetics, MDS-UPDRS = MDS version of Unified Parkinson's Disease Rating Scale.

a Study Exit procedures to be conducted at the end of Visit 4 or within 3 days of Visit 4, or during an early withdrawal visit.

b 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. During Visits 1 and 3, vital signs are recorded at predose, 2, 4, and 8 hours postdose. During Visits 2 and 4, vital signs are recorded at predose, 2, 4, and 10 hours postdose.

c Weight only.

d C-SSRS: Columbia Suicide Severity Rating Scale. See Appendix F.

e See Appendix J.

f ECGs done at Screening and during Visits 1 - 4, at predose and 2 hours postdose.

g Montreal Cognitive Assessment in the "on" state: see Appendix C.

h MDS-UPDRS Parts I, II, and IV: At Screening, Parts I, II and IV will be conducted during the "on" state, and at Visits 2 and 4 will be done at predose.

i MDS-UPDRS Part III (Motor Examination): At Screening, Part III is conducted during both the "on" and "off" state. Ensure that the MDS-UPDRS Part III total score in the "off" state is at least 20 units and is at least 25% or at least 10 units greater than in the "on" state. Part III is performed by a rater blinded to treatment assignment at predose and hourly for up to 8 hours postdose for Visits 1 and 3; Part III is performed at predose and hourly for up to 10 hours postdose for Visits 2 and 4.

j Assessment of Subject's Motor State: Rated assessment of motor state ("on" and "off," and state of dyskinesia) performed by a rater blinded to treatment assignment at –1, –0.5, and 0, and at half hourly intervals postdose for up to 8 hours on Visits 1 and 3 and for up to 10 hours on Visits 2 and 4.

k Train at Screening and then as needed at subsequent visits.

l Dispense PD and dosing diaries and Kinesia 360 at Screening, Visit 1, and Visit 3. Call Subjects 4 days prior to Visits 1, 2 and 4 and to remind them to begin PD Diary and Dosing Diary. Subjects record diary information for 3 consecutive days prior to each of the visits (Days -3, -2, and -1). Subjects wear their Kinesia 360 sensor bands on the more affected side immediately upon awakening and throughout their waking hours on each of the 3 days prior to the visits (Days -3, -2, and -1). Call subjects the day prior to each visit to remind them to bring the diaries, Kinesia 360, and all study medication and PD and non-PD medication to the site visits.

m Review PD and Dosing diaries and Kinesia 360 at Visits 1, 2, and 4.

n PK Sampling: Day 1 of each treatment period (Visits 1 and 3) – at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, and 8 hours postdose. Day 15 of each treatment period (Visits 2 and 4) – at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours postdose.

o Reminder phone calls to notify individuals who successfully complete screening procedures following review of all study entry criteria and clinical laboratory results that they may enroll in the study. The interval between Screening and Visit 1 should not exceed 2 weeks. Call subjects at least 4 days prior to Visit 1 to remind them to complete their PD diary and Dosing diary and to put on the Kinesia 360 sensor bands. Subjects will record diary information for 3 consecutive days starting 3 days prior to Visit 1 (Days -3, -2, and -1). Subjects should wear their Kinesia 360 sensor bands on the more

affected side immediately upon awakening and throughout their waking hours on each of the 3 days prior to each of the visits (Days -3, -2, and -1).

p Reminder phone calls on the days prior to all treatment visits (Visits 1-4), remind subjects to:

- Call subjects 4 days prior to Visits 1, 2 and 4 to remind them to begin PD and Dosing Diaries and the Kinesia 360 system. Call subjects the day prior to Visits 1, 2 and 4 to remind them to bring the diaries and the Kinesia 360 system to the office on Visits 1, 2 and 4.
- Take their last doses of CD-LD no later than 10:00 PM on the evening prior to Visits 1 and 3. Withhold their last dose of study medication for at least 5 hours prior to arriving at the clinic for Visits 2 and 4. Inform subjects that their first morning dose of CD-LD (study medication) will be administered at the study site under the supervision of site personnel. Subjects should not withhold their non-CD-LD medications.
- Fast for at least 8 hours prior to arriving at the clinic except that coffee, tea, water, and juice are allowed for up to 1 hour predose. Breakfast containing approximately 5 grams of protein will be served at the study site approximately 1 hour postdose (Appendix L).
- Report to the study site early the next morning.
- Continue to take all of their other non-CD-LD medications per their usual routine prescription instructions and schedule until they arrive at the study site for each treatment visit.
- Bring all their current PD and non-PD medication containers to the study site for each treatment visit (Visits 1-4). Concomitant non-CD-LD medications (including non-PD medications) will be made available to subjects with site staff oversight during the treatment visits so that subjects can take their regular medications per their usual schedule.

8.1. Screening Visit

After the subject has signed the informed consent and HIPAA authorization, complete the following procedures and assessments:

- Obtain an identification number from the interactive web response system (IWRS).
- Review and record study entry criteria (Section 7).
- Perform urine pregnancy test for females of childbearing potential.
- Perform urine screen for drugs of abuse.
- Perform alcohol breath test.
- Complete medical history.
- Perform physical examination, including height and weight.
- Assess vital signs after subject is supine for at least 5 minutes (blood pressure, heart rate, temperature and respiratory rate) and then assess orthostatic blood pressure and heart rate after subject is standing (for approximately 2 minutes).
- Record current CD-LD regimen, other PD medications and their dosing schedule, and other concomitant medications.
- Conduct an ECG.
- Administer C-SSRS (Appendix F).
- Determine MoCA Score in the “on” state (Appendix C).
- Collect blood and urine samples for clinical laboratory studies (Appendix J).
- Determine Hoehn and Yahr staging of PD (part of Part III Motor Examination of the MDS-UPDRS (Appendix D).

- Determine MDS-UPDRS Parts I through IV in the "on" state, and Part III also done in the "off" state (Appendix D). Determine the more affected side.
- Dispense 3-day PD diaries (Appendix H) and train the subject how to complete the PD diary to assess his/her "on" and "off" states, including assessment of any dyskinesia. Then instruct the subject to complete the PD diary on 3 consecutive days prior to Visit 1.
- Dispense 3-day Dosing diaries and train the subject how to complete the Dosing diary. Then instruct the subject to complete the Dosing diary on 3 consecutive days prior to Visit 1. These should be the same 3 days that the PD diary is being completed.
- Dispense the Kinesia 360 system and the subject instruction sheet (Appendix G). Train the subject on how to use the system and how to attach the sensor bands to the wrist and ankle of the more affected side. Instruct the subject to attach the sensor bands immediately after waking on the morning that the PD and Dosing diaries are started and to continue to wear the sensor bands on each of the 3 days prior to Visit 1 while the subject is awake. The Kinesia 360 sensor bands should be removed during showers, baths, swimming, and before going to bed at night.

Notify individuals who successfully complete screening procedures following review of all study entry criteria and clinical laboratory results.

The interval between Screening and Visit 1 (Day 1) should not exceed 2 weeks.

8.2. Visits 1 and 3

8.2.1. Prior to Visit 1

Contact the subject at least 4 days prior to Visit 1 to remind him/her to complete the 3-day PD and Dosing diaries, and to use the Kinesia 360 sensor bands starting 3 days prior to Visit 1.

The day prior to Visit 1, remind subjects to bring their completed 3-day PD diary and Dosing diary and the Kinesia 360 system to the clinic.

8.2.2. Prior to Visits 1 and 3

Contact the subject the day before each Visit to remind the subject about the following:

- Take their last doses of CD-LD no later than 10:00 PM on the evening prior to each treatment visit.
- Withhold first morning dose of CD-LD medication and inform subjects that their first morning dose of CD-LD (study medication) will be administered at the study site under the supervision of site personnel. Subjects should not withhold their non-CD-LD medications.
- Fast for at least 8 hours prior to arriving at the clinic except that coffee, tea, water, and juice are allowed up to 1 hour predose. Breakfast containing approximately 5 grams of protein will be served at the study site approximately 1 hour postdose (Appendix L).

- Report to the study site early the next morning.
- Continue to take all of their other non-CD-LD medications (including PD and non-PD medications) per their usual routine prescription instructions and schedule until they arrive at the study site for each treatment visit.
- Bring all their current PD and non-PD medication containers to the study site for each treatment visit. Concomitant medications will be made available to subjects with site staff oversight during the treatment visits so that subjects can take their regular medications per their usual schedule.
- Bring the 3-day PD Diary, the 3-day Dosing diary, and the Kinesia 360 system with them to the clinic (Visit 1 only).

8.2.3. Predose at Visit 1

- On the morning of Visit 1, collect and review the subject's 3-day PD and Dosing Diaries and ensure that the subject continues to meet study inclusion criteria.
- Review the use of the Kinesia 360 system, if needed.
- At Visit 1, randomize eligible subjects using the IWRS.

8.2.4. Predose at Visits 1 and 3

For Visits 1 and 3 complete the following procedures:

- Record any AEs and update changes in concomitant medication since the previous visit.
- Measure predose vital signs (temperature, respiratory rate, blood pressure, heart rate after supine for at least 5 minutes and orthostatic pulse and blood pressure after standing for approximately 2 minutes).
- Conduct a predose ECG.
- Collect a predose PK blood sample (6 mL) within 1 hour predose.
- Qualified clinical staff blinded to the subject's treatment assignment perform the following predose assessments in the "off" state: 1) MDS-UPDRS Part III (Motor Examination) at predose; 2) Assessment of Subject's Motor State (of "on" and "off," and state of dyskinesia) –1, –0.5, and 0 hour.
- Administer C-SSRS.
- Administer the study medication upon completion of predose procedures. To ensure unbiased data, treatments should be administered by clinical staff not directly involved in the assessment of the MDS-UPDRS Part III (Motor Examination) and Assessment of Subject's Motor State.

8.2.5. Postdose at Visits 1 and 3

- Collect postdose blood samples (6 mL) for PK analysis at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, and 8 hours postdose.

- Qualified staff who are blinded to treatment assignment perform Assessment of Subject's Motor State (of "on" and "off," and state of dyskinesia) at half-hour intervals at approximately 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, and 8 hours postdose. For each subject, the preference is to have the same rater perform the assessment at every time point throughout the study.
- Qualified staff who are blinded to treatment assignment perform MDS-UPDRS Part III (Motor Examination) hourly at approximately 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose. For each subject, the preference is to have the same rater perform the assessment at every time point throughout the study.
- When PK sampling and other procedures or measurements are scheduled at the same time, the PK sampling should occur as close as possible to the nominal time.
- Provide a breakfast containing approximately 5 grams of protein approximately 1 hour following the morning dose (Appendix L). Lunch may be provided no earlier than 4 hours following the morning dose. Subjects may be provided dinner if needed. Subjects may also be provided snacks as long as it is not within 1 hour before or after their morning dose.
- Perform 12-lead ECG at 2 hours postdose.
- Assess vital signs at 2, 4, and 8 hours postdose: blood pressure, heart rate, and respiratory rate will be measured after the subject has been supine for at least 5 minutes. Orthostatic blood pressure and heart rate will be measured after the subject has been standing for approximately 2 minutes.
- If a subject experiences an "off" state for ≥ 3 consecutive hours postdose, the subject may receive rescue medication. Subjects who need rescue during the IR CD-LD treatment will receive a dose of IR CD-LD that corresponds to their typical pretreatment regimen based on the subject's dosing diary. For rescue during the IPX203 treatment, subject will receive a dose of IPX203 that the subject would typically have received following their morning dose (see Table 4). At the Investigator's discretion, the subject may be rescued prior to 3 hours. Site staff will record the time of administration of any rescue medication. **PK sampling and pharmacodynamic assessments will continue after subject receives rescue medication.**
- After completion of the 8-hour PK sampling and pharmacodynamic assessments:
  - Provide study medication and dosing instructions to the subject. Inform the subject to call the site prior to making changes to the dose regimen.
  - Inform the subject that the site will be calling every 1-3 days over the next 9 days to discuss dosing.
  - Provide PD and dosing diaries and the Kinesia 360 system to subject.

8.3. Days 2-14 (Visits 1 and 3)

Days 2 to 9:

- Site staff should follow-up with the subject every 1-3 days to check how the subject is doing and to facilitate any dose regimen changes.
- Site staff should record any changes to the dosing regimen.
- The subject should be instructed to call the site and report to site staff before making changes in dosing regimen.
- The subject's dosing regimen may be adjusted during Days 2 to 9. The dosing regimen should not be modified after this period.
- Site staff should check with subject on Day 9 and remind the subject to not make changes in dosing regimen for the rest of the treatment period.

Days 10 through 14:

- The subject should remain on a stable dosing regimen until the next visit (Visit 2 or Visit 4).

8.4. Washout Period (Between Visit 2 and 3)

Following the completion of Visit 2, subjects will return to their prestudy PD medication regimen during the 1-week (± 2 days) washout period between Visits 2 and 3.

