Title: Open Label Extension (OLE) Study of the Safety and Clinical Utility of IPX203 in PD Patients with Motor Fluctuations

Date: November 26, 2018

NCT03877510

IPX203 (CARBIDOPA-LEVODOPA) EXTENDED-RELEASE CAPSULES

IPX203-B16-03

AN OPEN-LABEL EXTENSION STUDY OF THE SAFETY AND CLINICAL UTILITY OF IPX203 IN PARKINSON'S DISEASE PATIENTS WITH MOTOR FLUCTUATIONS

SPONSOR

Impax Laboratories, LLC

400 Crossing Boulevard, Third Floor

Bridgewater, NJ 08807-2863

Original Protocol, 25 April 2018

Amendment 1, 22 June 2018

Amendment 2, 26 November 2018

SIGNATURE PAGE

Reviewed and approved by:

[redacted]

28 NOV 2018
Date

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28 Nov 18
Date

INVESTIGATOR'S AGREEMENT

Protocol No.: IPX203-B16-03

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

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.

Role	Name and Contact Information
Sponsor	Impax Laboratories, LLC 400 Crossing Boulevard, Third Floor Bridgewater, NJ 08807-2863 (732) 595-4600
[redacted]	
Serious Adverse Event Reporting	FAX: (866) 954-2057

1. SYNOPSIS

Name of Sponsor/Company: Impax Laboratories, LLC (Impax)
Name of Investigational Product: IPX203 (carbidopa-levodopa) Extended-Release Capsules
Name of Active Ingredients: carbidopa (CD), levodopa (LD)
Protocol Title: An Open-Label Extension Study of the Safety and Clinical Utility of IPX203 in Parkinson's Disease Patients with Motor Fluctuations
Protocol No.: IPX203-B16-03
Study center(s): Multicenter
Phase of Development: Phase 3
Objectives: To evaluate the long-term safety and clinical utility of IPX203 in the treatment of subjects with advanced Parkinson's disease (PD) who have motor fluctuations.
Methodology: This is a 9-month, multicenter open-label safety extension study. Subjects who have successfully completed Study IPX203-B16-02 (A Randomized Controlled Study to Compare the Safety and Efficacy of IPX203 with Immediate-Release Carbidopa-Levodopa in Parkinson's Disease Patients with Motor Fluctuations) may have the opportunity to enroll in this open-label study. This study will consist of a baseline visit (Visit 1) followed by 3 visits (Visits 2 to 4) spaced at approximately 3-month intervals. For subjects who successfully complete Study IPX203-B16-02, the baseline visit (Visit 1) of this study will occur coincident with the End of Study (EOS) Visit 7 of the preceding study. After providing written informed consent (and signing Health Insurance Portability and Accountability Act [HIPAA] authorization for subjects at United States [US] sites only), confirmation of eligibility and baseline procedures will be performed. Subjects will be initially started on the final IPX203 dosing regimen that was determined during the IPX203 dose conversion period of Study IPX203-B16-02. Investigators are permitted to adjust the dosing regimen of IPX203 during this study to achieve the optimal balance of efficacy and safety and any changes will be recorded. Subjects may continue to take their non-LD-containing PD concomitant medications (including dopamine agonists, amantadine, and selective monoamine oxidase-B (MAO-B) inhibitors [safinamide, rasagiline and selegiline]) during the study. Changes in doses or in dosing regimens of all non-CD-LD PD medications and/or the addition of new non-CD-LD PD medications will be captured. Supplemental CD and benserazide, apomorphine, and the addition of catechol-O-methyltransferase (COMT) inhibitors (eg, entacapone, opicapone, and tolcapone) can be initiated during this study. Adverse events (AEs), supine and standing orthostatic vital signs, and concomitant medications will be evaluated throughout the course of the study. Electrocardiograms (ECGs), clinical laboratory tests, physical examinations, and the Columbia-Suicide Severity Rating Scale (C-SSRS) will also be performed. The following clinical utility measures will be assessed: Patient Global Impression of Severity (PGI-S), Clinician Global Impression of Severity (CGI-S), Treatment Satisfaction Assessment (TSA), Parkinson's Disease Sleep Scale-

2 (PDSS-2), the 39-item Parkinson's Disease Questionnaire (PDQ-39), Parkinson Anxiety Scale (PAS), Non-Motor Symptom assessment scale (NMSS) for Parkinson's disease, Gastroparesis Cardinal Symptom Index (GCSI), The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I to IV, 12-Item Zarit Burden Interview (ZBI-12), and Early Morning Symptoms Questionnaire (EMSQ). Visit 4 is the end of study visit (EOS).

Number of subjects (planned): Subjects who successfully complete IPX203-B16-02 will be eligible to enroll in this open-label extension (OLE) study; it is estimated that approximately 300 subjects will enroll.

Diagnosis and main criteria for inclusion:

Inclusion Criteria

- Successfully completed Study IPX203-B16-02.
- Able to provide written informed consent prior to the conduct of any study-specific procedures.
- Female subjects of childbearing potential must have a negative urine pregnancy test at the baseline visit (Visit 1).
- Agrees to use a medically acceptable method of contraception throughout the study and for 6 weeks after completing the study.

Exclusion Criteria

- Intends to use any doses of Rytary® or Duopa™ during this study.
- Plans to use an investigational treatment other than IPX203 during the course of this study.
- Neurosurgical ablation treatment for PD is planned or anticipated during the study period. Implantation of a deep brain stimulator (DBS) for the treatment of PD is permitted during this study.
- Subjects who, in the opinion of the clinical investigator, should not participate in the study.

Investigational product, dosage and mode of administration: IPX203 (carbidopa-levodopa) Extended-Release capsules for oral administration, provided in 4 dose strengths:

- IPX203 35-140 mg CD-LD capsule
- IPX203 52.5-210 mg CD-LD capsule
- IPX203 70-280 mg CD-LD capsule
- IPX203 87.5-350 mg CD-LD capsule

Reference therapy, dosage and mode of administration: None

Duration of treatment: Nine (9) months of open-label therapy with IPX203.

Criteria for evaluation:

- **Safety:** AEs, supine and standing orthostatic vital signs, and concomitant medications evaluated throughout the course of the study. ECGs, clinical laboratory tests, physical

examinations, and the C-SSRS will also be performed. • **Clinical Utility Measures:** PGI-S, CGI-S, TSA, PDSS-2, PDQ-39, PAS, NMSS, GCSI, MDS-UPDRS Part I to IV, ZBI-12, and EMSQ will be assessed at every visit.
Statistical methods: For MDS-UPDRS, the total score (Parts I+II+III+IV), each of its components (Parts I through IV), and Parts II + Part III will be summarized across each of the time points in the trial (Baseline/Visit 1, Month 3, Month 6, and Month 9) to allow for assessment of the sustainability of the clinical effect of IPX203 over the 9-month study duration. Similarly, the PGI-S, CGI-S, TSA, PDSS-2, PDQ-39, PAS, NMSS, GCSI, ZBI-12, and EMSQ will be summarized over time. The safety analysis will include all subjects who received at least one dose of study medication. The incidence of treatment-emergent AEs and serious adverse events (SAEs) will be summarized. Additionally, laboratory test data, physical examinations, vital signs, ECGs, and C-SSRS will be summarized across each time point in the trial.

