A Phase 2, Randomized, Double-Blind, Placebo Controlled, 3-Period Crossover, Positive Control, QT-Evaluation Study of APL-130277 in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

PROTOCOL NUMBER:	CTH-201
IND:	110955
EUDRACT:	2016-001762-29
PROTOCOL DATE:	28 August 2017
PROTOCOL VERSION	5.00
SPONSORED BY:	Sunovion Pharmaceuticals Inc. 84 Waterford Drive Marlborough, MA 01752, USA +1 (508) 481-6700

RESTRICTED DISTRIBUTION OF PROTOCOLS

This document contains information confidential and/or of proprietary interest to Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc. (including their predecessors, subsidiaries or affiliates). The information cannot be disclosed to any third party or used for any purpose other than the purpose for which it is being submitted without the prior written consent of the appropriate Sumitomo Dainippon Pharma company.

This information is being provided to you for the purpose of conducting a clinical study for Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc. You may disclose the contents of this protocol to the study personnel under your supervision and to your Institutional Review Board or Independent Ethics Committee for the above purpose. You may not disclose the contents of this protocol to any other parties, unless such disclosure is required by government regulations or laws, without the prior written permission of Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc.

Any data gathered during the conduct of this protocol and supplemental information (eg, a protocol amendment) that may be added to this document is also proprietary to Sumitomo Dainippon Pharma Co. Ltd. and/or Sunovion Pharmaceuticals Inc., and should be handled consistently with that stated above.

1 EMERGENCY CONTACT INFORMATION

Sponsor Contact:

[redacted]
Senior Director Clinical Development
Sunovion Pharmaceuticals Inc.
84 Waterford Drive Marlborough, MA
[redacted]

North American Medical Monitor:

[redacted]
Medical Director
INC Research
[redacted]

European Union Medical Monitor

[redacted]
Executive Medical Director
INC Research
[redacted]

SAE Reporting

[redacted]

2 INVESTIGATOR APPROVAL STATEMENT

I have read the protocol, CTH-201, Version 5.0, "A Phase 2, Randomized, Double-Blind, Placebo Controlled 3-Period Crossover, Positive Control, QT-Evaluation Study of APL-130277 in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)," and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB/REB/IEC approval.

Principal Investigator

Printed Name: _____

Signature: _____

Date: _____

PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo Controlled, 3-Period Crossover, Positive Control, QT-Evaluation Study of APL-130277 in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Protocol: 28 Aug 2017

Version: 5.0

3 PROTOCOL SYNOPSIS

TITLE	A Phase 2, Randomized, Double-Blind, Placebo Controlled 3-Period Crossover, Positive Control, QT-Evaluation Study of APL-130277 in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)
STUDY PHASE	Phase 2
OBJECTIVES	The primary objective is to evaluate the effect of APL-130277 compared to placebo on QTc intervals in subjects with Parkinson's disease (PD) complicated by motor fluctuations. The secondary objectives include the evaluation of safety and pharmacokinetics of APL-130277 and the comparison of efficacy of the highest tolerated dose level and the lowest APL-130277 dose resulting in a full "ON" during the Dose Titration Phase.
NUMBER OF SUBJECTS	The study will require forty-two (42) subjects to complete the 3-period, single dose crossover phase. Recruitment will continue until the required number of subjects complete the study.
PATIENT POPULATION	**Inclusion Criteria** Subjects who meet each of the following criteria will be eligible for participation in the study: 1. Male or female ≥ 18 years of age. 2. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria (excluding the "more than one affected relative" criterion). 3. Clinically meaningful response to Levodopa (L-Dopa). Subjects with or without well-defined "OFF" episodes, as determined by the Investigator, will be allowed. 4. Receiving stable doses of L-Dopa/carbidopa (immediate or sustained release) administered at least 3 times per day OR Rytary™ administered 3 times per day, for at least 4 weeks before the initial Screening Visit (SV1). Subjects receiving L-Dopa/carbidopa 3 times a day must also be on stable treatment with adjunctive PD medication regimens. These regimens must be maintained at a stable dose for at least 4 weeks prior to the initial Screening Visit (SV1) with the exception that MAO-B inhibitors must be maintained at a stable level for at least 8 weeks prior to the initial Screening Visit (SV1). 5. No planned medication change(s) or surgical intervention anticipated during the course of study. 6. The subject must be able to have a drug withdrawal induced "OFF" episode. 7. Stage III or less on the modified Hoehn and Yahr scale in the "ON" state. 8. Mini–Mental State Examination (MMSE) score > 21. 9. If female and of childbearing potential, must agree to use one of the following methods of birth control throughout the study and until at least 30 days after final drug administration: • Oral contraceptive; • Contraceptive patch;