8.5. Visits 2 and 4

8.5.1. Prior to Visits 2 and 4

Four days prior to Visits 2 and 4, site staff should contact the subject and ensure that the study medication regimen is stable. Remind him/her to complete the 3-day PD and Dosing diaries starting 3 days prior to the next visit (Visit 2 or Visit 4). Also remind the subject to use their Kinesia 360 system on each of the 3 days prior to the next visit.

One day prior to Visit 2 and 4, site staff should contact the subject to remind him/her of the following:

- Withhold dosing of study medication for at least 5 hours before arriving at the site; the first morning dose will be administered at the study site under the supervision of site personnel. Subjects should not withhold their non-CD-LD medications.
- Subjects must be fasting for at least 8 hours prior to dosing (except that coffee, tea, water, and juice are allowed up to 1 hour predose).
- Bring all their current PD and non-PD medication containers to the study site for each treatment visit (Visits 2 to 4). Concomitant medications will be made available to subjects with site staff oversight during the treatment visits so that subjects can take their regular medications per their usual schedule.
- Bring the Kinesia 360 system and their completed 3-day PD and Dosing diaries to the clinic.

8.5.2. Predose at Visits 2 and 4

For Visits 2 and 4 complete the following procedures:

- Record any AEs and update changes in concomitant medication since the previous visit.
- Measure predose vital signs (temperature, respiratory rate, blood pressure, and heart rate after supine for at least 5 minutes; orthostatic pulse and blood pressure after standing for approximately 2 minutes).
- Conduct a predose ECG.
- Collect a predose PK blood sample (6 mL) within 1 hour predose.
- Qualified clinical staff blinded to the subject's treatment assignment perform the following predose assessments: 1) MDS-UPDRS Parts I-IV; 2) Assessment of Subject's Motor State (of "on" and "off," and state of dyskinesia) –1, –0.5, and 0 hour.
- Administer C-SSRS.
- Administer the study medication upon completion of predose procedures. The IR CD-LD and IPX203 dosing regimens during the clinic visit for Day 15 should be the same as the regimens reflected on the last day in the Dosing diary on Days 12-14. To ensure unbiased data, treatments should be administered by clinical staff not directly involved in the assessment of the MDS-UPDRS Part III (Motor Examination) and Assessment of Subject's Motor State.

8.5.3. Postdose at Visits 2 and 4

- Collect postdose blood samples (6 mL) for PK analysis at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours postdose.
- Qualified staff who are blinded to treatment assignment perform Assessment of Subject's Motor State (of "on" and "off," and state of dyskinesia) at half-hour intervals at approximately 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, and 10 hours postdose. For each subject, the preference is to have the same rater perform the assessment at every time point throughout the study.
- Qualified staff who are blinded to treatment assignment perform MDS-UPDRS Part III (Motor Examination) hourly at approximately 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 hours postdose. For each subject, the preference is to have the same rater perform the assessment at every time point throughout the study.
- When PK sampling and other procedures or measurements are scheduled at the same time, the PK sampling shall be done as close as possible to the nominal time.
- Provide a breakfast containing approximately 5 grams of protein approximately 1 hour following the morning dose (Appendix L). Lunch may be provided no earlier than 4 hours following the morning dose. Subjects may be provided dinner if needed. Subjects may also be provided snacks as long as it is not within 1 hour before or after their morning dose.

- Perform 12-lead ECG at 2 hours postdose.
- Assess vital signs at 2, 4, and 10 hours postdose: blood pressure, heart rate, and respiratory rate will be measured after the subject has been supine for at least 5 minutes. Orthostatic blood pressure and heart rate will be measured after the subject has been standing for approximately 2 minutes.
- After completion of the10-hour PK sampling and pharmacodynamic assessments instruct the subject to switch back to taking their prestudy PD medications, including CD-LD, taking into account the timing of the last dose of study medication (Visits 2 and 4) and to maintain this regimen until 10:00 PM on the night before the next visit (Visit 2 only).
- If the current study medication is IPX203, it is recommended that the next dose of CD-LD be withheld for at least 5 hours after the last dose of IPX203.

8.6. Study Exit/Early Withdrawal Procedures

All enrolled subjects must complete Study Exit procedures at the end of Visit 4 or within 3 days of Visit 4, or during an early withdrawal visit:

- Complete physical examination.
- Vital signs (temperature, respiration, blood pressure and heart rate after supine for at least 5 minutes) and orthostatic standing vital signs (blood pressure and heart rate after standing for approximately 2 minutes).
- Perform a 12-lead ECG.
- Perform C-SSRS.
- Obtain samples for clinical laboratory evaluations (chemistry, hematology, and urinalysis).
- Update concomitant medications.
- Update AEs. All ongoing AEs must be followed until the event has resolved or has stabilized.
- Instruct the subject to switch back to their prestudy PD medications and regimen (including IR CD-LD) and to maintain this dosing regimen unless or until they receive alternative instructions from their regularly treating physician or health care provider.

8.7. Early Withdrawal

Subjects who withdraw early should complete Study Exit procedures.

8.8. Blood Volume

Safety blood draws: Approximately 10 mL of blood will be drawn at Screening and at Study Exit, for a combined total of 20 mL.

PK blood draws: Up to 472 mL will be drawn for subjects who complete both treatment periods.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

Study drugs will be provided by Impax for this study:

- IPX203 (carbidopa-levodopa) Extended-Release Capsules, in two strengths, containing 180 mg and 270 mg of LD, for oral administration.
- Immediate-release carbidopa-levodopa (IR CD-LD) tablet containing 100 mg of LD, for oral administration.

Table 6: Study Drugs for Study IPX209-B16-01

Investigational Product	Dosage Form and Strength	Manufacturer
IPX203 (carbidopa-levodopa) Extended-Release Capsules	45-180 mg 67.5-270 mg oral administration	Impax
Sinemet® (carbidopa levodopa) tablets (IR CD-LD)	25-100 mg oral administration	Merck & Co, Inc.

9.2. Concomitant Medications

9.2.1. Permitted PD Medications

Concomitant therapy with amantadine, selective monoamine oxidase (MAO) type B inhibitors (eg, selegiline, rasagiline), anticholinergic PD medications (eg, benztropine, trihexyphenidyl), GABAergic hypnotics, and/or dopamine agonists (except apomorphine) is allowed provided the doses and regimens have been stable for at least 4 weeks prior to Visit 1 and the therapy is intended to be constant throughout the course of the study. Use of CR CD-LD as a single bedtime dose is permitted during the wash-out period if this was part of their pre-study regimen.

9.2.2. Prohibited PD Medications

Prohibited medications include the following:

- Received within 4 weeks of Visit 1 or planning to take during participation in the clinical study: any doses of a controlled-release (CR) LD apart from a single daily bedtime dose or any doses of Rytary, additional CD (eg, Lodosyn) or benserazide (eg, Serazide), or catechol-O-methyl transferase inhibitors (entacapone or tolcapone) or medications containing these inhibitors (Stalevo).
- Received within 4 weeks of Visit 1 or planning to take during participation in the clinical study: nonselective MAO inhibitors, apomorphine, or dopaminergic blocking agents including antiemetics.

- Treatment with any dopamine antagonist antipsychotic agents for the purposes of psychosis or bipolar disorder within the last 2 years. Use of antipsychotics to treat conditions other than psychosis or bipolar disorders may be allowed only after consultation with the medical monitor.

A subject who reports the use of any prohibited medications will be discontinued.

All medications taken within 30 days prior to signing the informed consent form (ICF) and all concomitant medications taken during the study will be recorded on the case report form (CRF).

9.3. Treatment Compliance

Study drug accountability and reconciliation will be performed by the study monitor.

9.4. Randomization and Blinding

At Visit 1, the subject will be randomized into 1 of 2 treatment sequences (Table 2).

This is an open-label study with pharmacodynamic assessments done by qualified raters who are blinded to treatment assignments.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

Study drugs include IPX203 and the reference treatment Sinemet IR (CD-LD: 25-100 mg).

IPX203 is an extended-release (ER) capsule formulation of CD-LD. IPX203 is manufactured by Impax and will be supplied by Impax.

Sinemet IR is commercially available and will be provided by Impax.

10.2. Study Drug Packaging and Labeling

Impax or designee will provide study medications in bottles with appropriate labeling affixed.

Labels on the study medication may include the following information:

- protocol number
- study medication name and strength
- unique bottle identifier
- investigator name and site number
- lot number
- number (quantity) of capsules or tablets
- directions for use
- caution statement: Caution: New Drug—Limited by Federal (or United States) law to investigational use.
- storage information: Store at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.
- sponsor's name and address

10.3. Study Drug Storage

The study medications should be stored at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). They should be stored in a tightly closed container, protected from light and moisture. Storage temperature excursions above 30°C (86°F) should be reported to Product Development at Impax or its designee.

10.4. Study Drug Administration

Subjects will be instructed to take their medications with approximately 240 mL of room-temperature water. The capsules or tablets should not be crushed or chewed.

IR CD-LD tablets may be split using a pill cutter.

10.5. Study Drug Dispensing and Accountability

The Investigator must ensure that all study medication received at the study site is inventoried and accounted for, and that dispensed study medication is recorded in the subject's source documents, the CRF, and the study medication inventory log. Site personnel must not relabel or reassign study medication to other subjects or to individuals not enrolled in the study. The study monitor verifies medication accountability during monitoring visits.

10.6. Study Drug Handling and Disposal

The Investigator must retain and properly store all partially used and unused study medication until authorized by Impax regarding disposition.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percent "off" time during waking hours, based on subject PD diaries for the last 3 days collected at the end of each treatment period.

11.2. Secondary Efficacy Endpoints

Secondary endpoints include the following:

- Subject PD diaries for the last 3 days collected at the end of each treatment period:
  - Average of (1) total "off" time (2) total "on" time with no troublesome dyskinesia [good on] (3) total "on" time with no dyskinesia (4) total "on" time with troublesome dyskinesia (5) total "on" time with non-troublesome dyskinesia (6) total time asleep
  - Proportion of subjects with an improvement of at least 0.5, 1, 1.5, 2, and 3 hours in the total "off" time based on PD Diaries from baseline
  - Proportion of subjects in "off" state within the first 30 minutes of awakening for the day immediately following the subject's usual nocturnal sleep period
  - Average total "off" time and total "on" time with no troublesome dyskinesia normalized for a 16-hour wake period
- Change in the dyskinesia, mobility, and tremor measures obtained using the Kinesia 360
- MDS-UPDRS collected predose on Day 15 of each treatment period – Average of
  - Total MDS-UPDRS score for the sum of Parts I to IV
  - Total scores for each of the 4 parts of the MDS-UPDRS
  - Total MDS-UPDRS score for the sum of Parts II and III

12. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

12.1. Pharmacokinetic Assessments

The following single-dose PK parameters will be calculated from CD and LD plasma concentrations for each treatment: observed maximum CD and LD plasma concentrations (C_{max}) and time to maximum concentration (T_{max}); area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}), and from time zero to infinity ($AUC_{0-\infty}$); apparent elimination half-life ($t_{1/2}$); and bioavailability of IPX203 relative to IR CD-LD. Additionally, time to 50% C_{max} of LD and duration > 50% C_{max} of LD will be calculated for IPX203, and IR CD-LD. Data after redosing on Day 1 (Visit 1 and 3) will not be included in these assessments.

The following parameters will be estimated for LD and CD using data on Day 15 (Visits 2 and 4):

- C_{max} over the dosing regimen
- T_{max} over the dosing regimen
- AUC_{0-10}
- Accumulation calculated as $AUC_{0-\tau}$ on Day 15/$AUC_{0-\tau}$ on Day 1
- Fluctuation calculated as $(C_{max} - C_{min})/C_{avg}$ (maximum [peak] drug concentration minus minimum drug concentration divided by average drug concentration), C_{avg} = average drug concentration.

12.1.1. Blood Sample Collection Schedule in Each Study Period

Blood samples (6 mL) for measurement of plasma LD and CD concentrations will be collected at the following time points:

- Day 1 of each treatment period (Visits 1 and 3) – at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, and 8 hours postdose.
- Day 15 of each treatment period (Visits 2 and 4) – at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, and 10 hours postdose.

12.1.2. Samples per Subject

A total of 60 PK blood samples will be collected if a subject completes the entire study.

12.1.3. Pharmacokinetic Blood Sample Collection and Processing

See Appendix K for blood-sample labeling, processing, storage, and shipment instructions.

12.2. Pharmacodynamic Assessments Endpoints

The Movement Disorders Society—Unified Parkinson's Disease Rating Scale and the Assessment of Subject's Motor State will be assessed by qualified clinical staff blinded to treatment.

12.2.1. MDS-UPDRS

The following endpoints will be used to evaluate the difference between IPX203 and IR CD-LD using MDS-UPDRS Part III — Day 1 and Day 15 of each treatment period:

- Average of change in MDS-UPDRS Part III score from Day 1 predose value at each time point
- Area under the curve (AUC) of change in MDS-UPDRS Part III motor score value from predose value on Day 1
- Average duration of effect estimated using the time point at which an improvement of at least (1) 4 points (2) 7 points (3) 13 points in the MDS-UPDRS Part III score from predose value on Day 1 is first observed and continuing until the time point at which the improvement is no longer observed.
- Average of change in sum of questions 4 through 8 and question 14 MDS-UPDRS Part III score from Day 1 predose value at each time point to assess bradykinesia.
- Average of change in each question 4, 5, 6, 7, 8 and 14 of MDS-UPDRS Part III separately from Day 1 predose value at each time point to assess bradykinesia.