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

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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
CD	carbidopa
CGI-S	Clinical Global Impression of Severity
CR	controlled release
CRF	case report form
COMT	catechol-O-methyltransferase
C-SSRS	Columbia-Suicide Severity Rating Scale
DBS	deep brain stimulator or deep brain stimulation
ECG	electrocardiogram
EMSQ	Early Morning Symptoms Questionnaire
EOS	end of study
ER	extended release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSI	Gastroparesis Cardinal Symptom Index
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
IWRS	interactive web response system
LD	levodopa
MAO	monoamine oxidase inhibitors
MAO-A	MAO type A inhibitors
MAO-B	MAO type B inhibitors
MDS-UPDRS	Movement Disorders Society version of the Unified Parkinson's Disease Rating Scale
M-EDL	Motor Aspects of Experiences of Daily Living
m-MIDI	Modified-Minnesota Impulsive Disorders Interview
nM-EDL	Non-Motor Aspects of Experiences of Daily Living
NMSS	Non-Motor Symptom assessment scale for PD
OLE	open-label extension
PAS	Parkinson Anxiety Scale
PD	Parkinson's disease
PDQ-39	39-item Parkinson's Disease Questionnaire
PDSS-2	Parkinson's Disease Sleep Scale-2
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic (adjective) pharmacokinetics (singular noun)
PI	principal investigator
SAE	serious adverse event
TSA	Treatment Satisfaction Assessment
US	United States
ZBI-12	12-Item Zarit Burden Interview

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).

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 and the drug effects 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 et al 1989, Engber et al 1989, Blanchet et al 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 et al 1988, Stocchi et al 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 et al 2001, Nyholm et al 2005, Stocchi et al 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, LLC (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 7 to 8 hours, based on the plasma LD concentration time profile observed in subjects with advanced PD (Study IPX203-B14-02 and IPX203-B16-01).

Study IPX203-B14-02 characterized the PK and pharmacodynamics of IPX203 following a single dose in subjects with advanced PD versus immediate-release (IR) CD-LD and Rytary®. Twenty-six (26) subjects were randomized with 25 subjects completing all 3 treatments. One subject discontinued study early due to subject withdrawal. Administration of IPX203 yielded an initial increase in LD plasma concentrations that was similar to both IR CD-LD and Rytary but maintained LD concentrations longer. IPX203 provided a longer pharmacodynamic duration of effect compared with IR CD-LD and Rytary, including "Off" time and "Good on" time based on the Assessment of Subject's Motor State and on several of the MDS-UPDRS Part III improvement thresholds. Of the 26 subjects who received at least one of the 3 treatments, 9 subjects (34.6%) reported at least one treatment-emergent adverse event (AE). None of these subjects reported a SAE nor did any subjects prematurely discontinue the study because of an AE. Adverse events were reported by more subjects during IR CD-LD (28.0%) and IPX203 (19.2%) than during Rytary (8.0%) treatment. None of the reported AEs were classified as severe. Adverse events reported by 2 or more subjects included dizziness (3 subjects), nausea (2 subjects), and hypertension (2 subjects). The numbers of subjects reporting these AEs during any single treatment period were small (0 to 2 subjects). Two subjects reported dizziness during IR CD-LD treatment and one subject each during IPX203 and Rytary treatments. Hypertension was reported by a total of 2 subjects, both reporting this AE during IPX203 and IR CD-LD treatments and 1 subject during Rytary treatment. Two subjects reported nausea only during the IR CD-LD treatment period. Of the 9 subjects reporting AEs, 6 (23.1%) subjects reported AEs that were assessed as related to treatment, including all of the reports of dizziness, nausea, and dyskinesia (1 subject). Most subjects reported AEs that were assessed as mild in severity, but during treatment with IPX203, 2 subjects (7.7%) reported moderate AEs (dyskinesia and hypertension), during IR CD-LD treatment 1 subject (4.0%) reported atrial flutter of moderate severity, and during Rytary treatment, 1 subject (4.0%) reported dyskinesia of moderate severity.

The pharmacokinetics and pharmacodynamics of IPX203 were studied in a randomized, open-label, rater-blinded, multicenter, 2-treatment, 2-period, multiple-dose crossover study (IPX203-B16-01). Twenty-eight (N=28) advanced PD subjects were randomized to 1 of 2 dosing sequences, with each treatment period lasting 15 days and separated by a 1-week wash-out period where subjects return to their usual stable pre-study CD-LD regimen. The objectives of this study are to compare the PK, pharmacodynamics, efficacy, and safety of IPX203 with IR CD-LD after single and multiple dosing. Subjects were permitted to take allowed non-CD-LD-based PD medications throughout the study if dosing regimens had been stable for at least 4 weeks. Subjects were instructed to take their last dose of CD-LD no later than 10:00 PM on the evening prior to Day 1 of each treatment period and to withhold dosing for at least 5 hours before arriving at the site on Day 15 of each treatment period. On Day 1 of the IR CD-LD treatment period, subjects were started with a single dose of their usual prestudy first morning IR CD-LD dose. On Day 1 of the IPX203 treatment period, subjects were started with a single dose of IPX203 based on their usual prestudy first morning IR CD-LD dose using a LD conversion of 100 mg IR LD to 360 mg of IPX203 LD. During the IR CD-LD treatment period, the initial dosing regimen of IR CD-LD was the same as the subject's stable prestudy regimen. During the IPX203 treatment period, the IPX203 regimen for subsequent doses for the day was determined by identifying the most frequent prestudy IR LD dose in milligrams that the subject

received in the afternoon and evening and administering IPX203 using a LD conversion of 100 mg IR LD to 270 mg of IPX203 LD. The protocol recommended that IPX203 be dosed approximately every 7 to 8 hours. During Days 1 through 9 of both treatment periods, investigators had the opportunity to adjust each subject's study medication regimen if necessary to optimize efficacy and safety. Pharmacokinetics and pharmacodynamics (MDS-UPDRS Part III and Assessments of Subject's Motor State) were periodically evaluated on Day 1 and Day 15 of each treatment period by qualified clinical staff who were blinded to dosing.

Data from this multiple-dose study confirmed the PK and pharmacodynamic results observed in the single dose study with IPX203:

- PK data from 27 subjects indicates IPX203 shows a rapid increase in LD concentrations followed by extended-release characteristics. Following IPX203; initial increases in LD concentrations were comparable to that from IR CD-LD. Bioavailability of LD following IPX203 was ~89% relative to IR CD-LD. LD plasma concentrations were sustained longer after IPX203 treatment than after IR CD-LD and support dosing every 8 hours. No accumulation of LD was evident at steady-state following IPX203 or IR CD-LD. Plasma LD concentrations following IPX203 were characterized by lower peak-to-trough fluctuation. No time-variant or time-dependent changes were noted in PK of CD or LD following IPX203.
- IPX203 demonstrated an onset of effect that was comparable to IR CD-LD in MDS-UPDRS Part III scores. IPX203 prolonged the duration over which MDS-UPDRS Part III scores were improved by prespecified threshold changes from baseline (≥4, ≥7, and ≥13 units).
- IPX203 provides a significant decrease in "Off" time and a significant increase in "Good on" time compared to IR CD-LD treatment on Day 1 and Day 15 when assessed by the Investigator's Assessment of Subject's Motor State. Subjects treated with IPX203 did not experience a significant increase in "On" time with troublesome dyskinesia compared to IR CD-LD.
- Subjects achieved significant improvements in "Off" time, "Good on" time, and frequency of motor state fluctuations based on the 3-day PD Diaries.
- Twenty-eight subjects were enrolled in the multiple-dose study and 27 subjects completed both treatments. Safety results were as follows:
  - One subject discontinued during the IPX203 treatment period due to an AE (orthostatic hypertension) that was considered possibly related to treatment.
  - A total of 39.3% (11/28) of treated subjects reported at least one treatment emergent AE, including 35.7% (10/28) during IPX203 treatment and 7.4% (2/27) during IR CD-LD treatment. Eight subjects reported AEs that were related to treatment (8 subjects during IPX203 treatment and 1 during IR CD-LD treatment).
  - Two subjects experienced serious adverse events (SAEs). One subject reported increased hypertension of mild severity during IPX203 treatment that was considered unrelated to treatment and resolved. A second subject reported

moderate to severe dehydration, diarrhea, and atrial fibrillation during the washout period that were considered unrelated to treatment and resolved.

- AEs reported in 2 or more subjects included nausea (2), dizziness (2), and dyskinesia (5), all of mild or moderate severity, and all during the IPX203 treatment.