	• Barrier (diaphragm, sponge or condom) plus spermicidal preparations; • Intrauterine contraceptive system; • Levonorgestrel implant; • Medroxyprogesterone acetate contraceptive injection; • Complete abstinence from sexual intercourse; • Hormonal vaginal contraceptive ring; or • Surgical sterilization or partner sterile (must have documented proof). 10. Male subjects must be either surgically sterile, agree to be sexually abstinent or use a barrier method of birth control (e.g., condom) from first study drug administration until at least 30 days after final drug administration. 11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study. 12. Able to understand the consent form, and to provide written informed consent. 13. Must be approved as a satisfactory candidate by the Enrollment Authorization Committee (EAC) and the Sponsor.
	Exclusion Criteria Subjects will be excluded from participation in the study for any of the following reasons: 1. Atypical or secondary parkinsonism. 2. Nausea associated with the use of dopamine agonists that requires treatment with an anti-emetic. 3. Previous treatment with any of the following: a neurosurgical procedure for PD; continuous subcutaneous (s.c.) apomorphine infusion; or Duodopa/Duopa. 4. Treatment with any form of s.c. apomorphine within 7 days prior to the initial Screening Visit (SV1). Subjects that stopped s.c. apomorphine for any reason other than systemic safety concerns or lack of efficacy may be considered. 5. Contraindications to moxifloxacin or APOKYN® or hypersensitivity to apomorphine hydrochloride or any macrolide antibiotic or any of the ingredients of APOKYN® (notably sodium metabisulfite). 6. Female who is pregnant or lactating. 7. Participation in a clinical trial within 30 days prior to the initial Screening Visit (SV1), with the exception of clinical studies related to APL-130277. 8. Receipt of any investigational (i.e., unapproved) medication within 30 days prior to the initial Screening Visit (SV1), with the exception of APL-130277. 9. Any selective $5HT_3$ antagonists (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (including Tigan [trimethobenzamide] and domperidone, but excluding quetiapine or clozapine) or dopamine depleting agents within 30 days prior to initial Screening Visit (SV1). 10. Drug or alcohol dependency in the past 12 months. 11. Subject has a history of malignancy within 5 years prior to SV1, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical

	cancer. Pituitary tumors of any duration are excluded. 12. Documented abnormalities with ECGs including, arrhythmias, clinically meaningful interval irregularities, structural heart abnormalities, myocardial infarction, presence or history of a pacemaker, or any abnormality of the ECG, that in the opinion of the Investigator, would interfere with the ability to measure the QT interval, or correct the QT interval for heart rate. 13. Male subjects with a screening corrected QT interval using Fridericia's formula (QTcF) of ≥ 450 ms; female subjects with a screening QT interval ≥ 470 ms. Eligibility will be based on the core laboratory ECG interpretation report. 14. HR at screening < 45 bpm or > 100 bpm. 15. QRS duration at screening > 120 ms. 16. PR interval at screening > 200 ms. 17. Subjects with a history of cataplexy, unexplained syncope or seizures. 18. Family history of sudden cardiac death. 19. Heart failure (NYHA Class II or greater) and/or a myocardial infarction. 20. Current use of any concomitant mediations that prolong the QT/QTc interval. Refer to https://crediblemeds.org for listing. 21. History of additional risk factors for TdP (i.e., heart failure, hypokalemia, family history of Long QT Syndrome). 22. Clinically significant medical, surgical, or laboratory abnormality in the opinion of the Investigator. 23. Subject has a positive screening laboratory test result for human immunodeficiency virus (HIV). 24. Subject has a positive screening laboratory test result for hepatitis B surface antigen or hepatitis C antibodies and has liver function test results at screening above the ULN for the reference laboratory. 25. Major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis (including Parkinson's disease psychosis), or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult. 26. History of clinically significant impulse control disorder(s). 27. Dementia that precludes providing informed consent or would interfere with participation in the study. 28. Current suicidal ideation within one year prior to the second Screening Visit (SV2) as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or attempted suicide within the last 5 years. 29. Donation of blood plasma in the 30 days prior to first dosing.
STUDY DESIGN	***Study Procedures*** *Screening* Before any study procedures are performed on any subject, informed consent must be obtained at an initial Screening Visit (SV1). Subjects recruited to participate in the study,