12.2.2. Assessment of Subject's Motor State

The following endpoints will be analyzed to compare IPX203 with IR CD-LD using Assessment of Subject's Motor State — Day 1 and Day 15 of each treatment period:

- Average of (1) total off time (2) total "on" time with no troublesome dyskinesia [good on] (3) total "on" time with no dyskinesia (4) total "on" time with troublesome dyskinesia (5) total "on" time with non-troublesome dyskinesia (6) total time asleep,
- Proportion of subjects who are "off" and proportion of subjects "on" without troublesome dyskinesia will be presented at each time point.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety will be assessed by the following parameters:

- ECGs, clinical laboratory tests, physical examinations, the C-SSRS, and vital signs.
- Adverse events and concomitant medications will be evaluated over the course of the study.

13.2. Adverse Events

13.2.1. Definition of Adverse Event

An adverse event (adverse experience) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs and any clinically significant physical examination findings, 12-lead ECG abnormalities, or clinical laboratory measurements occurring during the study that were not present prior to administration of study medication and that continue at Study Exit should be followed and evaluated with additional tests, if necessary, until the AEs are medically stable or resolved. Follow-up on these AEs should be recorded on the source documents and reported to Impax.

13.2.2. Recording Adverse Events

Elicit information about AEs with nonselective questions such as: "Have you experienced any changes in your health status since your last visit?" Encourage subjects to report AEs at onset.

Record information for any AE that emerges from the time the subject signs the ICF until Study Exit.

Monitor each subject closely for the development of AEs and record all such events on the AE page of the CRF. Whenever possible, group signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped as upper respiratory infection.

For each AE, record the onset date, severity, seriousness, relationship to study medication, date of resolution (or continuing), action taken, and outcome in the CRF. The Investigator is to make a causality assessment (relationship to study medication) for every AE.

13.2.3. Follow-up

The Investigator must follow each AE until resolved or medically stable.

13.2.4. Relationship to Study Drug

The Investigator documents his/her opinion of the relationship of the AE to the study medication as follows:

- Not Related—the experience can be readily explained by the subject's underlying medical condition or concomitant medications and no relationship exists between the study medication and the experience.
- Unlikely Related—the temporal relationship between the AE and the administration of the study medication is uncertain and it is likely that the AE can be explained by the subject's medical condition or other therapies.
- Possibly Related—there is some logical temporal relationship between the AE and the administration of the study medication and the experience is unlikely to be explained by the subject's medical condition or other therapies.
- Related—the temporal relationship is compelling between the administration of the study medication and the AE cannot be explained by the subject's medical condition or other therapies.

13.2.5. Assessment of Severity

Grade each AE for severity and note in the description of the AE. Determine the severity category of mild, moderate, or severe, as defined below, and enter the information on the AE page of the CRF.

- Mild—causing no limitation of usual activities
- Moderate—causing some limitation of usual activities
- Severe—causing inability to carry out usual activities

13.3. Serious Adverse Events

13.3.1. Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes, regardless of relationship to the study medication:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.3.2. Reporting Serious Adverse Events

Any SAE that occurs from the time the subject signs an ICF until 30 days after taking the final dose of study medication must be reported by the investigative staff to the Sponsor or the Sponsor's representative within 24 hours of knowledge of the event (see Study Contact Information).

An SAE form must be completed and sent to the Sponsor and/or the Sponsor's representative. All SAEs must also be recorded on the AE page of the CRF. Additionally, all SAEs must be reported to the institutional review board (IRB) per the IRB's requirements.

Those SAEs that are considered both serious and unexpected and related to the study drug are subject to expedited reporting. An "unexpected AE" is any AE where the nature or severity is not consistent with the current investigator brochure (IB) or if an IB is not required or available, the specificity or severity is not consistent with the provided risk information.

Unexpected fatal or life-threatening SAEs related to the study drug must be reported by the Sponsor to the appropriate regulatory authority in an expedited manner (ie, first report within 7 days of first knowledge by the Sponsor). The Sponsor will provide a final written report to that authority within 15 days of initial receipt of information on the event. The Sponsor or the Sponsor's representative will also inform all participating Investigators of the SAE.

Unexpected SAEs that are not fatal or life-threatening must be reported by the Sponsor to the appropriate regulatory authority as soon as possible but no later than 15 calendar days after first knowledge of the SAE by the Sponsor. The Sponsor or the Sponsor's representative also informs all participating Investigators of the SAE.

Subjects withdrawn from the study due to any SAE will be followed until the SAE is resolved or medically stable. Record all SAEs, regardless of severity and whether or not related to the study medication, on the appropriate page of the CRF.

The Investigator must determine whether the seriousness of the event warrants removal of the subject from the study. He/she should, in any case, institute appropriate diagnostic and therapeutic measures and keep the subject under observation for as long as is medically indicated, or refer the subject to appropriate health professionals.

13.4. Pregnancy

Any pregnancy that occurs from the time the subject signs an ICF until 30 days after taking the final dose of study medication must be reported within 24 hours to the Sponsor or the Sponsor's representative and the subject should be terminated from the study. All pregnancies will be followed through to delivery of the infant. If the subject experiences a termination of the pregnancy, it should be reported as defined in Section 13.3.2.

13.5. Other Safety Parameters and Related Information

Additional safety parameters (laboratory tests, 12-lead ECGs, physical examinations, and vital signs), the C-SSRS, and concomitant medications are collected as shown in the Schedule of Assessments in Table 5 and evaluated over the course of the study. Clinical laboratory studies are listed in Appendix J.

14. STATISTICS

14.1. Study Design and Sample Size Estimation

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

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

For efficacy, a subject will be considered a completer if the subject receives treatments in both periods and has at least 2 days of evaluable PD diary data for each period.

For pharmacodynamic assessments, a completer will be defined as a subject who has received both treatments and has completed at least 4 postdose Assessments of Subjects' Motor State in each period.

14.2. Demographics/Baseline Comparability

The demographics and baseline characteristics for all subjects enrolled in the study will be summarized.

14.3. Analysis of Pharmacokinetic Data

The following PK parameters will be calculated from the CD and LD plasma concentrations following single doses of each treatment (IPX203 and IR CD-LD):

C_{max}	maximum observed plasma concentration
T_{max}	time to maximum concentration
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	AUC value extrapolated to infinity will be calculated as the sum of AUC_{0-t} and the area extrapolated to infinity, calculated by the last measurable concentration (C_{last}) divided by λ_z
$t_{1/2}$	apparent elimination half-life ($t_{1/2}$) values will be calculated as $0.693/\lambda_z$
λ_z	apparent elimination rate constant will be estimated by linear regression of the log-transformed plasma concentrations during the terminal log-linear decline phase

The bioavailability of IPX203 relative to IR CD-LD will also be calculated.

Additionally, time to 50% C_{max} of LD and duration > 50% C_{max} of LD will be calculated for IPX203, and IR CD-LD. Data after redosing on Day 1 (Visit 1 and 3) will not be included in these assessments.

The following parameters will be estimated for LD and CD following multiple dosing (Day 15):

- C_{max} over the dosing regimen
- T_{max} over the dosing regimen
- AUC_{0-10}
- Accumulation
- Fluctuation

Descriptive statistics will be presented by treatment group and LD dose for the PK parameters for IR CD-LD and IPX203. Following natural logarithm transformation, analyses of variance (ANOVA) will be performed on CD and LD AUC and C_{max} adjusted for dose, fluctuation, and accumulation. Additionally, duration of LD plasma concentration above 50% of C_{max} values will be analyzed using ANOVA. Comparisons will be performed using a mixed-effect ANOVA model that includes treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect for the following treatments: IPX203 versus IR CD-LD. All PK analyses will be done following current recommendations (Food and Drug Administration 2003).

14.4. Analysis of Efficacy Data

Descriptive statistics and frequency distributions will be displayed for all endpoints.

14.4.1. Primary Efficacy Endpoint

The primary efficacy parameter for this study will be the average percent "off" time during waking hours based on subject PD diaries collected at the end of each treatment period. For each day it will be calculated as the number of half-hour intervals in which "off" is checked. The average percent "off" time will be defined as the average of percent "off" time (total "off" time divided by the total time not "asleep," (ie, waking hours) from the subject PD diaries completed for the 3 days immediately prior to the visit. The difference between the average percent "off" time between treatments will be analyzed using a standard mixed-model analysis of variance at a 0.05 level of significance. This model will include the fixed-effect factors of treatment, and period and the random-effect inter- and intra-subject factors.

14.4.2. Secondary Efficacy Endpoint

The continuous efficacy endpoints will be evaluated for differences between treatments using a standard mixed-model analysis of variance at a 0.05 level of significance. This model will include the fixed-effect factors of treatment, sequence and period and the random-effect inter- and intra-subject factors. All comparisons of secondary endpoint will be tested at 5% significance level without any multiplicity correction.

The following efficacy parameters will be analyzed using mixed-model analysis in a fashion similar to the primary efficacy endpoint:

- Average off time – From the subject PD diaries, the number of half-hour intervals marked "off" will be calculated. The difference between the averages of total "off" time between the two treatments will be analyzed.
- Average time "on" with no troublesome dyskinesia (good on) – From the subject PD diaries, the sum of the number of half-hour intervals marked "on without dyskinesia" and "on with non-troublesome dyskinesia" will be calculated. The difference between the averages of total time "on with no troublesome dyskinesia" between the two treatments will be analyzed.
- Average of total "on" time with no dyskinesia – From the subject PD diaries, the sum of the number of half-hour intervals marked "on without dyskinesia" will be calculated. The difference between the averages of total time "on time with no troublesome dyskinesia" between the two treatments will be analyzed.
- Average of total "on" time with troublesome dyskinesia – From the subject PD diaries, the sum of the number of half-hour intervals marked "on with troublesome dyskinesia" will be calculated. The difference between the averages of total time "on with troublesome dyskinesia" between the two treatments will be analyzed.
- Average of total "on" time with non-troublesome dyskinesia – From the subject PD diaries, the sum of the number of half-hour intervals marked "on with non-troublesome dyskinesia" will be calculated. The difference between the averages of total time "on with non-troublesome dyskinesia" between the two treatments will be analyzed.
- Average of total time asleep – From the subject PD diaries, the sum of the number of half-hour intervals marked "asleep" will be calculated. The difference between the averages of total time "asleep" between the two treatments will be analyzed.
- Average of total off time normalized for 16 waking hours: Normalize the off time by multiplying the proportion of off time during the waking hours with 16 hours. The difference between the averages of total off time normalized for 16 waking hours between the two treatments will be analyzed.
- Average of total on time with no troublesome dyskinesia normalized for 16 waking hours: Normalize the on time with no troublesome dyskinesia by multiplying the proportion of on time with no troublesome dyskinesia time during the waking hours with 16 hours. The difference between the averages of total on time with no troublesome dyskinesia normalized for 16 waking hours between the two treatments will be analyzed.
- Average of total MDS-UPDRS Score – The sum of the scores of Parts I, II, III and IV will be calculated. The difference between the averages of the total MDS-UPDRS scores for the two treatments will be analyzed.
- Average of total Score of individual Parts of MDS-UPDRS: The total scores of each of the 4 parts of the MDS-UPDRS will be calculated and the difference between the averages of scores of each part for the two treatments will be analyzed.

- Average of total of MDS-UPDRS Parts II and III: Since both treatments are likely to have the greatest effect on Part II (activities of daily living) and Part III (motor examination), the sum of these two parts will be analyzed. The difference between the averages of the total MDS-UPDRS Parts II and III scores for the two treatments will be analyzed.
- Change in the dyskinesia, mobility, and tremor measures obtained using the Kinesia 360.

The proportion of subjects with an improvement of at least 0.5, 1, 1.5, 2, and 3 hours in the "off" time will be analyzed using generalized estimating equations methods. The model will include treatment and period. The proportion of subjects in "off" state within the first 30 minutes of awakening for the day immediately following the subject's usual nocturnal sleep period will also tabulated by day. The proportion of subjects who may have no, 1, 2 or 3 instances of "off" over the three days will also be analyzed.

14.5. Analysis of Pharmacodynamics Data

Descriptive statistics and frequency distributions will be displayed for all pharmacodynamic endpoints.