Study IPX203-B16-02 is a randomized, double-blind, double-dummy, active-control, parallel-group, multicenter study designed to compare the efficacy, safety and tolerability of IPX203 with IR CD-LD in CD-LD-experienced subjects with advanced PD and motor fluctuations following 13 weeks of therapy.

Subjects who successfully complete Study IPX203-B16-02 may have the opportunity to enroll in this 9-month, open-label safety extension study.

5. TRIAL OBJECTIVES

The objective of this study is to evaluate the long-term safety and clinical utility of IPX203 in subjects with advanced Parkinson's disease (PD) who have motor fluctuations.

6. INVESTIGATIONAL PLAN

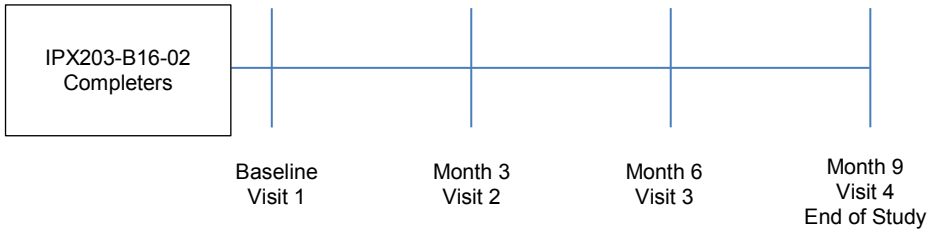
6.1. Overall Study Design

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

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

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

Figure 1: IPX203-B16-03 Study Flow Chart



6.2. Number of Subjects

Subjects who successfully complete IPX203-B16-02 are eligible to enroll in this open-label extension (OLE) study; it is estimated that approximately 300 subjects will enroll.

6.3. Treatment Assignment

All subjects will receive IPX203.

6.4. Dosing and Dose Determination Criteria

Subjects will start on the IPX203 dosing regimen that was determined at the end of the IPX203 dose conversion period of Study IPX203-B16-02 (Visit 4 of Study IPX203-B16-02).

6.5. Dose Adjustment Criteria

Investigators are permitted to adjust the dosing regimen of IPX203 during the study to achieve the optimal balance of efficacy and safety; all dosing changes will be recorded.

Recommendations for dosing IPX203 are provided in Appendix A.

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

Subjects must meet all of the following inclusion criteria to qualify for enrollment. Subjects who have any of the following exclusion criteria will not be enrolled in the study.

7.1. Subject Inclusion Criteria

1. Successfully completed Study IPX203-B16-02.
2. Able to provide written informed consent prior to the conduct of any study-specific procedures.
3. Female subjects of childbearing potential must have a negative urine pregnancy test at the baseline visit (Visit 1).
4. 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).

7.2. Subject Exclusion Criteria

1. Intends to use any doses of Rytary or Duopa™ during this study.
2. Plans to use an investigational treatment other than IPX203 during the course of this study.
3. Neurosurgical ablation treatment for PD is planned or anticipated during the study period. Implantation of a deep brain stimulator (DBS) for the treatment of PD is permitted during this study.
4. Subjects who, in the opinion of the clinical investigator, should not participate in the study.

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
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. The reason or reasons for discontinuation will be specified and documented.

8. STUDY PROCEDURES

The procedures to be performed at each study visit are summarized in Table 2.

Table 2: Events Schedule for Study IPX203-B16-03

	Visit 1 Baseline	9 Months of IPX203 Therapy					
		Study Drug Resupply Months 1-2	Visit 2	Study Drug Resupply Months 4-5	Visit 3	Study Drug Resupply Months 7-8	Visit 4/ Early Termination
Study Month	**0**		**3**		**6**		**9**
ICF and HIPAA Authorization	X						
Check Inclusion/Exclusion Criteria	X						
Update Medical History	X						
Physical Examination	X						X
Vital Signs	X		X		X		X
Weight	X		X		X		X
C-SSRS	X		X		X		X
Clinical Laboratory Tests	X		X		X		X
Urine Pregnancy Test	X						
ECG	X		X		X		X
MDS-UPDRS Parts I-IV	X		X		X		X
PGI-S	X		X		X		X
CGI-S	X		X		X		X
PDQ-39	X		X		X		X
GCSI	X						X
NMSS	X		X		X		X
PDSS-2	X		X		X		X
PAS	X		X		X		X
TSA			X		X		X

	Visit 1 Baseline	9 Months of IPX203 Therapy					
		Study Drug Resupply Months 1-2	Visit 2	Study Drug Resupply Months 4-5	Visit 3	Study Drug Resupply Months 7-8	Visit 4/ Early Termination
Study Month	**0**		**3**		**6**		**9**
ZBI-12	X		X		X		X
EMSQ	X		X		X		X
Contact phone calls			X		X		X
Contact IWRS to dispense study medication	X	X	X	X	X	X	
Collect empty medication bottles and any unused study drug/Perform study drug accountability		X	X	X	X	X	X
Adverse Events	X		X		X		X
Concomitant Medications	X		X		X		X

[a] Visit 1 is expected to occur on the same day as the End-of-Study Visit (Visit 7) of Study IPX203-B16-02 but not later than 1 week. After the subject provides consent for this study, carry over and record information from procedures at the End-of-Study Visit of IPX203-B16-02 as the Baseline data for this study.
[b] Subjects enrolled at sites in the United States (US) must sign HIPAA authorization prior to the conduct of any study-specific procedures.
[c] Record vital signs (blood pressure, heart rate, respiratory rate, and temperature [Visit 1 and Study Exit only]) after subject has been resting supine for at least 5 minutes, then record orthostatic blood pressure and heart rate after subject has been standing for approximately 2 minutes.
[d] See Appendix B.
[e] See Appendix C.
[f] This test will be performed at Visit 1 of this study.
[g] See Appendix D.
[h] See Appendix E.
[i] See Appendix F.
[j] See Appendix G.
[k] See Appendix H.
[l] See Appendix I.
[m] See Appendix J.
[n] See Appendix K.
[o] See Appendix L.
[p] See Appendix M.
[q] See Appendix N.

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

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

8.1. Visit 1 (Baseline)

Visit 1 is expected to occur on the same day as the End-of-Study Visit (Visit 7) of Study IPX203-B16-02. After the subject provides consent for this study, carry over and record information from procedures at the End-of-Study Visit of IPX203-B16-02 as the baseline data for this study.

After the subject has signed the informed consent (and HIPAA authorization for subjects at US sites), complete the following procedures and assessments:

- Review and record study entry criteria (Section 7).
- Update the subject's medical history.
- Perform urine pregnancy test for females of childbearing potential.
- Complete the 12-Item Zarit Burden Interview (ZBI-12) (Appendix M).
- Administer the Early Morning Symptoms Questionnaire (EMSQ) (Appendix N).
- Contact the interactive web response system (IWRS) to dispense study drug.
- Instruct the subject on dosing.
- After Visit 1, contact subjects weekly for the first month and then approximately monthly thereafter to discuss the subject's dosing regimen. Record the subject's current IPX203 dose regimen.
- Instruct subjects to call the study site before making any changes to their IPX203 dosing regimen.
- Subjects may return for study drug resupply approximately every 1 to 2 months as needed.

8.2. Visit 2 (Month 3)

8.2.1. Prior to Visit 2

Call the subjects prior to Visit 2 and remind them to bring any unused study medication and empty medication bottles to Visit 2.

8.2.2. At Visit 2

- Collect unused study drug and empty bottles.
- Review study drug accountability.
- Update IPX203 regimen (dose, frequency, number of capsules) and concomitant medications.
- 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 AEs.