	and who have provided full consent to participate, will be asked to attend a second Screening Visit (SV2), having taken their last dose of L-Dopa and any other adjunctive PD medication no later than midnight the evening prior to the visit. Their normal morning dose of L-Dopa (***without*** adjunctive PD medication) will be administered in the clinic following confirmation of an "OFF" episode by the Investigator, to ensure that they experience an "ON" response. Eligibility criteria will be assessed by the Investigator and approved by the EAC prior to enrollment. Subjects will be asked to return to the clinic the morning of Titration Visit 1 (TV1) for the Dose Titration Phase of the study. *Dose Titration Phase* Depending on the Investigator's decision, subjects will be asked to arrive at the clinic: • after their usual morning dose of PD medications; but before taking their next dose of medication; OR • after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior). During the Dose Titration Phase of the study, subjects will start with a dose of 10 mg APL-130277 and increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full "ON" state. Once a full "ON" state is achieved, dosing will continue for 2 additional visits to a maximum dose of 60 mg (i.e., if a subject experiences the first full "ON" at 10 mg, dosing will continue up until a dose of 20 mg). For those subjects who do not achieve a full "ON" response, titration should continue until the maximum tolerated dose of APL-130277 is determined. **Note:** For subjects who have previously participated in the CTH-300 or CTH-301 study, the subject will begin titration at the effective dose used in the respective previous study. Similarly dose titration of these subjects will increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full "ON" state. Once a full "ON" state is achieved, dosing will continue for 2 additional visits to a maximum dose of 60 mg (i.e., if a subject experiences the first full "ON" at 35 mg, dosing will continue up until a dose of 50 mg). At Titration Visit 1 (TV1), once the subject's "OFF" state has been confirmed by both the Investigator and subject, the subject will be treated with 10 mg APL-130277. Subjects who tolerate the 10 mg APL-130277 will restart their normal PD medications and will be asked to return to the clinic the next business day for Titration Visit 2 (TV2), to assess the next highest dose (i.e., 15 mg) in a manner identical to that of Titration Visit 1 (TV1). Doses of APL-130277 will increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until a full "ON" state is achieved, then dosing will continue for 2 additional visits to a maximum dose of 60 mg. This will sequentially be 20 mg [TV3], 25 mg [TV4], 30 mg [TV5], 35 mg [TV6], 40 mg [TV7], 50 mg [TV8] and 60 mg [TV9]. For Titration Visit 3 (TV3), Titration Visit 4 (TV4), Titration Visit 5 (TV5), and Titration Visit 6 (TV6) subjects should be dosed with the next highest dose of study medication within 4 hours of the initial dose, as long as the subject achieves another "OFF" state that