The continuous endpoints will be evaluated for differences between treatments using a standard mixed-model analysis of variance at a 0.05 level of significance. This model will include the fixed-effect factors of treatment, sequence and period and the random-effect inter- and intra-subject factors. The following analysis will be conducted for Day 1 and Day 15 endpoints:

- Average total "off" time will be derived from the Assessment of Subject's Motor State every 30 minutes. It will be based on the sum of half-hour intervals marked "off".
- Average total time "on" without troublesome dyskinesia (good on): Estimated using total "on" time without dyskinesia and "on" with nontroublesome dyskinesia based on the sum of half-hour intervals marked "on" without dyskinesia and "on" with non-troublesome dyskinesia.
- Average total time "on" with no dyskinesia: Estimated using total "on" with no dyskinesia based on sum of half-hour intervals marked "on" without dyskinesia.
- Average total time "on" with troublesome dyskinesia: Estimated using total "on" with troublesome dyskinesia will be based on sum of half-hour intervals marked "on" with troublesome dyskinesia.
- Average total time "on" with non-troublesome dyskinesia: Estimated using total "on" with non-troublesome dyskinesia based on sum of half-hour intervals marked "on" with non-troublesome dyskinesia.
- Average total time asleep: Estimated using total time asleep based on sum of half-hour intervals marked asleep.
- Average of change in MDS-UPDRS Part III score from Day 1 predose value to each postdose time point.

- To determine the effect of IPX203, average of the area under the curve (AUC) for the change from predose in the MDS-UPDRS Part III score
- Duration of effect using time points at which an improvement of at least 4 points in the MDS-UPDRS Part III score from predose is observed will be estimated. The difference in mean duration of effect between treatments will be analyzed using a mixed-effect ANOVA model which will include treatment, period, and sequence as fixed effects and subject-within-sequence as a random effect. To determine the duration of effect, the midway point between two adjacent time points will be used. For example, if a subject does not have 4 units of improvement from the predose MDS-UPDRS Part III assessment at the 1-hour postdose assessment, but has an improvement at the 2-hour postdose assessment, and loses the 4-unit improvement at the 3-hour assessment, the duration of effect will be considered as 1 hour using the interpolated time value. Similar analysis will be conducted for an improvement of at least 7 and 13 points in the MDS-UPDRS Part III score from predose.
- Average of change in sum of questions 4 through 8 and question 14 MDS-UPDRS Part III score from Day 1 predose value at each time point to assess bradykinesia.
- Average of change in each question 4, 5, 6, 7, 8 and 14 of MDS-UPDRS Part III separately from Day 1 predose value at each time point to assess bradykinesia.

The categorical endpoints will be analyzed using generalized estimating equations methods. The model will include treatment and period. All comparisons of secondary endpoint will be tested at 5% significance level without any multiplicity correction.

14.6. Analysis of Dosing Data

The IPX203 daily dose and frequency of dosing will be collected during this study to further assess optimal dosing and dosing instructions for advanced-stage PD population subjects who were treated with IR CD-LD previously.

14.7. Population Analysis and Handling of Dropouts

Subjects who discontinue early will not be replaced.

All subjects treated with any study medication will be included in the safety analyses.

For pharmacodynamic analysis, all available data obtained on subjects who receive both treatments and have at least 4 postdose Assessment of Subject's Motor State for each treatment will be included in the analysis.

For subjects who receive rescue medication or who discontinue the study assessments prior to the Hour 8 (Visit 1 and 3) and Hour 10 (Visit 2 and 4) assessment on Day 1, the following rules will be applied for various evaluations:

- Assessment of Subject's Motor State—all half-hour assessments after rescue medication is administered will be considered as "off" for the remainder of the evaluation period.
- MDS-UPDRS Part III—the predose sum of MDS-UPDRS Part III will be carried forward for all time points after rescue medication administration.

Imputation of missing data for subject PD diaries will be required if the PD diary is not completed for a day (6 am to 6 am). In this case, the method of imputation will be dependent upon the amount and pattern of missing data:

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

14.8. Safety

The safety analysis will include all subjects who receive at least 1 dose of study medication. Reported AEs will be coded to standard terms using a standard dictionary (Medical Dictionary for Regulatory Activities [MedDRA]). All AEs will be summarized by body system, and by preferred terms within a body system, by severity, and by relation to study medication. Each AE (based on preferred terminology) is counted only once for a given subject within a treatment. If the same AE occurred on multiple occasions, the highest severity and least complimentary relationship was assumed. If two or more AEs were reported as a unit, the individual terms will be reported as separate AEs.

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

The secondary safety variables including early termination data, laboratory test data, physical examination data, vital signs, ECGs, the C-SSRS and concomitant medications will be tabulated. Clinical laboratory values are to be summarized by visit, including change from baseline. Medically significant laboratory values outside of normal reference ranges will also be tabulated and assessed.

15. ADMINISTRATIVE PROCEDURES

15.1. Guidelines for Good Clinical Practice

This study will be conducted in accordance with principles of Good Clinical Practice (GCP) as promulgated by the ICH. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of human subjects are protected under current ethical principles, and that the clinical trial data are credible. Current GCP standards may be found in ICH Guidance E6 (Good Clinical Practice: Consolidated Guidance). This guidance describes the principles of GCP and the obligations of the institutional review board (IRB), the Investigator and the Sponsor in conducting this study in accordance with those principles.

15.2. Institutional Review Board Approval

The review of this protocol by an IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must be in accordance with principles enunciated in the ICH and GCP Guidelines and by the appropriate regulatory authorities.

The Investigator is responsible for preparing documents for submission to the relevant IRB and obtaining written approval for this study. Institutional Review Board approval must be obtained prior to the initiation of the study. The Investigator's continued participation in the study is contingent on renewing approval with the IRB at least annually.

15.3. Informed Consent

Site personnel should prepare an Informed Consent Form (ICF) incorporating the necessary elements of consent. The ICF is to be approved by Impax prior to submission to the IRB. The Investigator or his/her staff must explain the nature of the investigation and the risks involved to each subject prior to screening, and obtain a signed ICF. The subject should also be informed that he/she is free to voluntarily withdraw from the study at any time.

15.4. Study Monitoring

Impax representatives or designees will conduct site visits to the investigational facilities for the purpose of monitoring the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relevant to study conduct. The Investigator must permit access to such records if a regulatory or compliance audit is required.

15.5. Protocol Amendments

All amendments to the protocol must be documented in writing, reviewed and approved by the Sponsor and Investigator, and submitted to the IRB for approval prior to implementation. If the protocol amendment substantially alters the study design or potential risk to the subject, a new written ICF for continued participation in the study must be obtained from each subject affected by the change.

15.6. Termination of Study

The Sponsor has the right to terminate this study and remove all study material from the site at any time for medical or administrative reasons. In this event, the Sponsor will endeavor to give adequate notice to allow safe withdrawal of subjects from the study.

15.7. Case Report Forms

Site personnel should collect and record data for the study as source documents, and transfer the data into the CRF.

The Investigator must ensure that complete data for the clinical study are collected and accurately documented in the appropriate sections of the CRF and adequately supported by the appropriate source documentation. In addition, it is the Investigator's responsibility to provide signatures where requested indicating concurrence with data in the CRF.

15.8. Investigator's Final Conduct Report

At the completion of the study, the Investigator must provide Impax a copy of the final conduct report that was submitted to their IRB, including a review of AEs.

15.9. Records Retention

International Conference on Harmonization, GCP, and US FDA guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, the essential documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. Records should never be destroyed without written approval from the Sponsor.

If an Investigator leaves the institution, he/she must transfer responsibilities for record retention to another individual willing to accept them. The Investigator must notify the Sponsor in writing of the transfer of study documents before the transfer of the study documents.

16. PUBLICATION POLICY

Study results may not be published without prior written approval from Impax.

17. LIST OF REFERENCES

Blanchet PJ, Calon F, Martel JC, et al. Continuous administration decreases and pulsatile administration increases behavioral sensitivity to a novel dopamine D2 agonist (U-91356A) in MPTP-exposed monkeys. J Pharmacol Exp Ther. 1995;272:854-859.

Engber TM, Susel Z, Juncos JL, Chase TN. Continuous and intermittent levodopa differentially affect rotation induced by D-1 and D-2 dopamine agonists. European Journal of Pharmacology. 1989;168:291-298.

Fahn S. Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs Later L DOPA. Arch Neurol. 1999 May;56(5):529-35.

Food and Drug Administration 2003. Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). March 2003.

Juncos JL, Engber TM, Raisman R, et al. Continuous and intermittent levodopa differentially affect basal ganglia function. Ann Neurol. 1989;25:473-478.

Kurlan R, Rothfield KP, Woodward WR, Nutt JG, Miller C, Lichter D, et al. Erratic gastric emptying of levodopa may cause "random" fluctuations of parkinsonian mobility. Neurology. 1988;38(3):419-21.

Melamed E, Bitton V, Zelig O. Delayed onset of responses to single doses of L-dopa in parkinsonian fluctuators on long-term L-dopa therapy. Clin Neuropharmacol. 1986;9(2):182-8.

Mizuno Y. Where do we stand in the treatment of Parkinson's disease? Neurology. 2007;254:13-18.

Nilsson D, Nyholm D, Aquilonius S-M. Duodenal levodopa infusion in Parkinson's disease--long-term experience. Acta Neurologica Scandinavica. 2001;104:343-348.

Nyholm D, Nilsson Remahl AI, Dizdar N, et al. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology. 2005;64:216-223.

Sinemet (Carbidopa-Levodopa) Tablets Prescribing Information. Whitehouse Station, NJ: Manufactured by Merck & Co., Inc.; Marketed by Bristol-Myers Squibb Company; 2013.

Stocchi F, Quinn NP, Barbato L, Patsalos PN, O'Connel MT, Ruggieri S, et al. Comparison between a fast and a slow release preparation of levodopa and a combination of the two: a clinical and pharmacokinetic study. Clinical Neuropharmacol. 1994;17(1):38-44.

Stocchi F, Vacca L, et al. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neurol. 2005:62(6):905-910.

18. APPENDICES

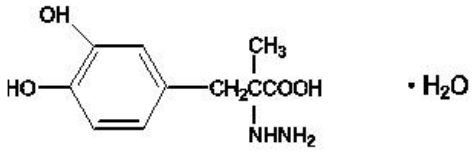
APPENDIX A. SINEMET PRESCRIBING INFORMATION

SINEMET®
(carbidopa levodopa)
Tablets

DESCRIPTION

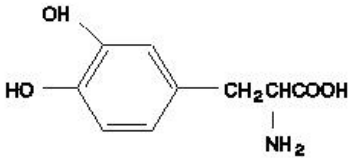
SINEMET® (carbidopa levodopa) is a combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (—)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (—)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is:



SINEMET is supplied as tablets in three strengths:
SINEMET 25-100, containing 25 mg of carbidopa and 100 mg of levodopa.
SINEMET 10-100, containing 10 mg of carbidopa and 100 mg of levodopa.
SINEMET 25-250, containing 25 mg of carbidopa and 250 mg of levodopa.

Inactive ingredients are hydroxypropyl cellulose, pregelatinized starch, crospovidone, microcrystalline cellulose, and magnesium stearate. SINEMET 10-100 and 25-250 Tablets also contain FD&C Blue #2/Indigo Carmine AL. SINEMET 25-100 Tablets also contain D&C Yellow #10 Lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Pharmacodynamics

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect, and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients, this reduction in nausea and vomiting will permit more rapid dosage titration.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.

Pharmacokinetics

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours. At steady state, the bioavailability of carbidopa from SINEMET tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa produced greater urinary excretion of levodopa in proportion to the excretion of dopamine than administration of the two drugs at separate times.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Special Populations

Geriatric: A study in eight young healthy subjects (21-22 yr) and eight elderly healthy subjects (69-76 yr) showed that the absolute bioavailability of levodopa was similar between young and elderly subjects following oral administration of levodopa and carbidopa. However, the systemic exposure (AUC) of levodopa was increased by 55% in elderly subjects compared to young subjects. Based on another study in forty patients with Parkinson's disease, there was a correlation between age of patients and the increase of AUC of levodopa following administration of levodopa and an inhibitor of peripheral dopa decarboxylase. AUC of levodopa was increased by 28% in elderly patients (≥ 65 yr) compared to young patients (< 65 yr). Additionally, mean value of Cmax for levodopa was increased by 24% in elderly patients (≥ 65 yr) compared to young patients (< 65 yr) (see PRECAUTIONS, *Geriatric Use*).

The AUC of carbidopa was increased in elderly subjects (n=10, 65-76 yr) by 29% compared to young subjects (n=24, 23-64 yr) following IV administration of 50 mg levodopa with carbidopa (50 mg). This increase is not considered a clinically significant impact.

INDICATIONS AND USAGE

SINEMET is indicated in the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Carbidopa allows patients treated for Parkinson's disease to use much lower doses of levodopa. Some patients who responded poorly to levodopa have improved on SINEMET. This is most likely due to decreased peripheral decarboxylation of levodopa caused by administration of carbidopa rather than by a primary effect of carbidopa on the nervous system. Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa.

Carbidopa may also reduce nausea and vomiting and permit more rapid titration of levodopa.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with SINEMET. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET. SINEMET may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (see PRECAUTIONS, *Drug Interactions*).

SINEMET is contraindicated in patients with known hypersensitivity to any component of this drug, and in patients with narrow-angle glaucoma.

WARNINGS

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least twelve hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See DOSAGE AND ADMINISTRATION section before initiating therapy.