- Weigh the subject.
- Perform a 12-lead ECG.
- Administer C-SSRS (Appendix B)
- Collect blood and urine samples for clinical laboratory studies (Appendix C).
- Administer MDS-UPDRS Parts I through IV (Appendix D).
- Determine PGI-S and CGI-S scores (Appendix E and Appendix F, respectively).
- Complete PDQ-39 (Appendix G).
- Perform NMSS (Appendix I).
- Complete the PDSS-2 (Appendix J).
- Complete PAS (Appendix K).
- Complete TSA (Appendix L).
- Complete the ZBI-12 (Appendix M).
- Administer the EMSQ (Appendix N).
- Contact IWRS and enter study drug dispensing information.
- Dispense study drug and provide dosing instructions.
- Subjects may return for study drug resupply approximately every 1 to 2 months as needed.
- Instruct subjects to call the study site before making any changes to their IPX203 dosing regimen.
- Call subjects approximately monthly to discuss IPX203 dosing. Record the subject's current IPX203 dose regimen.

8.3. Visit 3 (Month 6)

8.3.1. Prior to Visit 3

Call the subjects prior to Visit 3 and remind them to bring any unused study medication and empty medication bottles to Visit 3.

8.3.2. At Visit 3

- Collect unused study drug and empty bottles.
- Review study drug accountability.
- Update IPX203 regimen (dose, frequency, number of capsules) and other concomitant medications.

- 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 AEs.
- Weigh the subject.
- Perform a 12-lead ECG.
- Administer C-SSRS (Appendix B).
- Collect blood and urine samples for clinical laboratory studies (Appendix C).
- Administer MDS-UPDRS Parts I through IV (Appendix D).
- Determine PGI-S and CGI-S scores (Appendix E and Appendix F, respectively)
- Complete PDQ-39 (Appendix G).
- Perform NMSS (Appendix I).
- Complete the PDSS-2 (Appendix J).
- Complete PAS (Appendix K).
- Complete TSA (Appendix L).
- Complete the ZBI-12 (Appendix M).
- Administer the EMSQ (Appendix N).
- Contact IWRS and enter study drug dispensing information.
- Dispense study drug and provide dosing instructions.
- Subjects may return for study drug resupply approximately every 1 to 2 months as needed.
- Instruct subjects to call the study site before making any changes to their IPX203 dosing regimen.
- Call subjects approximately monthly to discuss IPX203 dosing. Record the subject's current IPX203 dose regimen.

8.4. Visit 4 – Study Completion (Month 9) or Early Discontinuation

8.4.1. Prior to Visit 4

Call the subjects prior to Visit 4 and remind them to bring any unused study medication and empty medication bottles to the visit.

8.4.2. At Visit 4

- Collect unused study drug and empty bottles.
- Review study drug accountability.

- Update IPX203 regimen (dose, frequency, number of capsules) and other concomitant medications.
- 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 AEs.
- Weigh the subject.
- Perform physical exam including weight.
- Perform a 12-lead ECG.
- Administer C-SSRS (Appendix B).
- Collect blood and urine samples for clinical laboratory studies (Appendix C).
- Administer MDS-UPDRS Parts I through IV (Appendix D).
- Determine PGI-S and CGI-S scores (Appendix E and Appendix F, respectively).
- Complete PDQ-39 (Appendix G).
- Complete GCSI (Appendix H).
- Perform NMSS (Appendix I).
- Complete the PDSS-2 (Appendix J).
- Complete PAS (Appendix K).
- Complete the TSA (Appendix L).
- Complete the ZBI-12 (Appendix M).
- Administer the EMSQ (Appendix N).
- Contact IWRS to report subject disposition.

8.5. Early Termination

Subjects who withdraw early should complete Study Exit procedures described in Section 8.4.

8.6. Blood Volume

Safety blood draws: Approximately 20 mL of blood will be drawn at each study visit for a combined total of 80 mL.

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 four strengths, containing 35-140 mg, 52.5-210 mg, 70-280 mg, and 87.5-350 mg of CD-LD, for oral administration.

Table 3: Study Drugs for Study IPX203-B16-03

Investigational Product	Dosage Form and Strength (mg CD-LD)	Manufacturer
IPX203 (carbidopa-levodopa) Extended-Release Capsules	35-140 mg capsule 52.5-210 mg capsule 70-280 mg capsule 87.5-350 mg capsule	Impax Laboratories, LLC

9.2. Concomitant Medications

9.2.1. Permitted PD Medications and Surgical Treatments

Concomitant therapy with amantadine, selective monoamine oxidase (MAO) type B inhibitors (eg, safinamide, selegiline, rasagiline), anticholinergic PD medications (eg, benztropine, trihexyphenidyl), hypnotics (including low doses of quetiapine ≤ 25 mg per day), dopamine agonists, including apomorphine, supplemental CD, and COMT inhibitors are allowed provided the doses and regimens (and any adjustments) are recorded on the concomitant medication form. Implantation of a deep brain stimulator (DBS) for the treatment of PD is permitted during this study provided the stimulation settings are recorded.

Although apomorphine, supplemental CD, COMT inhibitors, and DBS were not permitted in Study IPX203-B16-02, these treatments may be initiated during the current study.

All concomitant medications taken during this study will be recorded.

9.2.2. Prohibited PD Medications and Surgical Treatments

Prohibited treatments during the study include the following:

- Any doses of Rytary and Duopa during this study.
- Nonselective MAO inhibitors or selective MAO type A inhibitors (MAO-A).
- Neurosurgical ablation treatment procedures for PD.
- Investigational agents other than IPX203.
- Dopamine antagonists with the exception of low doses (≤ 25 mg) of quetiapine for sleep.

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

9.3. Treatment Compliance

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

9.4. Randomization and Blinding

This is a nonrandomized open-label study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The study drug is IPX203 (carbidopa-levodopa) Extended-Release capsules for oral administration, provided in 4 dose strengths:

- IPX203 35-140 mg CD-LD capsule
- IPX203 52.5-210 mg CD-LD capsule
- IPX203 70-280 mg CD-LD capsule
- IPX203 87.5-350 mg CD-LD capsule.

IPX203 will be supplied 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:

- Name, address, and phone number of the Sponsor.
- Pharmaceutical dosage form/route of administration, quantity of dosage units, the name/identifier, and strength/potency.
- Batch and/or code number to identify the contents and packaging operation.
- Trial reference code (protocol number).
- Trial subject identification number and where relevant, the visit number.
- Name of Investigator.
- Directions for use: Take capsule(s) orally with water as directed.
- For clinical trial use only.
- Storage information: Store at room temperature between 15-30°C (59-86°F).
- Protect from light and moisture.
- Period of use (use-by date, expiry date or retest date as applicable), in month/year format and in a manner that avoids any ambiguity.
- Keep out of reach of children.
- Caution statement: Caution: New Drug—Limited by Federal (or United States) law to investigational use.

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 below 15°C (59°F) or 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 should not be crushed or chewed.

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

To allow for assessment of the sustainability of the clinical effect of IPX203 over the 9-month study duration, the following clinical utility measures will be assessed at every visit: PGI-S, CGI-S, TSA, PDSS-2, PDQ-39, PAS, NMSS, MDS-UPDRS Parts I to IV, ZBI-12 and EMSQ.

11.1. Patient and Investigator Global Assessments

- Patient Global Impression of Severity (PGI-S) (Appendix E): The subject will determine the severity of the disease on a 7-point scale ranging from "Normal, not at all ill" (1) to "Extremely severely ill" (7) at the time of the assessment.
- Clinical Global Impression of Severity (CGI-S) (Appendix F): The clinician will determine the severity of the disease on a 7-point scale ranging from "Normal, not at all ill" (1) to "Among the most extremely ill of subjects" (7) at the time of the assessment.

11.2. Treatment Satisfaction Assessment (TSA)

The TSA is a single-question, self-reported questionnaire (Appendix L). The subject will determine his/her treatment satisfaction using a 7-point scale ranging from "Very much dissatisfied" (1) to "Very much satisfied" (7) at the time of the assessment.

11.3. Parkinson's Disease Sleep Scale-2 (PDSS-2)

The PDSS-2 is 15-item self-reported questionnaire (Appendix J). Three domains are defined: disturbed sleep (Questions 1-3, 8, 14), motor symptoms at night (Questions 4-6, 12, 13), PD symptoms at night (Questions 7, 9-11, 15).