	day. TV3 should be paired with TV4 (20 mg and 25 mg can be dosed on the same day), TV4 should be paired with TV5 (25 mg and 30 mg can be dosed on the same day), TV5 should be paired with TV6 (30 mg and 35 mg can be dosed on the same day) and TV6 should be paired with TV7 (35 mg and 40 mg can be dosed on the same day). Should the subject be unable to tolerate either of the two additional dose levels after reaching a full "ON" state, in the Investigator's opinion, due to adverse events commonly associated with apomorphine (e.g., orthostatic hypotension, nausea, vomiting, etc.), subjects will be randomized to the previous dose. Dosing days in the Dose Titration Phase should be scheduled on consecutive business days and a maximum of 2 days between visits may be permitted with Medical Monitor approval. All visits in the Dose Titration Phase must be completed within 14 days. Safety and efficacy assessments will be performed at each visit according to the protocol. *Three-Way Balanced Randomized Crossover Assessment Phase (Period 1, Period 2, Period 3)* Subjects who successfully complete the Dose Titration Phase of the study, and are approved by the Sponsor to proceed to randomization, will be asked to return to the clinic for Period 1 Dosing Visit 1 (P1V1). This visit will occur between 2 and 7 days after the final visit in the Dose Titration Phase of the study. Depending on the Investigator's decision, subjects will be asked to arrive at the clinic: • after their usual morning dose of PD medications; but before taking their next dose of medication; OR • after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior). Subjects will be randomized in equal numbers to six possible sequences of each of the three treatments being studied: 1. Treatment A: APL-130277 at the dose determined in the Dose Titration Phase, 2. Treatment B: Matched placebo APL-130277, 3. Treatment C: A single 400 mg dose of moxifloxacin. Following confirmation by both the Investigator and subject that the subject is in the "OFF" state, the subject will be dosed according to the subject's random treatment assignment. APL-130277 and placebo APL-130277 will be administered in a double-blind fashion and moxifloxacin will be administered open-label in a three-way balanced crossover. All subjects will be exposed to all three treatments. The six possible treatment sequences are: 1) ABC; 2) ACB; 3) BCA; 4) BAC; 5) CAB; and 6) CBA. Subjects will return to clinic 3 days after Period 1 and will be dosed for Period 2 with one of the other two treatments. Subjects will return to clinic 3 days after Period 2 and will be dosed for Period 3 with the third and last treatment.
INVESTIGATIONAL DRUG	APL-130277 (10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg [given as 2 sublingual thin films consisting of 20 mg followed by 15 mg], 40 mg [given as 2 sublingual thin films consisting of 20 mg followed by 20 mg], 50 mg [given as 2 sublingual thin films

	consisting of 25 mg followed by 25 mg] and 60 mg [given as 2 sublingual thin films consisting of 30 mg followed by 30 mg]). To administer the 35 mg dose, study staff will administer the 20 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, immediately administer the 15 mg sublingual thin film for another 3 minutes (total dosing time should be 6 minutes). To administer the 40 mg dose, study staff will administer the 20 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 20 mg dose, and staff will ensure the sublingual space is free of excess water. The second 20 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes). To administer the 50 mg dose, study staff will administer the 25 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 25 mg dose, and staff will ensure the sublingual space is free of excess water. The second 25 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes). To administer the 60 mg dose, study staff will administer the 30 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 30 mg dose, and staff will ensure the sublingual space is free of excess water. The second 30 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).
REFERENCE PRODUCT	Matching Placebo APL-130277 Moxifloxacin 400 mg
TREATMENT REGIMENS	Dose Titration starting at 10 mg APL-130277 will be administered in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full “ON” state and will continue titration for two additional visits to a maximum dose of 60 mg. This will be followed by a three-way balanced randomized crossover phase using the highest APL-130277 tolerated dose or matched placebo APL-130277, in a double-blind fashion, or treatment with open-label moxifloxacin.
CONCOMITANT AND CO-ANALGESIC TREATMENT	All subjects: stable doses of a L-Dopa formulation and other stable adjunctive PD medications.
PROHIBITED TREATMENT	• Any form of s.c. apomorphine from 7 days prior to the initial Screening Visit (SV1) until study completion. • Any selective $5HT_3$ antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron) from 30 days prior to the initial Screening Visit (SV1) until study completion. • Dopamine antagonists (including Tigan [trimethobenzamide] and domperidone, but excluding quetiapine or clozapine) or dopamine depleting drugs. • Deep brain stimulation or other neurosurgical PD treatment, continuous s.c. apomorphine infusion, or Duodopa/Duopa.