The addition of carbidopa with levodopa in the form of SINEMET reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa permits more levodopa to reach the brain and more dopamine to be formed, certain adverse central nervous system (CNS) effects, e.g., dyskinesias (involuntary movements), may occur at lower dosages and sooner with SINEMET than with levodopa alone.

All patients should be observed carefully for the development of depression with concomitant suicidal tendencies.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Falling Asleep During Activities of Daily Living and Somnolence

Patients taking SINEMET alone or with other dopaminergic drugs have reported suddenly falling asleep without prior warning of sleepiness while engaged in activities of daily living (includes operation of motor vehicles). Road traffic accidents attributed to sudden sleep onset have been reported. Although many patients reported somnolence while on dopaminergic medications, there have been reports of road traffic accidents attributed to sudden onset of sleep in which the patient did not perceive any warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Sudden onset of sleep has been reported to occur as long as one year after the initiation of treatment.

Falling asleep while engaged in activities of daily living usually occurs in patients experiencing pre-existing somnolence, although some patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving or operating machines during treatment with SINEMET. Patients who have already experienced somnolence or an episode of sudden sleep onset should not participate in these activities during treatment with SINEMET.

Before initiating treatment with SINEMET, advise patients about the potential to develop drowsiness and ask specifically about factors that may increase the risk for somnolence with SINEMET such as the use of concomitant sedating medications and the presence of sleep disorders. Consider discontinuing SINEMET in patients who report significant daytime sleepiness or episodes of falling asleep during

activities that require active participation (e.g., conversations, eating, etc.). If treatment with SINEMET continues, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hyperpyrexia and Confusion

Sporadic cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in association with dose reductions or withdrawal of certain antiparkinsonian agents such as levodopa, carbidopa levodopa, or carbidopa levodopa extended release. Therefore, patients should be observed carefully when the dosage of levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS; however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

General

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided the intraocular pressure is well-controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Dyskinesia

Levodopa alone, as well as SINEMET, is associated with dyskinesias. The occurrence of dyskinesias may require dosage reduction.

Hallucinations / Psychotic-Like Behavior

Hallucinations and psychotic-like behavior have been reported with dopaminergic medications. In general, hallucinations present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Hallucinations may be accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming.

SINEMET may have similar effects on thinking and behavior. This abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Ordinarily, patients with a major psychotic disorder should not be treated with SINEMET, because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of SINEMET.

Impulse Control / Compulsive Behaviors

Reports of patients taking dopaminergic medications (medications that increase central dopaminergic tone), suggest that patients may experience an intense urge to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or

the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or the caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with SINEMET. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking SINEMET [see Information for Patients].

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using SINEMET for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Information for Patients

The patient should be informed that SINEMET is an immediate-release formulation of carbidopa levodopa that is designed to begin release of ingredients within 30 minutes. It is important that SINEMET be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a 'wearing-off' effect may occur at the end of the dosing interval. The physician should be notified if such response poses a problem to lifestyle.

Patients should be advised that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of SINEMET. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multivitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa or carbidopa levodopa therapy.

Patients should be alerted to the possibility of sudden onset of sleep during daily activities, in some cases without awareness or warning signs, when they are taking dopaminergic agents, including levodopa. Patients should be advised to exercise caution while driving or operating machinery and that if they have experienced somnolence and/or sudden sleep onset, they must refrain from these activities. (See WARNINGS, Falling Asleep During Activities of Daily Living and Somnolence.)

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including SINEMET. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with SINEMET. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking SINEMET. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking SINEMET (See PRECAUTIONS, Impulse Control / Compulsive Behaviors).

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase (LDH), and bilirubin. Abnormalities in blood urea nitrogen (BUN) and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or carbidopa levodopa therapy.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension occurred when SINEMET was added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required.

For patients receiving MAO inhibitors (Type A or B), see CONTRAINDICATIONS. Concomitant therapy with selegiline and carbidopa levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa levodopa alone (see CONTRAINDICATIONS).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Use of SINEMET with dopamine-depleting agents (e.g., reserpine and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

SINEMET and iron salts or multivitamins containing iron salts should be coadministered with caution. Iron salts can form chelates with levodopa and carbidopa and consequently reduce the bioavailability of carbidopa and levodopa.

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year bioassay of SINEMET, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

In reproduction studies with SINEMET, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

Pregnancy

Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET. There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of SINEMET in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers

Levodopa has been detected in human milk. Caution should be exercised when SINEMET is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended.

Geriatric Use

In the clinical efficacy trials for SINEMET, almost half of the patients were older than 65, but few were older than 75. No overall meaningful differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals to adverse drug reactions such as hallucinations cannot be ruled out. There is no specific dosing recommendation based upon clinical pharmacology data as SINEMET is titrated as tolerated for clinical effect.

ADVERSE REACTIONS

The most common adverse reactions reported with SINEMET have included dyskinesias, such as choreiform, dystonic, and other involuntary movements, and nausea.

The following other adverse reactions have been reported with SINEMET:

Body as a Whole

Chest pain, asthenia.

Cardiovascular

Cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal

Dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic

Agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

Hypersensitivity

Angioedema, urticaria, pruritus, Henoch-Schönlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal

Back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric

Psychotic episodes including delusions, hallucinations, and paranoid ideation, bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

Respiratory

Dyspnea, upper respiratory infection.

Skin

Rash, increased sweating, alopecia, dark sweat.

Urogenital

Urinary tract infection, urinary frequency, dark urine.

Laboratory Tests

Decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), LDH, bilirubin, BUN, Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa levodopa formulations, and may occur with SINEMET are:

Body as a Whole

Abdominal pain and distress, fatigue.

Cardiovascular
Myocardial infarction.
Gastrointestinal
Gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.
Metabolic
Edema, weight gain, weight loss.
Musculoskeletal
Leg pain.
Nervous System/Psychiatric
Ataxia, extrapyramidal disorder, falling, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.
Respiratory
Pharyngeal pain, cough.
Skin
Malignant melanoma (see also CONTRAINDICATIONS), flushing.
Special Senses
Oculogyric crises, diplopia, blurred vision, dilated pupils.
Urogenital
Urinary retention, urinary incontinence, priapism.
Miscellaneous
Bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.
Laboratory Tests
Decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

OVERDOSAGE

Management of acute overdosage with SINEMET is the same as management of acute overdosage with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION

The optimum daily dosage of SINEMET must be determined by careful titration in each patient. SINEMET tablets are available in a 1:4 ratio of carbidopa to levodopa (SINEMET 25-100) as well as 1:10 ratio (SINEMET 25-250 and SINEMET 10-100). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Usual Initial Dosage

Dosage is best initiated with one tablet of SINEMET 25-100 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight tablets of SINEMET 25-100 a day is reached.

If SINEMET 10-100 is used, dosage may be initiated with one tablet three or four times a day. However, this will not provide an adequate amount of carbidopa for many patients. Dosage may be increased by one tablet every day or every other day until a total of eight tablets (2 tablets q.i.d.) is reached.

How to Transfer Patients from Levodopa

Levodopa must be discontinued at least twelve hours before starting SINEMET. A daily dosage of SINEMET should be chosen that will provide approximately 25% of the previous levodopa dosage. Patients who are taking less than 1500 mg of levodopa a day should be started on one tablet of SINEMET 25-100 three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is one tablet of SINEMET 25-250 three or four times a day.

Maintenance

Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, one tablet of SINEMET 25-100 may be substituted for each tablet of SINEMET 10-100. When more levodopa is required, SINEMET 25-250 should be substituted for SINEMET 25-100 or SINEMET 10-100. If necessary, the dosage of carbidopa levodopa 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Because both therapeutic and adverse responses occur more rapidly with SINEMET than with levodopa alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with SINEMET than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Addition of Other Antiparkinsonian Medications

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET is being administered, although dosage adjustments may be required.

Interruption of Therapy

Sporadic cases of hyperpyrexia and confusion have been associated with dose reductions and withdrawal of SINEMET. Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET is required, especially if the patient is receiving neuroleptics. (See WARNINGS.)

If general anesthesia is required, SINEMET may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

No. 3916A — SINEMET 25-100 Tablets are yellow, round, uncoated tablets, that are coded "650" on one side and plain on the other. They are supplied as follows:

NDC 0006-3916-68 bottles of 100.

No. 3915 — SINEMET 10-100 Tablets are light dapple-blue, round, uncoated tablets, that are coded "647" on one side and plain on the other. They are supplied as follows:

NDC 0006-3915-68 bottles of 100.

No. 3917 — SINEMET 25-250 Tablets are light dapple-blue, round, uncoated tablets, that are coded "654" on one side and plain on the other. They are supplied as follows:

NDC 0006-3917-68 bottles of 100.

Storage and Handling

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tightly closed container, protected from light and moisture.

Dispense in a tightly closed, light-resistant container.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Mylan Pharmaceuticals, Inc.
Morgantown, WV 26505, USA

Revised: 07/2014

uspi-mk0295b-t-1406r003

Rx Only

APPENDIX B. UNITED KINGDOM PARKINSON'S DISEASE SOCIETY BRAIN BANK DIAGNOSTIC CRITERIA FOR PARKINSON'S DISEASE

Step 1: Diagnosis of Parkinsonism
Bradykinesia **and** at least one of the following: • Muscular rigidity • 4–6 Hz resting tremor • postural instability not caused by primary visual, vestibular, cerebellar or Proprioceptive dysfunction
Step 2: Features tending to exclude Parkinson's disease as the cause of Parkinsonism
• History of repeated strokes with stepwise progression of parkinsonian features • History of repeated head injury • History of definite encephalitis • Neuroleptic treatment at onset of symptoms • >1 affected relatives • Sustained remission • Strictly unilateral features after 3 years • Supranuclear gaze palsy • Cerebellar signs • Early severe autonomic involvement • Early severe dementia with disturbances of memory, language and praxis • Babinski's sign • Presence of a cerebral tumour or communicating hydrocephalus on computed tomography scan • Negative response to large doses of levodopa (if malabsorption excluded) • MPTP exposure
Step 3: Features that support a diagnosis of Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)
• Unilateral onset • Rest tremor present • Progressive disorder • Persistent asymmetry affecting the side of onset most • Excellent (70–100%) response to levodopa • Severe levodopa-induced chorea • Levodopa response for ≥5 years • Clinical course of ≥10 years

APPENDIX C. MONTREAL COGNITIVE ASSESSMENT (MOCA)

Montreal Cognitive Assessment
(MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from 1 then to A then to 2 and so on. End here* [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern:
1 –A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: "*Copy this drawing as accurately as you can, in the space below*".

Scoring: One point is allocated for a correctly executed drawing.
- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a **clock**. Put in all the numbers and set the time to 10 past 11".*

Scoring: One point is allocated for each of the following three criteria:
- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: *"Tell me the name of this animal"*.

Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: *"This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them"*. Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *"I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.
At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, *"I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them*". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.*" Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.*: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*".

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: *"Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: *"I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]: ***I only know that John is the one to help today."*** Following the response, say: *"Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]: ***The cat always hid under the couch when dogs were in the room."***

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: *"Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready?* [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop."*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: *"Tell me how an orange and a banana are alike"*. If the subject answers in a concrete manner, then say only one additional time: *"Tell me another way in which those items are alike"*. If the subject does not give the appropriate response *(fruit)*, say, *"Yes, and they are also both fruit."* Do not give any additional instructions or clarification. After the practice trial, say: *"Now, tell me how a train and a bicycle are alike"*. Following the response, administer the second trial, saying: *"Now tell me how a ruler and a watch are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:
Train-bicycle = means of transportation, means of travelling, you take trips in both;
Ruler-watch = measuring instruments, used to measure.
The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark (√) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues.**

Optional:
Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (√) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *"Which of the following words do you think it was, NOSE, FACE, or HAND?"*
Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE:	category cue: part of the body	multiple choice: nose, face, hand
VELVET:	category cue: type of fabric	multiple choice: denim, cotton, velvet
CHURCH:	category cue: type of building	multiple choice: church, school, hospital
DAISY:	category cue: type of flower	multiple choice: rose, daisy, tulip
RED:	category cue: a colour	multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*

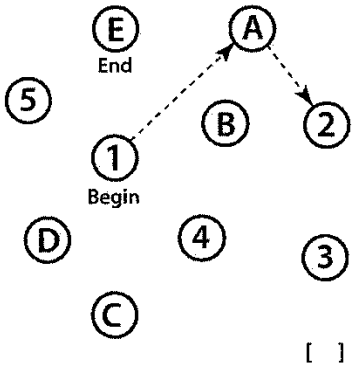
Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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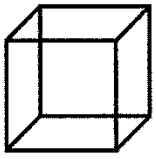


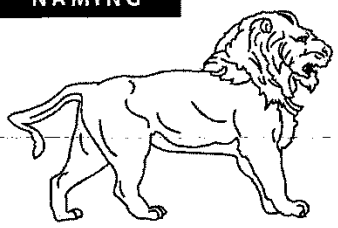
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING



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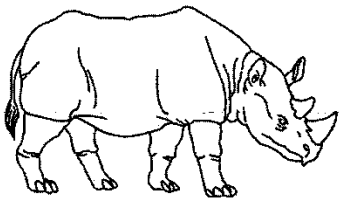

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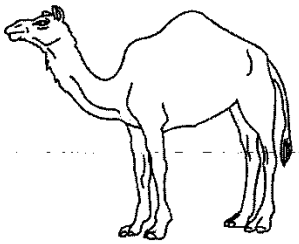

[ ] ___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX D. MDS-UPDRS

MDS-UPDRS Permissions

Permission is required to use the MDS-developed Rating Scales (with the exception of personal/individual use). Reproduction, translation, modification, sale, or distribution of any portion of the MDS Rating Scales is strictly prohibited. MDS Rating Scales may not be incorporated into clinical trials, training or certification programs or materials, software programs, or otherwise except through use of the Permissions Request Form and payment of applicable fees.