11.4. Parkinson's Disease Questionnaire-39 (PDQ-39)

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

11.5. Parkinson Anxiety Scale (PAS)

The PAS is a 12-item subject- or observer-rated questionnaire with 3 domains: persistent anxiety (Questions A.1-A.5), episodic anxiety (Questions B.1-B.4) and avoidance anxiety (Questions C.1-C.3) (Appendix K).

11.6. Non-Motor Symptom Assessment Scale for Parkinson's Disease (NMSS)

The NMSS is a 30-item, investigator-rated questionnaire (Appendix I). The NMSS contains 9 domains: cardiovascular (Questions 1, 2), sleep/fatigue (Questions 3-6), mood/cognition

(Questions 7-12), perceptual problems (Questions 13-15), attention/memory (Questions 16-18), gastrointestinal (Questions 19-21), urinary (Questions 22-24), sexual function (Questions 25, 26), and miscellaneous (Questions 27-30).

11.7. Movement Disorders Society Version of Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS has 4 parts (Appendix D):

- Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL) has 2 components. Component IA contains a number of behaviors assessed by the investigator with all pertinent information from the subjects and caregivers. Component IB is completed by the subject with or without help from the caregiver but independent of the investigator. These sections can be reviewed by the rater to ensure all questions are answered clearly and the rater can help explain any ambiguities.
- Part II: Motor Aspects of Experiences of Daily Living (M-EDL) is a self-administered questionnaire but can be reviewed by the investigator to ensure completeness and clarity.
- Part III: Motor Examination assesses the motor signs of PD and has instructions for the rater to give to or to demonstrate to the subject. It is completed by the rater.
- Part IV: Motor Complications integrates subject-derived information with the rater's clinical observations and judgements and is completed by the rater. It contains instructions for the rater and instructions to be read to the subject.

11.8. 12-Item Zarit Burden Interview (ZBI-12)

The Zarit Burden Interview (ZBI) is used to assess the perceived burden of family caregivers who provide assistance to patients with long-term progressive neurological disorders, including PD. The ZBI-22 consists of 22 items with five ordered frequency-related response categories scored 0 (never) to 4 (nearly always), except for the final item, which has 5 ordered intensity-related response categories (0 = not at all; 4 = extremely). All 22 items are used to calculate a total score that can range between 0 and 88 (88 = more burden). A total score of 21 has been suggested as a burden cut point. The ZBI-12 is a 12-item short form of the ZBI-22 and has been shown to be reliable and valid and to produce results that are similar to the longer version (Hagell et al 2017, Bédard et al 2001) (Appendix M) while minimizing respondent time and burden. The ZBI-12 should be completed by the same caregiver during each visit.

11.9. Early Morning Symptom Questionnaire (EMSQ)

The EMSQ is a 3-question, subject-rated questionnaire (Appendix N) that is used to assess whether a subject is experiencing any of 10 early morning PD symptoms by answering questions about prevalence (Question 1), severity (Question 2), and response to the first morning dose of PD medications (Question 3). Study site staff will complete this questionnaire by questioning subjects during each study visit.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety will be assessed by the following parameters:

- Electrocardiograms (ECGs), clinical laboratory tests, physical examinations, the Columbia-Suicide Severity Rating Scale (C-SSRS), and vital signs, including supine and standing orthostatic blood pressure and heart rate.
- Adverse events and concomitant medications will be evaluated throughout the course of the study.
- The Gastroparesis Cardinal Symptom Index (GCSI) at Screening, and Visit 4 (Exit) only.

12.2. Adverse Events

12.2.1. 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.

12.2.2. 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 constitutes 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.

12.2.3. Follow-up

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

12.2.4. 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.

12.2.5. 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

12.3. Serious Adverse Events

12.3.1. 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.

12.3.2. 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.

12.4. 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 12.3.2.

12.5. Other Safety Parameters and Related Information

Additional safety parameters (laboratory tests, 12-lead ECGs, physical examinations, and vital signs), the C-SSRS, the GCSI, and concomitant medications are collected as shown in the Schedule of Assessments in Section 8 and evaluated over the course of the study. Clinical laboratory assessments are listed in Appendix C.

13. STATISTICS

13.1. Study Design and Sample Size Estimation

This study is an open-label study in PD subjects. All subjects who successfully complete IPX203-B16-02 are eligible to enroll in this study; it is estimated that approximately 300 subjects will be enrolled.

13.2. Demographics and Baseline Characteristics

Prestudy subject demographics and baseline characteristics will be summarized to describe the subject population.

13.3. Analysis of Efficacy/Clinical Utility Data

The MDS-UPDRS Parts I to IV, PGI-S, CGI-S, PDQ-39, PDSS-2, PAS, NMSS, ZBI-12, and EMSQ will be assessed at every visit. The TSA will be assessed at every visit postbaseline. These data, along with the IPX203 dose and frequency information, will help characterize the clinical utility of IPX203. These measures will be analyzed as follows:

MDS-UPDRS – The Total MDS-UPDRS and each of its components (Parts I through IV), and Parts II and III combined, as well as the changes from Baseline in these scores, will be summarized across each of the time points in the trial (Baseline/Visit 1, Month 3, Month 6, Month 9) to allow for clinical assessment of the continuing effect of IPX203 and of switching to IPX203 for those who were randomized to IR CD-LD. For example, subjects randomized to IR CD-LD in Study IPX203-B16-02, will be examined for clinical improvement when switching to and following on IPX203 treatment. Subjects randomized to IPX203 in Study IPX203-B16-02 will be examined for maintaining clinical effect on IPX203.

PGI-S – Subjects' global impression of the severity of their PD and its treatment with IPX203 will be summarized at Months 3, 6, and 9 to assess the overall impact of IPX203 treatment over time. The mean changes from Baseline/Visit 1 in PGI-S as well as the frequencies and percentages of each component of the PGI-S will be summarized over time. The proportion of subjects with a PGI-S ≥ 4 and PGI-S ≥ 5 will also be summarized over time.

CGI-S – Clinicians' global impression of the severity of the subject's PD and its treatment with IPX203 will be summarized at Months 3, 6, and 9 to assess the overall impact of IPX203 treatment over time. The mean changes from Baseline/Visit 1 in CGI-S as well as the frequencies and percentages of each component of the CGI-S will be summarized over time. The proportion of subjects with a CGI-S ≥ 4 and CGI-S ≥ 5 will also be summarized over time.

PDQ-39 – The PDQ-39 and its domains will be assessed in the same manner as the MDS-UPDRS.

PAS – The PAS and its subscales (persistent anxiety, episodic anxiety, and avoidance behavior) will be assessed in the same manner as the MDS-UPDRS.

NMSS – The NMSS and individual domain will be assessed in the same manner as the MDS-UPDRS.

PDSS-2 – The PDSS-2 (the total score and each component) will be summarized across all visits.

TSA – The TSA will be summarized across all visits.

ZBI-12 – The ZBI-12 will be summarized across all visits.

EMSQ – The proportions of subjects with each of the early morning symptoms, the severity of each symptom, and whether the symptom improves after Parkinson's medication will be summarized across all visits. The change from baseline in total severity score will also be summarized across all visits.

13.4. Analysis of Dosing Data

Frequency of daily dosing and total daily dose of IPX203 at each visit after the baseline visit (Visit 1) will be summarized and compared against the baseline/Visit 1 daily dosing frequency. Percentages of subjects who require up-titration and down-titration, as well as the number of titration steps, will be summarized.

13.5. Population Analysis and Handling of Dropouts

Assessments will be made on available data with no adjustments for dropouts.

13.6. Analysis of Safety

The safety analysis will include all subjects who received at least one dose of study medication. Adverse events, supine and standing orthostatic vital signs, concomitant medications, electrocardiograms (ECGs), clinical laboratory tests, physical examinations, and the Columbia-Suicide Severity Rating Scale (C-SSRS) will be evaluated throughout the course of the study.