	• Any medication that can prolong QT. Refer to https://crediblemeds.org for listing.
STUDY DURATION	Participation is anticipated to be a maximum of 46 days.
INVESTIGATIVE SITES OR COUNTRIES	This is a multicenter study to be conducted at up to 10 sites in Europe and up to 20 sites in North America.
STUDY ENDPOINTS	*Primary Endpoint* 1. Time-matched change from baseline in QTc, placebo-adjusted and corrected for HR based on the Fridericia correction method (QTcF) method (ΔΔQTcF). Assay sensitivity will be demonstrated by inclusion of a positive control, moxifloxacin. *Secondary Endpoints* 1. Pharmacokinetics of apomorphine and apomorphine metabolites. 2. Evaluation of safety and tolerability of APL-130277 as measured by adverse events, physical examination including assessment of oropharyngeal adverse events, 12-lead ECGs, vital signs including orthostatic hypotension (OH), clinical laboratory tests, and C-SSRS assessments. 3. ECG assessments including QTc with Bazett correction (QTcB), heart rate, PR interval, QRS interval, uncorrected QT interval, ECG morphology and presence of cardiac arrhythmias such as ventricular tachycardia or Torsade de Pointes (TdP). 4. MDS-UPDRS Part III change from pre-dose to 30, 60, 90 minutes after dosing during the titration phase at the highest tolerated APL-130277 dose level and the lowest APL-130277 dose resulting in a full "ON". 5. Time to "ON" during Titration Phase at the highest tolerated APL-130277 dose level and the lowest APL-130277 dose resulting in a full "ON". 6. Duration of "ON" during Titration Phase at the highest tolerated APL--130277 dose level and the lowest APL-130277 dose resulting in a full "ON".
STATISTICAL METHODS SUMMARY	All subjects who receive at least one dose of study medicine `will be included in the safety analysis set. The PK analysis set includes all subjects with at least one PK evaluation. The efficacy analysis set includes subjects who have efficacy assessments at the lowest dose level resulting in a full "ON". The super-efficacy analysis set includes subjects who have efficacy assessments at both the lowest dose that provides a full "ON", the highest tolerated dose level during the Titration Phase. The evaluation of the ECG data is focused on the corrected QT interval (QTc). Both the formula by Bazett and by Fridericia will be used for the correction, though the Fridericia correction will be considered primary, and the Bazett correction data is presented for historical purposes. Both central tendency (mean changes from pre-dose) and outliers will be evaluated. Assay sensitivity will be demonstrated by evaluating the placebo corrected change from baseline for QTcF for the positive control, moxifloxacin, at predesignated timepoints. The pharmacokinetic parameters will be summarized with descriptive statistics for each dose level.

	The safety data other than ECG (vital signs including orthostatic blood pressure, physical examinations including oral assessments, premature discontinuations, adverse events, C-SSRS, and safety laboratory variables) will be summarized with descriptive statistics for APL-130277 overall and separately for each dose level. The main efficacy endpoint of this study is the change in MDS-UPDRS Part III at 30 minutes. The MDS-UPDRS Part III will be analyzed using a Mixed Model for Repeated Measures with data from the lowest dose level resulting in a full "ON" and at the highest tolerated dose level during the Titration Phase as response variables. The baseline (SV2) value will be included as a covariate and the day (1 = assessment at the lowest dose level resulting in a full "ON", 2 = assessment at the highest tolerated dose level) and dose level (10 mg, 15 mg, 20 mg, …, 60 mg) as fixed factors in the model. Separate models will be used for each time point (30, 60 and 90 minutes).
SAMPLE SIZE CALCULATION	Forty-two (42) subjects will provide approximately 80% power to detect a mean difference of 7 ms in the change in QTc between APL-130277 and placebo, assuming that the true difference between APL-130277 and placebo can be up to 3 ms, (adding up to the predefined threshold of 10 ms) and a standard deviation of 14 ms [12] for ΔΔQTcF with one-sided significance level of 0.05.