Continue to p. 2 to view the MDS-UPDRS

MDS-UPDRS

The *Movement* Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi,
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Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:
In administering Part IA, the examiner should use the following guidelines:

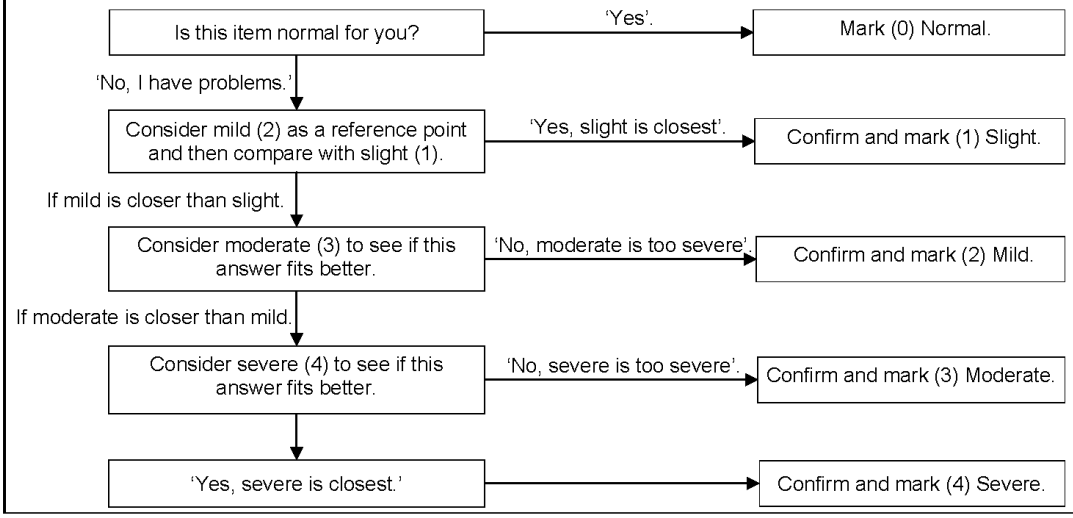
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:
After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



___ ___ ___ ___ ___ ___ ___ ___ Patient Name or Subject ID	___ ___ ___ Site ID	___ ___ - ___ ___ - ___ ___ ___ ___ (mm-dd-yyyy) Assessment Date	___ ___ ___ Investigator's Initials

MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part 1A: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT	**SCORE**
Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver. *Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information]* 0: Normal: No cognitive impairment. 1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions. 2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions. 3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions. 4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patients insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patients [and caregiver]: Over the past week have you seen, heard, smelled or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No hallucinations or psychotic behaviour. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instruction to the patient (and caregiver): Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people?* If yes, examiner asks patient or caregiver to elaborate and probes for information] 0: Normal: No depressed mood. 1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.4 ANXIOUS MOOD Instructions to examiner: Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patients [and caregiver]: Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people*? [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No anxious feelings. 1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐
1.5 APATHY Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression. *Instructions to patients (and caregiver): Over the past week, have you felt indifferent to doing activities or being with people?* If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No apathy. 1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions. 2: Mild: Apathy interferes with isolated activities and social interactions. 3: Moderate: Apathy interferes with most activities and social interactions. 4: Severe: Passive and withdrawn, complete loss of initiative.	☐

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

SCORE

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients.

0: Normal:	No problems present.	
1: Slight:	Problems are present but usually do not cause any difficulties for the patient or family/caregiver.	☐
2: Mild:	Problems are present and usually cause a few difficulties in the patient's personal and family life.	
3: Moderate:	Problems are present and usually cause a lot of difficulties in the patient's personal and family life.	
4: Severe:	Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.	

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐
Part II: Motor Aspects of Experiences of Daily Living (M-EDL)	
2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA & DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knifes, spoons, chopsticks? 0: Normal: Not at all (No problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another persons to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor. 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐
This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.	

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:
ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking , and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

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	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight.: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 3 cm in maximal amplitude. 3: Moderate: 3 - 10 cm in maximal amplitude. 4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: < 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 2 cm in maximal amplitude. 3: Moderate: > 2 cm but < 3 cm in maximal amplitude. 4: Severe: > 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

	SCORE
3.18 CONSTANCY OF REST TREMOR Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating. 0: Normal: No tremor. 1: Slight: Tremor at rest is present < 25% of the entire examination period. 2: Mild: Tremor at rest is present 26-50% of the entire examination period. 3: Moderate: Tremor at rest is present 51-75% of the entire examination period. 4: Severe: Tremor at rest is present > 75% of the entire examination period.	☐
DYSKINESIA IMPACT ON PART III RATINGS A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes	
HOEHN AND YAHR STAGE 0: Asymptomatic. 1: Unilateral involvement only. 2: Bilateral involvement without impairment of balance. 3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test. 4: Severe disability; still able to walk or stand unassisted. 5: Wheelchair bound or bedridden unless aided.	☐

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and Dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A . DYSKINESIAS [exclusive of OFF-state dystonia]

4.1 TIME SPENT WITH DYSKINESIAS

SCORE

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]. Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculation).

0: Normal:	No dyskinesias.	
1: Slight:	≤ 25% of waking day.	
2: Mild:	26 - 50% of waking day.	1. Total Hours Awake: _____
3: Moderate:	51 - 75% of waking day.	2. Total Hours with Dyskinesia: _____
4: Severe:	> 75% of waking day.	3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS | **SCORE**

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

☐

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (Use this number for your calculations).

☐

0: Normal:	No OFF time.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable. (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal: No dystonia OR NO OFF TIME.

1: Slight: < 25% of time in OFF state.

2: Mild: 26-50% of time in OFF state.

3: Moderate: 51-75% of time in OFF state.

4: Severe: > 75% of time in OFF state.

☐

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100): _____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials
_____	___ ___ ___	___ ___ - ___ ___ - ___ ___ ___ ___	___ ___ ___

MDS UPDRS Score Sheet

1.A	Source of information ☐ Patient ☐ Caregiver ☐ Patient + Caregiver		3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire ☐ Patient ☐ Caregiver ☐ Patient + Caregiver		3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping–Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest	
2.12	Walking and balance			Were dyskinesias presen	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication? ☐ No ☐ Yes			Hoehn and Yahr Stage	
3b	Patient's clinical state ☐ Off ☐ On		**Part IV**		
3c	Is the patient on Levodopa? ☐ No ☐ Yes		4.1	Time spent with dyskinesias	
3.C1	If yes. minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

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APPENDIX E. COMPONENTS OF IPX203

Active ingredients: carbidopa and levodopa

Inactive ingredients: The excipients in the IPX203 investigational formulations include the following: microcrystalline cellulose, mannitol, amino methacrylate copolymer, sodium lauryl sulfate, methacrylic acid copolymer Type A, copovidone, cellulose acetate, croscarmellose sodium, talc, triethyl citrate, povidone, magnesium stearate. All these excipients are United States Pharmacopeia and National Formulary. The investigational formulations will be enclosed in hard gelatin capsules.

APPENDIX F. COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead — **Yes** ☐ **No** ☐
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

2. Non-Specific Active Suicidal Thoughts — **Yes** ☐ **No** ☐
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — **Yes** ☐ **No** ☐
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — **Yes** ☐ **No** ☐
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — **Yes** ☐ **No** ☐
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX G. KINESIA 360 SYSTEM

The Kinesia 360 system allows for continuous, passive symptom monitoring using motion sensors worn on the wrist and ankle. Data collected by the motion sensors is transformed and analyzed using validated algorithms to provide data on tremor, akinesia, dyskinesia, and mobility.

Included in the Kinesia 360 system is a smartphone configured with the Kinesia 360 application and two motion sensors. Upon waking on the scheduled days of use, subjects press the Start button within the Kinesia 360 application and put the motion sensors on the wrist and ankle of the more affected side of the body. Subjects then go about their day as they normally would. At the end of the day before going to bed, subjects remove the motion sensors and press the End button within the Kinesia 360 application. Motion sensor data is uploaded to the cloud where it is processed using validated algorithms, and a report is generated which displays symptom detection and severity details. Overnight, the motion sensors and smartphone recharge so they are ready for the next day of use.

Please see the following Quick Start Guide for instructions on set up and use of the Kinesia 360 system.

SETUP AND USE GUIDE

IPX203-B16-01

Patient Quick Start Guide

SETTING UP THE SYSTEM

Kinesia 360 Parts

Tablet

Sensor Bands

Charging Pad

AC Adapter

USB Cable

Unpack the box near a power outlet and follow Steps 1 through 4 the day before you are scheduled to use Kinesia 360.

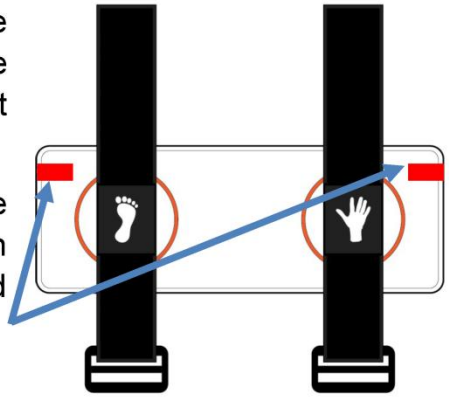
Step 1. Connecting the Charging Pad

Plug the small end of the power cable into the charging pad and plug the opposite end into a wall outlet.

Step 2. Charging the Sensors

Place the sensor bands on the charging pad in the orange circles with the hand and foot symbols facing up.

When the sensor bands are properly placed, red lights on each side of the charging pad will illuminate.



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Step 3. Connecting the Tablet to the Charging Pad

Plug the large end of the USB cable into the charging pad and plug the smaller end of the USB cable into the tablet

Charge Pad and Large USB Connector

Tablet and Small USB Connector

Step 4. Turning on the Tablet

Turn the tablet on by pressing, holding, and releasing the power button once the screen has illuminated. When plugged in, the tablet screen will display a charging message.

Charging message

Power button

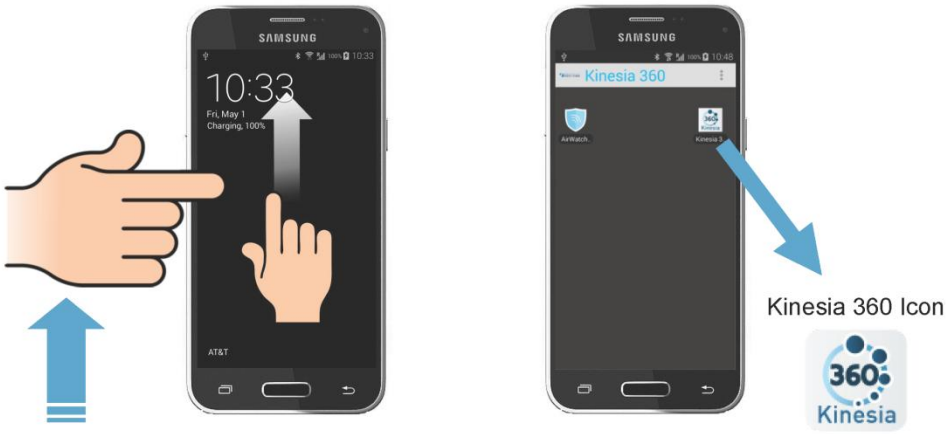
System setup is now complete. Leave everything connected for at least four hours before using the sensor bands.

OVERVIEW

The Kinesia 360 Tablet Application communicates with the sensor bands to measure your Parkinson's symptoms throughout the day.

Accessing the Kinesia 360 Application

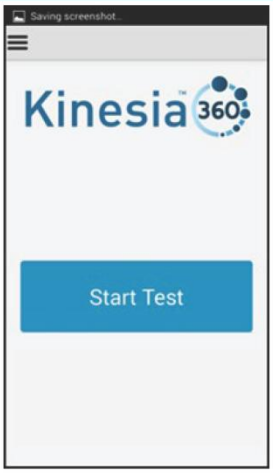
Press and release the power button to illuminate the screen. Swipe your finger from the bottom to the top of the screen to unlock the tablet. Tap the Kinesia 360 icon to open the application.