Adverse events will be collected and summarized both for the time in the open-label extension trial and the time of overall IPX203 exposure. For summary and reporting purposes, "unlikely related," "possibly related," and "related" will be combined and will be counted as "related."

Vital signs and ECGs will be summarized across the entire IPX203 exposure including information from the open-label extension and the prior IPX203-B16-02 study into which the subjects were enrolled.

14. ADMINISTRATIVE PROCEDURES

14.1. 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.

14.2. 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.

14.3. 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.

14.4. 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.

14.5. 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.

14.6. 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.

14.7. 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.

14.8. 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.

14.9. 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.

15. PUBLICATION POLICY

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

16. LIST OF REFERENCES

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17. APPENDICES

APPENDIX A. RECOMMENDATIONS FOR IPX203 DOSING

Subjects will be initially started on the final IPX203 dosing regimen that was determined during the IPX203 dose conversion period of Study IPX203-B16-02. Investigators are permitted to adjust the dosing regimen of IPX203 during this study to achieve the optimal balance of efficacy and safety and any dosing changes will be recorded at the study visit.

1. It is recommended that the subject takes IPX203 doses approximately every 8 hours apart (for example, a subject may take IPX203 at 6 AM, 2 PM, and 10 PM) with the exception that subjects who converted from a total daily dose of less than 125-500 mg IR CD-LD may take IPX203 every 12 hours. Some subjects may benefit from a shorter or longer dosing interval. The dosing interval may vary but should not be more frequent than every 6 hours.
2. The Investigator (or his/her staff) is advised to be in telephone contact with the subject, especially during the initial weeks of this study, to assess the need for dosage adjustment with the goal of minimizing "Off" time without causing troublesome dyskinesia or other dopaminergic side effects. Calls to the subject can be reduced when the subject reaches an acceptable stable dosing regimen.
3. If dose adjustment is necessary, consider the following options recognizing that the number of capsules at each dose may be varied to achieve an optimal response.
    a. If turning "On" is slow following the first morning dose, consider taking the morning IPX203 dose in the fasted state and/or increasing the dose by one capsule (35-140 mg IPX203 CD-LD).
    b. If turning "On" is slow later in the day or to reduce "end-of-dose" "Off" time, consider increasing the dose by one capsule (35-140 mg IPX203 CD-LD) before reducing the dosing interval.
    c. In case of troublesome dyskinesias, consider reducing the dose by one capsule (35-140 mg IPX203 CD-LD) prior to increasing the dosing interval.
4. Initially, all subjects will be dispensed 2 capsule dosage strengths, one of which will be the 35-140 mg IPX203 CD-LD capsules. Following dose regimen stabilization, up to 2 capsule dosage strengths may be dispensed from those available (35-140 mg, 52.5-210 mg, 70-280 mg, and 87.5-350 mg IPX203 CD-LD)

APPENDIX B. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

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 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 ☐
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 ☐
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 ☐
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 ☐
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 ☐

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	____

C-SSRS—Since Last Visit (Version 1/14/09)
Page 1 of 2

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:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**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* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

APPENDIX C. 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		

PREGNANCY TEST

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

APPENDIX D. MOVEMENT DISORDERS SOCIETY VERSION OF THE UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

START TIME ___:___ *(hh:mm, 24-hr clock)*

MDS-UPDRS

Given formatting concerns, this MDS-UPDRS source document does not track the Patient ID on each page of the assessment. DO NOT remove the staple binding this MDS-UPDRS packet.

July 1, 2008

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. 3 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
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July 1, 2008

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:

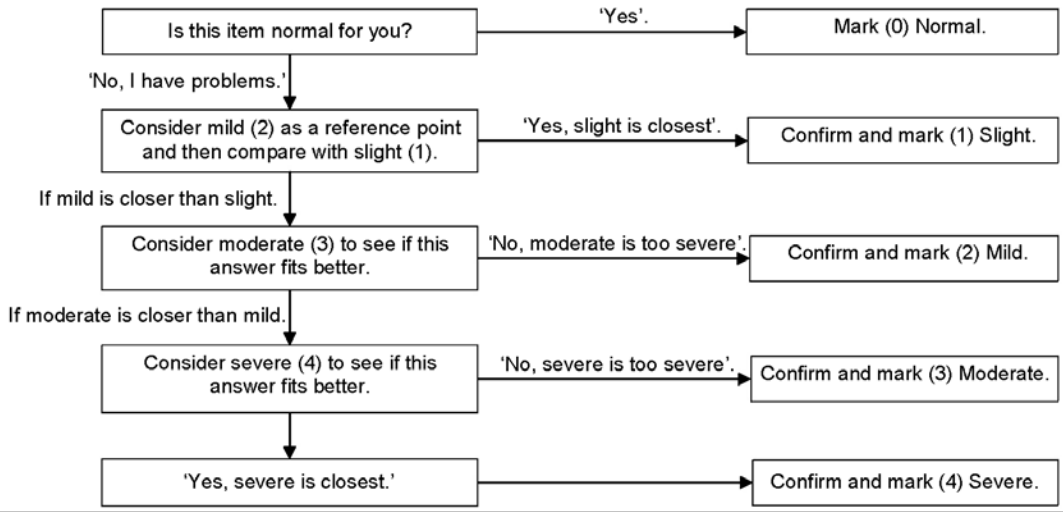
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (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.



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 patient's 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 behavior. 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 AND 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, knives, 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 person 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

	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: Mild 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]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

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 calculations).

0: Normal:	No dyskinesias.
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 with Dyskinesia: _____
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 general 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.

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 present?	☐ 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. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

The subject will independently rate the following question of Patient Global Impression of Severity (PGI-S) based on his/her overall impression of the study medication at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 9) or early discontinuation.

Patient Global Impression of Severity Scale

Severity of Illness

Considering the severity of your Parkinson's disease, how severe is your condition at this time?

Severity Score:

❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7
Normal, not at all ill	Borderline ill	Mildly ill	Moderately ill	Markedly ill	Severely ill	Extremely severely ill

APPENDIX F. CLINICAL GLOBAL IMPRESSION OF SEVERITY (CGI-S)

The Investigator will independently rate the following question of Clinical Global Impression of Severity (CGI-S) based on his/her overall impression of the study medication at Visit 2 (Month 3), Visit 3 (Month 6), and Visit 4 (Month 9) or early discontinuation.

Clinical Global Impression of Severity Scale

Severity of Illness

Considering your total clinical experience with this particular population, how ill is the patient at this time?

Severity Score:

❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7
Normal, not at all ill	Borderline ill	Mildly ill	Moderately ill	Markedly ill	Severely ill	Among the most extremely ill of subjects

Guy W. ECDEU assessment manual for psychopharmacology publication; ADM, 76-338. Washington DC, US. Department of health, education and welfare, 1976.

APPENDIX G. 39-ITEM PARKINSON'S DISEASE QUESTIONNAIRE (PDQ-39)

Parkinson's Disease Quality of Life Questionnaire (PDQ-39)

Due to having Parkinson's disease,
how often during the last month have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	had difficulty doing the leisure activities you would like to do?	☐	☐	☐	☐	☐
2.	had difficulty looking after your home, for example, housework, cooking or yardwork?	☐	☐	☐	☐	☐
3.	had difficulty carrying grocery bags?	☐	☐	☐	☐	☐
4.	had problems walking half a mile?	☐	☐	☐	☐	☐
5.	had problems walking 100 yards (approximately 1 block)?	☐	☐	☐	☐	☐
6.	had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	had difficulty getting around in public places?	☐	☐	☐	☐	☐
8.	needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please verify that you have ***checked one box for each question***
before going on to the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
9.	felt frightened or worried about falling in public?	☐	☐	☐	☐	☐
10.	been confined to the house more than you would like?	☐	☐	☐	☐	☐
11.	had difficulty showering and bathing?	☐	☐	☐	☐	☐
12.	had difficulty dressing?	☐	☐	☐	☐	☐
13.	had difficulty with buttons or shoelaces?	☐	☐	☐	☐	☐
14.	had problems writing clearly?	☐	☐	☐	☐	☐
15.	had difficulty cutting up your food?	☐	☐	☐	☐	☐
16.	had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17.	felt depressed?	☐	☐	☐	☐	☐
18.	felt isolated and lonely?	☐	☐	☐	☐	☐

Please verify that you have ***checked one box for each question***
before going on to the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **check one box** for each question*

	Never	Occasionally	Sometimes	Often	Always
19. felt weepy or tearful?	☐	☐	☐	☐	☐
20. felt angry or bitter?	☐	☐	☐	☐	☐
21. felt anxious?	☐	☐	☐	☐	☐
22. felt worried about your future?	☐	☐	☐	☐	☐
23. felt you had to hide your Parkinson's from people?	☐	☐	☐	☐	☐
24. avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25. felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26. felt worried about other people's reaction to you?	☐	☐	☐	☐	☐
27. had problems with your close personal relationships?	☐	☐	☐	☐	☐

Please verify that you have ***checked one box for each question***
before going on to the next page.

Due to having Parkinson's disease,
how often during the last month have you...

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
28.	lacked the support you needed from your spouse or partner? *If you do not have a spouse or Partner, please check here* ☐	☐	☐	☐	☐	☐
29.	lacked the support you needed from your family or close friends?	☐	☐	☐	☐	☐
30.	unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31.	had problems with your concentration, for example when reading or watching TV?	☐	☐	☐	☐	☐
32.	felt your memory was failing?	☐	☐	☐	☐	☐
33.	had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34.	had difficulty speaking?	☐	☐	☐	☐	☐
35.	felt unable to communicate effectively?	☐	☐	☐	☐	☐
36.	felt ignored by people?	☐	☐	☐	☐	☐

Please verify that you have ***checked one box for each question***
before going on to the next page.

Due to having Parkinson's disease,
how often during the last month have you…

*Please **check one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
37.	had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38.	had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39.	felt uncomfortably hot or cold?	☐	☐	☐	☐	☐

Please verify that you have ***checked one box for each question.***

Thank you for completing the questionnaire.

APPENDIX H. GASTROPARESIS CARDINAL SYMPTOM INDEX (GCSI)

GCSI

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *circle the number* that best describes how *severe* the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	VerySevere
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5

Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. Qual Life Res. 2004;13(4):833-44

Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. Aliment Pharmacol Ther. 2003;18(1):141-50

APPENDIX I. NON-MOTOR SYMPTOM ASSESSMENT SCALE FOR PARKINSON'S DISEASE (NMSS)

Non-Motor Symptom assessment scale for Parkinson's Disease

Patient ID No: _____ **Initials:** _____ **Age:** _____

Symptoms assessed over the last month. Each symptom scored with respect to:

Severity: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week); 4 = Very Frequent (daily or all the time)

Domains will be weighed differentially. Yes/ No answers are not included in final frequency x severity calculation.
(Bracketed text in questions within the scale is included as an explanatory aid).

Domain 1: Cardiovascular including falls	**Severity**	**Frequency**	**Frequency x Severity**
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐
Domain 2: Sleep/fatigue			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reding).	☐	☐	☐
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	☐	☐	☐
5. Does the patient have difficulties falling or staying asleep?	☐	☐	☐
6. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	☐	☐	☐
SCORE:			☐
Domain 3: Mood /Cognition			
7. Has the patient lost interest in his/her surroundings?	☐	☐	☐
8. Has the patient lost interest in doing things or lack motivation to start new activities?	☐	☐	☐
9. Does the patient feel nervous, worried or frightened for no apparent reason?	☐	☐	☐
10. Does the patient seem sad or depressed or has he/she reported such feelings?	☐	☐	☐
11. Does the patient have flat moods without the normal "highs" and " lows"?	☐	☐	☐
12. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	☐	☐	☐
SCORE:			☐
Domain 4: Perceptual problems/hallucinations			
13. Does the patient indicate that he/she sees things that are not there?	☐	☐	☐
14. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	☐	☐	☐
15. Does the patient experience double vision? (2 separate real objects and not blurred vision)	☐	☐	☐
SCORE:			☐

	Severity	Frequency	Frequency x Severity
Domain 5: Attention/ Memory			
16. Does the patient have problems sustaining concentration during activities? (For example, reading or having a conversation)	☐	☐	☐
17. Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?	☐	☐	☐
18. Does the patient forget to do things? (For example, take tablets or turn off domestic appliances?)	☐	☐	☐
SCORE:			☐
Domain 6: Gastrointestinal tract			
19. Does the patient dribble saliva during the day?	☐	☐	☐
20. Does the patient having difficulty swallowing?	☐	☐	☐
21. Does the patient suffer from constipation? (Bowel action less than three times weekly)	☐	☐	☐
SCORE:			☐
Domain 7: Urinary			
22. Does the patient have difficulty holding urine? (Urgency)	☐	☐	☐
23. Does the patient have to void within 2 hours of last voiding? (Frequency)	☐	☐	☐
24. Does the patient have to get up regularly at night to pass urine? (Nocturia)	☐	☐	☐
SCORE:			☐
Domain 8: Sexual function			
25. Does the patient have altered interest in sex? (Very much increased or decreased, please underline)	☐	☐	☐
26. Does the patient have problems having sex?	☐	☐	☐
SCORE:			☐
Domain 9: Miscellaneous			
27. Does the patient suffer from pain not explained by other known conditions? (Is it related to intake of drugs and is it relieved by antiparkinson drugs?)	☐	☐	☐
28. Does the patient report a change in ability to taste or smell?	☐	☐	☐
29. Does the patient report a recent change in weight (not related to dieting)?	☐	☐	☐
30. Does the patient experience excessive sweating? (not related to hot weather)	☐	☐	☐
SCORE:			☐
TOTAL SCORE:			☐

Developed by the International Parkinson's Disease Non- Motor Group.
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APPENDIX J. PARKINSON'S DISEASE SLEEP SCALE-2 (PDSS-2)

Parkinson's Disease Sleep Scale (PDSS-2)

Please rate the severity of the following based on your experiences during the past week (7 days). Please circle your answer.

Very often (This means 6 to 7 days a week)
Often (This means 4 to 5 days a week)
Sometimes (This means 2 to 3 days a week)
Occasionally (This means 1 day a week)
Never

	Very often	Often	Sometimes	Occasionaly	Never
1. Overall, did you sleep well during the last week?	0	1	2	3	4
2. Did you have difficulty falling asleep each night?	4	3	2	1	0
3. Did you have difficulty staying asleep?	4	3	2	1	0
4. Did you have restlessness of legs or arms at nights causing disruption of sleep?	4	3	2	1	0
5. Was your sleep disturbed due to an urge to move your legs or arms?	4	3	2	1	0
6. Did you suffer from distressing dreams at night?	4	3	2	1	0
7. Did you suffer from distressing hallucinations at night (seeing or hearing things that do not exist)?	4	3	2	1	0
8. Did you get up at night to urinate?	4	3	2	1	0
9. Did you feel uncomfortable at night because you were unable to turn over in bed or move due to immobility?	4	3	2	1	0
10. Did you feel pain in your arms or legs which woke you up while you were sleeping during the night?	4	3	2	1	0
11. Did you have muscle cramps in your arms or legs which woke you up while you were sleeping during the night?	4	3	2	1	0
12. Did you wake up earlier than usual with painful posturing of arms and legs?	4	3	2	1	0
13. On waking in the morning or during the night, did you experience tremor?	4	3	2	1	0
14. Did you feel tired and sleepy after waking up in the morning?	4	3	2	1	0
15. Did you wake up at night due to snoring or difficulties with breathing?	4	3	2	1	0

PDSS-2 - United States/English - Version of 30 Jul 15 - Mapi
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Trenkwalder C, Kohnen R, Högl B, Metta V, Sixel-Döring F, Frauscher B, Hülsmann J, Martinez-Martin P, Chaudhuri KR. Parkinson's disease sleep scale--validation of the revised version PDSS-2. Mov Disord. 2011;26(4):644-52

APPENDIX K. PARKINSON ANXIETY SCALE (PAS)

The Parkinson Anxiety Scale (PAS); English version

A. Persistent anxiety

Please mark one circle for each item below

In the past four weeks, to what extent did you experience the following symptoms?