Kinesia 360 Application Home Screen

When you first open the Kinesia 360 application, you will see one option:

1. **Start Test** is pressed to start using the wrist and ankle sensor bands



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USING THE MOTION SENSORS

Starting Your Day and Putting the Sensors On

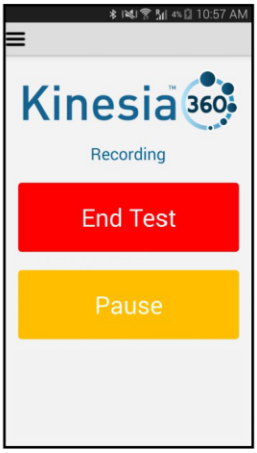
To start using the sensors, make sure the sensors are on the charging pad, tap **Start Test** then tap **Next**.

Place the sensor with the "Hand" logo on your wrist and the sensor with the "Foot" logo on your ankle. The sensors should be worn on the side of the body more affected by your Parkinson's symptoms, with the logos face down against your skin.

Once you have both sensor bands on, tap **Start** .

During the Day

If you need to remove the sensors temporarily, tap **Pause.** After putting the sensors back on, tap **Resume** to continue the test.



End of the Day

Before going to bed, plug the small USB connector into the tablet. Tap **End Test** and follow the instructions. Be sure to tap **End** once the sensor bands are on the charging pad.

Your test is now complete. You do not need to take further action. Leave the system plugged in to charge overnight.

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SCHEDULED DAYS OF USE

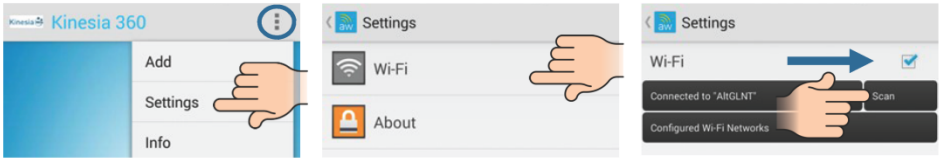
Below are the dates you are scheduled to use the Kinesia 360 system. The day before, follow the instructions on pages 2 and 3 to charge the tablet and wrist and ankle sensors. This will ensure all parts are charged and ready for the next day's use.

Date	Completed
	☐
	☐
	☐
	☐
	☐
	☐
	☐
	☐
	☐
	☐

CONNECTING TO WI-FI

If you need to connect to a Wi-Fi network:

1. Press the home button on the bottom of the phone. Then tap the menu icon ⋮ in the upper right hand corner of the phone screen.
2. Tap **Settings** then tap **Wi-Fi**.
3. Ensure that the box in the upper right hand corner is checked to turn on 'Wifi'. Tap the **Scan** button.
4. Select the network from the list and tap the password box to enter the password

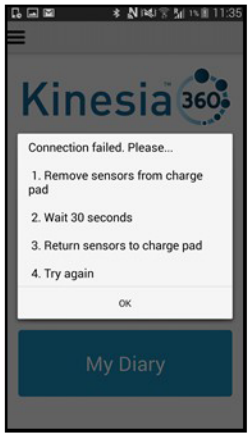


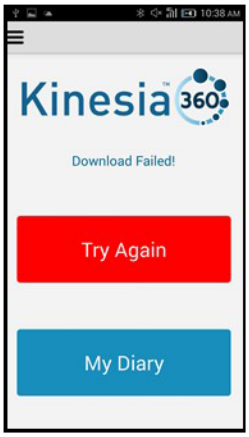
TRAINING NOTES

QUESTIONS?

The sensors are on the charge pad, but I keep getting an error when I try to start or end a test.

- Remove the sensors from the charge pad. Restart the tablet by holding the power button and selecting 'Restart'. After the tablet turns back on and the lock screen appears, place the sensors back on the charge pad and try the Start or End process again





When I put the sensors on the charge pad, I don't see the red lights.

- Make sure the power cable is securely connected to the charge pad and is not loose. Also check the connection to the wall outlet.
- Ensure the sensors are placed within the orange circles and that the "Hand" and "Foot" symbols are facing up.

The tablet will not turn on.

- Press and hold the power button. If the tablet still does not turn on, the battery may be dead. Plug in the USB cable and press the power button.

I did not mean to press that button, how do I go back?

- You can navigate backwards by pressing this button on the phone, below and to the right of the tablet screen.

For additional questions, please contact:

_____ _____

Name Phone

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APPENDIX H. PARKINSON'S DISEASE DIARY

PARKINSON'S DISEASE DIARY

NAME _____ DATE _____

Instructions: For each half-hour time period place one check mark to indicate your predominant states during most of that period.
ON = Time when medication is providing benefit with regard to mobility, slowness, and stiffness.
OFF = Time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness.
Dyskinesia = involuntary twisting, turning movements. These movements are an effect of medication and occur during ON time.
Non-troublesome dyskinesia does not interfere with function or cause meaningful discomfort. Troublesome dyskinesia interferes with function or causes meaningful discomfort.
Tremor is shaking back and forth and is not considered dyskinesia.

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00 AM					
:30					
7:00 AM					
:30					
8:00 AM					
:30					
9:00 AM					
:30					
10:00 AM					
:30					
11:00 AM					
:30					
12:00 PM					
:30					
1:00 PM					
:30					
2:00 PM					
:30					
3:00 PM					
:30					
4:00 PM					
:30					
5:00 PM					
:30					

time	asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
6:00 PM					
:30					
7:00 PM					
:30					
8:00 PM					
:30					
9:00 PM					
:30					
10:00 PM					
:30					
11:00 PM					
:30					
12:00 AM					
:30					
1:00 AM					
:30					
2:00 AM					
:30					
3:00 AM					
:30					
4:00 AM					
:30					
5:00 AM					
:30					

APPENDIX I. ASSESSMENT OF SUBJECT'S MOTOR STATE

Time (hours)	Asleep	OFF	ON without dyskinesia	ON with non-troublesome dyskinesia	ON with troublesome dyskinesia
–1 predose[a]					
–0.5 (predose)					
0 (predose)					
0.5					
1					
1.5					
2					
2.5					
3					
3.5					
4					
4.5					
5					
5.5					
6					
6.5					
7					
7.5					
8					
8.5					
9					
9.5					
10					

APPENDIX J. CLINICAL LABORATORY STUDIES

HEMATOLOGY

hemoglobin	% lymphocytes	absolute lymphocytes
hematocrit	% monocytes	absolute monocytes
red blood cell count	% basophils	absolute basophils
white blood cell count	% eosinophils	absolute eosinophils
% neutrophils	absolute neutrophils	platelet count

CHEMISTRY

sodium	calcium	indirect bilirubin
potassium	phosphorous	alkaline phosphatase
chloride	albumin	alanine aminotransferase (ALT, SGPT)
carbon dioxide	total protein	aspartate aminotransferase (AST, SGOT)
blood urea nitrogen (BUN)	uric acid	creatine phosphokinase
creatinine	total bilirubin	lactate dehydrogenase
glucose	direct bilirubin	

URINALYSIS

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

URINE DRUG TEST

amphetamines

barbiturates

cannabinoids

cocaine metabolites

opiates

phencyclidines

benzodiazepines

ALCOHOL BREATH TEST

PREGNANCY TEST
Urine pregnancy test (to be completed on site) for female subjects of childbearing potential.

APPENDIX K. BLOOD SAMPLE LABELING, PROCESSING, STORAGE AND SHIPMENT

Sample Labeling: The labels for all sample collection and storage containers will contain the subject ID (include all six digits), the subject's initials, dosing period, nominal time, collection date, study number, and sample number (sequentially per period, eg, 1-1 to 1-15 for Period 1 and 2-1 to 2-15 for Period 2).

Collection of PK Blood Samples: Blood samples for PK analysis will be collected at times as specified in the protocol. The actual time of sample collection will be recorded.

Sample Processing and Storage: One 6 mL sample of blood will be drawn at each sampling time point. Approximately 2 mL of blood will be drawn and discarded before collection of each PK sample, except for the predose PK sample. Prior to dosing, an IV catheter will be inserted into an arm vein. The catheter site will be covered with a clear sterile dressing and the catheter will be maintained until after the 10-hour PK sample has been obtained. Each PK sample will be collected into a chilled (~4°C) 6 mL K_2-EDTA vacutainer tube. The tube must be placed immediately into an ice bath or a Kryorack (or similar) that has been chilled in the freezer (~0°C) overnight and equilibrated at room temperature for 1 hour before use to prevent hemolysis due to freezing. Each Kryorack should only be used for a maximum of 6 hours. Therefore, samples from later time points must use a freshly equilibrated Kryorack.

Blood samples must be centrifuged within 30 minutes of collection for approximately 15 minutes at approximately 3400 rpm at 4°C. Immediately pipette 1.0 mL of plasma from each sample into each of 2 polypropylene tubes pretreated with sodium metabisulfite and hydrazine dihydrochloride (see below) labeled as "Aliquot A" and "Aliquot B" and vortex for approximately 20 seconds. Immediately store samples at –70°C ± 15°C until shipment.

The time between sample collection and freezer storage should not exceed 1.5 hours. The prepared plasma samples will be shipped to a bioanalytical laboratory for sample analysis.

For each 1 mL of plasma, each pretreated polypropylene tube must contain 25 µL of 20% (w/v) hydrazine dihydrochloride solution and 25 µL of 20% (w/v) sodium metabisulfite solution. The 20% (w/v) hydrazine dihydrochloride solution and the 20% (w/v) sodium metabisulfite solution should be prepared and stored separately not more than 4 days before each treatment period. The solutions should not be used after 4 days. The pretreated tubes should be prepared on the day of use or at the earliest on Day –1. If prepared on Day –1, the capped pretreated tubes should be kept in fridge (4°C) but may be kept at room temperature away from heat and tightly capped. Detailed instructions for the preparation of the two solutions and the pretreated tubes are provided in a separate document.

In cases where the plasma volume is less than 1.0 mL, use the following guide to correct the volume.

Plasma volume (mL)	20% (w/v) hydrazine dihydrochloride solution (µL)	20% (w/v) sodium metabisulfite solution (µL)
0.8	20	20
0.7	18	18
0.6	15	15
0.5	13	13
0.4	10	10

Transfer or Shipment of Samples: The sample inventory record must accompany the frozen plasma samples.

For sample transfer, the inventoried samples will be released to the custody of the bioanalytical laboratory staff for audit, inventory control, and storage. Notification of sample transfer must be communicated to the Sponsor in writing.

For shipment, the samples should be packed in ample dry ice within a container and shipped by overnight express to the bioanalytical laboratory. Notification of sample shipment should be communicated in writing to the bioanalytical laboratory and Sponsor. The samples should be tracked by clinical site staff to confirm delivery in a safe and timely manner. The second set of samples must only be shipped after the Bioanalytical laboratory has confirmed receipt of the first set.

BIOANALYTICAL LAB:

Biotrial Bioanalytical Services
3885 Blvd Industriel, Laval, Quebec, H7L 4S3 Canada
Attention: Mr. Nick Diakoumakos
Phone: 450-663-6724 Ext.: 451
nick.diakoumakos@biotrial.com

APPENDIX L. EXAMPLES OF PROTEIN CONTENT

American diet typically comprises 12% to 15% protein; a low protein diet contains 4% to 8% protein.

egg	6 grams per each
lean meat, fish, poultry	25–30 grams per 3 1/2 oz.
tofu	20 grams per cup- 8oz.
tempeh	30 grams per cup-8oz.
milk	8–9 grams per cup-8oz.
yogurt	8–10 grams per cup-8oz.
cream cheese	2 grams per oz.
cheddar/jack	7 grams per oz.
parmesan	10 grams per oz.
cottage cheese	28 grams per cup
nuts and seeds	2–3 grams per tablespoon
rice, cooked	5 grams per cup
corn meal, cooked	2 grams per cup
bulgar, cooked	8 grams per cup
oatmeal, cooked	5 grams per cup
wheat germ, toasted	8 grams per 1/4 cup
bread	2-11 grams per slice check the label

adzuki beans, cooked	17 grams per cup
kidney beans, cooked	15 grams per cup
potato, baked with skin, medium	5 grams
nutritional yeast, flakes	4 grams per heaping tablespoon.
most fruits	1 gram per fruit
vegetables	1-3 grams per 1/2 cup

Source: http://krispin.com/protein_basics.htm#sources_of_protein

Summary of Changes
Study IPX203-B16-01 Amendment 2

Protocol No.: IPX203-B16-01, Amendment 2

Protocol Title: A Randomized, Multiple Dose Study to Assess the Pharmacokinetics and Pharmacodynamics of IPX203 in Subjects with Advanced Parkinson's Disease

Date: October 5, 2016

The main purpose of issuing Amendment 2 for the IPX203-B16-01 protocol is summarized as follows:

- Wording was added to inclusion criteria #10 for clarification purposes.
- Wording was added to the IPX203 dose adjustment instructions in Section 6.4.2 for clarification and to Table 4 to accommodate subjects who may be taking levodopa doses in 25 mg units and subjects whose most frequent afternoon/evening dose of LD is 300 mg.
- Wording deleted throughout protocol regarding a 100-mg unit dose of IR LD converting to approximately an approximately 360-mg unit dose of IPX203 due to the fact that this conversion ratio applies only to the morning dose, but not to the afternoon/evening doses.
- The definition of a "bedtime dose" was changed throughout the protocol.
- Additional study design details were included in Section 6.1.
- The wording of subject withdrawal criteria # 5 in Section 7.3 was modified.
- Wording was added in Section 8.2.2 for clarification purposes.
- Three staff members were changed on the Approval Signature page, and one staff member was changed in the Study Contact Information table.
- The instructions for cutting pills were modified.
- The footnote in Appendix I was deleted.
- Minor wording changes were made in Appendix K in regards to information to be included on plasma sample labels.