A.1. Feeling anxious or nervous
0. Not at all, or never
1. Very mild, or rarely
2. Mild, or sometimes
3. Moderate, or often
4. Severe, or (nearly) always

A.2. Feeling tense or stressed
0. Not at all, or never
1. V y mild, or rarely
2. Mild, or sometimes
3. Moderate, or often
4. Severe, or (nearly) always

A.3. Being unable to relax
0. Not at all, or never
1. Very mild, or rarely
2. Mild, or sometimes
3. Moderate, or often
4. Severe, or (nearly) always

A.4. Excessive worrying about everyday matters
0. Not at all, or never
1. Very mild, or rarely
2. Mild, or sometimes
3. Moderate, or often
4. Severe, or (nearly) always

A.5. Fear of something bad, or even the worst, happening
0. Not at all, or never
1. Very mild, or rarely
2. Mild, or sometimes
3. Moderate, or often
4. Severe, or (nearly) always

Leentjens AFG, Dujardin D, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale Mov. Disord 2014;29:1035-43. doi: 10.1002/mds.25919.

B. Episodic anxiety

Please mark one circle for each item below

In the past four weeks, did you experience episodes of the following symptoms?

B.1. Panic or intense fear
0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

B.2. Shortness of breath
0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

B.3. Heart palpitations or heart beating fast (not related to physical effort or activity)
0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

B.4. Fear of losing control
0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

Leentjens AFG, Dujardin D, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale Mov. Disord 2014;29:1035-43. doi: 10.1002/mds.25919.

C. Avoidance behavior

Please mark one circle for each item below

In the past four weeks, to what extent did you fear or avoid the following situations?

C.1. Social situations (where one may be observed, or evaluated by others, such as speaking in public, or talking to unknown people)

0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

C.2. Public settings (situations from which it may be difficult or embarrassing to escape, such as queues or lines, crowds, bridges, or public transportation)

0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

C.3. Specific objects or situations (such as flying, heights, spiders or other animals, needles, or blood)

0. Never
1. Rarely
2. Sometimes
3. Often
4. Nearly always

APPENDIX L. TREATMENT SATISFACTION ASSESSMENT (TSA)

The subject independently answers the following question of treatment satisfaction based on his/her overall impression of the study medication at Visits 2, 3, and 4.

Treatment Satisfaction Assessment:

In general, how satisfied are you with your current Parkinson's disease medication?

❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7
Very much dissatisfied	Very dissatisfied	Somewhat dissatisfied	Neither satisfied nor dissatisfied	Somewhat satisfied	Very satisfied	Very much satisfied

APPENDIX M. 12-ITEM ZARIT BURDEN INTERVIEW (ZBI-12)

ZARIT BURDEN INTERVIEW

INSTRUCTIONS: The following is a list of statements, which reflect how people sometimes feel when taking care of another person. After each statement, indicate how often you feel that way; never, rarely, sometimes, quite frequently, or nearly always. There are no right or wrong answers.

	Never	Rarely	Sometimes	Quite Frequently	Nearly Always
1) Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	0	1	2	3	4
2) Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0	1	2	3	4
3) Do you feel angry when you are around the relative?	0	1	2	3	4
4) Do you feel that your relative currently affects your relationships with other family members or friends in a negative way?	0	1	2	3	4
5) Do you feel strained when you are around your relative?	0	1	2	3	4
6) Do you feel that your health has suffered because of your involvement with your relative?	0	1	2	3	4
7) Do you feel that you don't have as much privacy as you would like because of your relative?	0	1	2	3	4
8) Do you feel that your social life has suffered because you are caring for your relative?	0	1	2	3	4
9) Do you feel that you have lost control of your life since your relative's illness?	0	1	2	3	4
10) Do you feel uncertain about what to do about your relative?	0	1	2	3	4
11) Do you feel you should be doing more for your relative?	0	1	2	3	4
12) Do you feel you could do a better job in caring for your relative?	0	1	2	3	4

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ZARIT BURDEN INTERVIEW

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APPENDIX N. EARLY MORNING SYMPTOMS QUESTIONNAIRE (EMSQ)

Questions:

1. ***Over the past week, when you awakened in the morning for the day from your night-time sleep, on how many days did you experience each of the following symptoms?***

a. Tremor	☐ 0	☐ 1-3	☐ 4-7
b. Stiffness	☐ 0	☐ 1-3	☐ 4-7
c. Slowness	☐ 0	☐ 1-3	☐ 4-7
d. Walking/Turning	☐ 0	☐ 1-3	☐ 4-7
e. Loss of Balance	☐ 0	☐ 1-3	☐ 4-7
f. Urinary Control	☐ 0	☐ 1-3	☐ 4-7
g. Anxious Feelings	☐ 0	☐ 1-3	☐ 4-7
h. Too Much Saliva	☐ 0	☐ 1-3	☐ 4-7
i. Depressed or Sad Feelings	☐ 0	☐ 1-3	☐ 4-7
j. Bodily Discomfort or Pain	☐ 0	☐ 1-3	☐ 4-7

2. ***If you experienced any symptom in the question (Q.1) above on at least one day over the past week, indicate for this symptom (or for these symptoms) the severity to which this symptom impaired your morning activities and social interactions using the severity definitions below***:

a. Tremor	☐ Mild	☐ Moderate	☐ Severe
b. Stiffness	☐ Mild	☐ Moderate	☐ Severe
c. Slowness	☐ Mild	☐ Moderate	☐ Severe
d. Walking/Turning	☐ Mild	☐ Moderate	☐ Severe
e. Loss of Balance	☐ Mild	☐ Moderate	☐ Severe
f. Urinary Control	☐ Mild	☐ Moderate	☐ Severe
g. Anxious Feelings	☐ Mild	☐ Moderate	☐ Severe
h. Too Much Saliva	☐ Mild	☐ Moderate	☐ Severe
i. Depressed or Sad Feelings	☐ Mild	☐ Moderate	☐ Severe
j. Bodily Discomfort or Pain	☐ Mild	☐ Moderate	☐ Severe

Severity Definitions:

Mild: Causes mild impact on one or more early morning ***functions*** but I am usually able to perform most morning activities and participate in most social interactions.

Moderate: Impacts one or more early morning ***functions*** to the point that I am usually not able to perform some morning activities and/or participate in some social interactions.

Severe: Impacts one or more early morning ***functions*** to the point that I am usually not able to perform most morning activities and/or participate in most social interactions.

3. Which of the <u>early morning symptoms</u> (if any) that you identified above and assessed severity in Q.2 above improved after taking a first morning dose of your Parkinson's medication(s)? For each symptom, indicate "YES" improved or "NO" did not improve. If you did not experience the symptom (ie, answered 0 in Q.1 above), indicate "Did not experience".

a. Tremor	☐ Yes	☐ No	☐ Did not experience
b. Stiffness	☐ Yes	☐ No	☐ Did not experience
c. Slowness	☐ Yes	☐ No	☐ Did not experience
d. Walking/Turning	☐ Yes	☐ No	☐ Did not experience
e. Loss of Balance	☐ Yes	☐ No	☐ Did not experience
f. Urinary Control	☐ Yes	☐ No	☐ Did not experience
g. Anxious Feelings	☐ Yes	☐ No	☐ Did not experience
h. Too Much Saliva	☐ Yes	☐ No	☐ Did not experience
i. Depressed or Sad Feelings	☐ Yes	☐ No	☐ Did not experience
j. Bodily Discomfort or Pain	☐ Yes	☐ No	☐ Did not experience

APPENDIX O. 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.