The table below provides the specific changes made to the protocol in Amendment 2. Bolded text indicates new text and strikethroughs indicate deletion.

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
Signature Page	Barbara Pruitt, RN, BS Associate Director, Clinical Operations	~~Barbara Pruitt, RN, BS~~ ~~Associate Director, Clinical Operations~~ **Weiru Hong, MS** **Senior CRA, Clinical Operations**
Signature Page	Daven Mody, PharmD, MBA Director, Regulatory Affairs	~~Daven Mody, PharmD, MBA~~ ~~Director, Regulatory Affairs~~ **Itrat Harrold, PhD** **Senior Associate, Regulatory Affairs**
Signature Page	Sarita Khanna, PhD Senior Director, Biostatistics and Data Management	~~Sarita Khanna, PhD~~ ~~Senior Director, Biostatistics and Data Management~~ **Phillip Dinh, PhD** **Director, Statistics**
Study Contact Information	Sarita Khanna, PhD Senior Director, Biostatistics and Data Management (510) 240-6425 E-mail: skhanna@impaxlabs.com	~~Sarita Khanna, PhD~~ ~~Senior Director, Biostatistics and Data Management~~ ~~(510) 240-6425~~ ~~E-mail: skhanna@impaxlabs.com~~ **Phillip Dinh, PhD** **Director, Statistics** **(510) 240-6402** **E-mail: Phillip.Dinh@impaxlabs.com**

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
Synopsis, 6.1 Overall Study Design, and 6.4.2 Study Drug Regimen following First In-Clinic Dose at Visits 1 and 3	A "bedtime dose" is defined as a dose of CR CD-LD taken within 2 hours of the subject's normal nighttime sleep period.	A "bedtime dose" is defined as a dose of CR CD-LD taken within ~~2~~ **1** hour~~s~~ of the subject's normal nighttime sleep period.
Synopsis, Methodology	During the IPX203 treatment period, the initial doses of IPX203 will be based on the subject's prestudy stable LD regimen and the initial response to IPX203. A 100-mg unit dose of IR LD converts approximately to a 360-mg unit dose of IPX203. The typical dosing regimen for IPX203 will be three times a day, dosed approximately every 7 to 8 hours.	During the IPX203 treatment period, the initial doses of IPX203 will be based on the subject's prestudy stable LD regimen and the initial response to IPX203. ~~A 100-mg unit dose of IR LD converts approximately to a 360-mg unit dose of IPX203.~~ The typical dosing regimen for IPX203 will be three times a day, dosed approximately every 7 to 8 hours.
Synopsis, Diagnosis and main criteria for inclusion:	• Responsive to CD-LD therapy and currently being treated on a stable regimen with CD-LD for at least 4 weeks and: o requires 100 to 250 mg of IR CD-LD for the morning dose	• Responsive to CD-LD therapy and currently being treated on a stable regimen with CD-LD for at least 4 weeks **prior to Visit 1** and: o requires 100 to 250 mg **(in units of 50 mg)** of IR CD-LD for the morning dose

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
6.1 Overall Study Design	On Day 1 of the IR CD-LD treatment period, subjects will start with a single dose of their usual prestudy first morning IR CD-LD dose.	**Within 2 weeks following Screening, eligible subjects will complete their PD and Dosing diaries, and will wear the Kinesia 360 sensor bands on the more affected side at home immediately after waking on each of the 3 days prior to Visit 1. Subjects will be instructed to take their last dose of CD-LD no later than 10:00 PM on the evening prior to Visits 1 and 3. The first morning dose of study medication will be administered at the study site.** On Day 1 of the IR CD-LD treatment period, subjects will start with a single dose of their usual prestudy first morning IR CD-LD dose.
6.1 Overall Study Design and 6.4 Dosing and Dose Determination Criteria	A 100-mg unit dose of IR LD converts approximately to a 360-mg unit dose of IPX203.	~~A 100-mg unit dose of IR LD converts approximately to a 360-mg unit dose of IPX203~~.
6.4 Dosing and Dose Determination Criteria	IR CD-LD will be supplied as tablets containing 100 mg of LD. IR CD-LD tablets may be split in half using a pill cutter to accommodate the 150 mg and 250 mg LD doses.	IR CD-LD will be supplied as tablets containing 100 mg of LD. IR CD-LD tablets may be split ~~in half~~ using a pill cutter ~~to accommodate the 150 mg and 250 mg LD doses.~~
6.4.1 Table 3 Title	Day 1 In-clinic Dosing — IPX203-B16-01	Day 1 In-clinic Dosing — ~~IPX203-B16-01~~**First Morning Dose of Study Medication**

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
6.4.1 Day 1 In-Clinic Dosing at Visit 1 and at Visit 3	**Rescue**: Subjects who need rescue during the IR CD-LD treatment will receive a dose of IR CD-LD that corresponds to their typical pretreatment regimen based on the subject's dosing diary. For rescue during the IPX203 treatment, subject will receive a dose of IPX203 that the subject would typically have received following their morning dose (see Section 6.4.2 for details).	**Rescue**: Subjects who need rescue during the IR CD-LD treatment will receive a dose of IR CD-LD that corresponds to their typical pretreatment regimen based on the subject's dosing diary. For rescue during the IPX203 treatment, subject will receive a dose of IPX203 that ~~the subject would typically have received following their morning dose~~ **is based on Table 4 in** ~~(see~~ Section 6.4.2 ~~for details)~~.
6.4.2 Title	Study Drug Regimen following In-Clinic Dosing Visits 1 and 3	Study Drug Regimen following **First** In-Clinic **Dose at** ~~ing~~ Visits 1 and 3

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
6.4.2 Study Drug Regimen following First In-Clinic Dose at Visits 1 and 3	**IPX203 Dose Adjustment (Days 1-9):** Table 4 outlines the suggested initial conversion from a prestudy regimen of CD-LD to an IPX203 regimen. The morning dose of IPX203 will be based on the recommended dose shown in Table 3. To determine the IPX203 regimen of subsequent doses for the day, determine the most frequent prestudy LD dose in milligrams that the subject receives in the afternoon and evening and administer IPX203 according to Table 4. Dose IPX203 three times a day, approximately every 7 to 8 hours.	**IPX203 Dose Adjustment (Days 1-9):** Table 4 outlines the suggested initial conversion from a prestudy regimen of CD-LD to an IPX203 regimen. **The suggested initial dosing of IPX203 is three times a day, approximately every 7 to 8 hours.** The **recommended** morning dose of IPX203 **is** ~~will be~~ based on ~~the recommended dose shown in~~ Table 3. To determine the IPX203 regimen of subsequent doses for the day, ~~determine~~ **identify** the most frequent prestudy LD dose in milligrams that the subject receives in the afternoon and evening and administer IPX203 according to Table 4. ~~Dose IPX203 three times a day, approximately every 7 to 8 hours.~~ • **If the subject takes different prestudy LD doses with equal frequency, determine the IPX203 dose based on the highest LD dose**. • **When determining the most frequent prestudy LD dose for subsequent IPX203 doses, consider all prestudy LD doses taken from noon to bedtime. If the subject takes a bedtime CR CD-LD dose and the subject also takes a dose of IR CD-LD within one hour of the bedtime dose of CR CD-LD, then add the CR and IR LD doses together.**

<table>
<tr><th>Section</th><th>Protocol Amendment 1 – September 1, 2016</th><th>Protocol Amendment 2 – October 5, 2016</th></tr>
<tr><td>Table 4, Section 6.4.2 Study Drug Regimen following First In-Clinic Dose at Visits 1 and 3</td><td>
<table>
<tr><th>Most Frequent Afternoon and Evening LD Unit Dose (mg)</th><th>IPX203 Regimen Post Morning Dose</th></tr>
<tr><td>100</td><td>270 (270 mg × 1) mg every 7 to 8 hours</td></tr>
<tr><td>150</td><td>450 (180 mg × 1 + 270 mg × 1) mg every 7 to 8 hours</td></tr>
<tr><td>200</td><td>630 (180 mg × 2 + 270 mg x 1) mg every 7 to 8 hours</td></tr>
<tr><td>250</td><td>810 (270 mg × 3) mg every 7 to 8 hours</td></tr>
</table>
</td><td>
<table>
<tr><th>Most Frequent Afternoon and Evening LD Unit Dose (mg)</th><th>IPX203 Regimen Post Morning Dose</th></tr>
<tr><td>100 - 125</td><td>270 (270 mg × 1) mg every 7 to 8 hours</td></tr>
<tr><td>150 - 175</td><td>450 (180 mg × 1 + 270 mg × 1) mg every 7 to 8 hours</td></tr>
<tr><td>200 - 225</td><td>540 (270 mg × 2) mg every 7 to 8 hours</td></tr>
<tr><td>250- 275</td><td>720 (270 mg × 2 + 180 mg × 1) mg every 7 to 8 hours</td></tr>
<tr><td>300</td><td>810 (270 mg × 3) mg every 7 to 8 hours</td></tr>
</table>
Note: a 100-mg unit dose of IR LD converts approximately to a 270-mg unit dose of IPX203.
</td></tr>
<tr><td>Section 6.4.2, Column Headers for Example Table</td><td>
<table>
<tr><th>Prestudy LD Morning IR Dose (mg)</th><th>Most Frequent IR LD Dose (mg) Afternoon and Evening</th></tr>
</table>
</td><td>
<table>
<tr><th>Pre-study IR LD Morning <s>IR</s> Dose (mg)</th><th>Most Frequent Pre-study <s>IR</s> LD Dose (mg) Afternoon and Evening</th></tr>
</table>
</td></tr>
<tr><td>7.1 Subject Inclusion Criteria</td><td>10. Responsive to CD-LD therapy and currently being treated on a stable regimen with CD-LD for at least 4 weeks and:
a. requires 100 to 250 mg of IR CD-LD for the morning dose…</td><td>10. Responsive to CD-LD therapy and currently being treated on a stable regimen with CD-LD for at least 4 weeks prior to Visit 1 and:
a. requires 100 to 250 mg (in units of 50 mg) of IR CD-LD for the morning dose…</td></tr>
</table>

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
7.3 Subject Withdrawal Criteria	5. Protocol violation	5. Protocol ~~violation~~**deviation**
8. Study Procedures footnote b	b Record vital signs (blood pressure, heart rate, temperature, 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. During Visits 1 and 3, vital signs are recorded at predose, 2, 4, and 8 hours postdose. During Visits 2 and 4, vital signs are recorded at predose, 2, 4, and 10 hours postdose.	b Record vital signs (blood pressure, heart rate, ~~temperature,~~ 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. During Visits 1 and 3, vital signs are recorded at predose, 2, 4, and 8 hours postdose. During Visits 2 and 4, vital signs are recorded at predose, 2, 4, and 10 hours postdose.
8.2.2 Prior to Visits 1 and 3	• Bring the 3-day PD Diary, the 3-day Dosing diary and the Kinesia 360 system with them to the clinic.	• Bring the 3-day PD Diary, the 3-day Dosing diary**,** and the Kinesia 360 system with them to the clinic **(Visit 1 only)**.
10.4 Study Drug Administration	IR CD-LD tablets may be split in half using a pill cutter to accommodate the 150 mg and 250 mg LD doses, as appropriate.	IR CD-LD tablets may be split ~~in half~~ using a pill cutter ~~to accommodate the 150 mg and 250 mg LD doses, as appropriate.~~

Section	Protocol Amendment 1 – September 1, 2016	Protocol Amendment 2 – October 5, 2016
Appendix I, Assessment of Subject's Motor State, footnote	[a] Confirm that subject is in the "off" state before starting -1 hour predose assessment	[a] ~~Confirm that subject is in the "off" state before starting -1 hour predose assessment~~
Appendix K Blood Sample Labeling, Processing, Storage and Shipment	Sample Labeling: The labels for all sample collection and storage containers will contain the subject ID, the subject's initials, dosing period, collection date and actual time, study number, and sample number (sequentially per period, eg, 1-1 to 1-15 for Period 1 and 2-1 to 2-15 for Period 2).	Sample Labeling: The labels for all sample collection and storage containers will contain the subject ID **(include all six digits)**, the subject's initials, dosing period, **nominal time,** collection date ~~and actual time~~, study number, and sample number (sequentially per period, eg, 1-1 to 1-15 for Period 1 and 2-1 to 2-15 for Period 2).