4 STUDY DESIGN FLOW CHART

4.1 Schedule of Events Table

Procedures	Screening Visits[2]		Titration Visit 1[1]	Titration Visit 2[1]	Titration Visit 3[1, 15]	Titration Visit 4[1, 15]	Titration Visit 5[1, 15]	Titration Visit 6[1, 15]	Titration Visit 7[1]	Titration Visit 8[1]	Titration Visit 9[1]	Randomization Procedures[16]	Period 1 Dosing Visit	Period 2 Dosing Visit	Period 3 Dosing visit	End of Study Visit
Study Visit	**SV1**	**SV2**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**TV7**	**TV8**	**TV9**		**P1V1**	**P2V2**	**P3V3**	**EOS**
Day	**-14 to -3**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**1**	**3 days after P1V1**	**3 days after P2V2**	**3-5 days after P3V3**
Maximum Study Duration (days)	**1 to 14**		**15 to 28**										**35**	**38**	**41**	**44 to 46**
Outpatient Visit[3]	X	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X	X	X		X	X	X	X
Written Informed Consent	X															
Reconfirmation of Consent		X	X	X	X	X	X	X	X	X	X		X	X	X	X
Review Entry Criteria	X	X														
Review Restriction Criteria			X	X	X	X	X	X	X	X	X		X	X	X	
Medical History/Demographics		X[2]														
Complete Physical Exam, including Oropharyngeal Exam[4]		X[2]														X
Abbreviated Physical Exam, including Oropharyngeal Exam[5]			X	X	X	X	X	X	X	X	X		X	X	X	
BMI, Weight and Height[6]		X[2]											X	X	X	X
Vital Signs (BP, HR, RR and Temp)[7, 8]		X[2]	X	X	X	X	X	X	X	X	X		X	X	X	X
12-Lead ECG (Holter)[8, 9]													X	X	X	
12-Lead ECG (Resting)[8, 10]		X[2]	X	X	X	X	X	X	X	X	X		X	X	X	X

Procedures	Screening Visits[2]		Titration Visit 1[1]	Titration Visit 2[1]	Titration Visit 3[1, 15]	Titration Visit 4[1, 15]	Titration Visit 5[1, 15]	Titration Visit 6[1, 15]	Titration Visit 7[1]	Titration Visit 8[1]	Titration Visit 9[1]	Randomization Procedures[16]	Period 1 Dosing Visit	Period 2 Dosing Visit	Period 3 Dosing visit	End of Study Visit
Study Visit	**SV1**	**SV2**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**TV7**	**TV8**	**TV9**		**P1V1**	**P2V2**	**P3V3**	**EOS**
Day	**-14 to -3**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**1**	**3 days after P1V1**	**3 days after P2V2**	**3-5 days after P3V3**
Maximum Study Duration (days)	**1 to 14**		**15 to 28**										**35**	**38**	**41**	**44 to 46**
Clinical Laboratory Tests[11]		X														X
PK[8, 12]													X	X	X	
MMSE		X														
Modified Hoehn and Yahr		X														
MDS-UPDRS Part III[8, 13]		X	X	X	X	X	X	X	X	X	X					
Confirmation of L-Dopa Responsiveness		X														
Clinical Confirmation of "OFF" or full "ON"		X	X	X	X	X	X	X	X	X	X		X	X	X	
Subject Confirmation of "OFF" or full "ON"		X	X	X	X	X	X	X	X	X	X		X	X	X	
Subject "OFF" versus "ON" Training		X														
In-Clinic Dosing			X	X	X	X	X	X	X	X	X		X	X	X	
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Previous/Current Concomitant Medications		X	X	X	X	X	X	X	X	X	X		X	X	X	X
C-SSRS[14]		X	X	X	X	X	X	X	X	X	X		X	X	X	X

[1] Dosing days in the Dose Titration Phase should be scheduled the following business day of the previous visit and all visits must be completed within 14 days. A maximum of 2 days between visits may be permitted with Medical Monitor approval.

[2] All screening procedures to be conducted within 14 days prior to Titration Visit 1 (TV1). If required by the Investigator, and following receipt of subject

consent, the Investigator may review the subjects' medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the subject may be eligible for study participation. Procedures performed on SV1 will not be repeated at SV2.

[3] Subjects may be monitored in the clinic overnight before Dose Titration Visits if such facilities exist and the subject consents.

[4] Physical examination to include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including mouth – oral cavity; musculoskeletal system; central and peripheral nervous system; and skin. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

[5] Abbreviated physical exam to include head-eyes-ears-nose and throat; heart; lungs; abdomen; and skin; to be done at t = 0 (just prior to dosing) and 120 minutes after dosing at TV1 to TV9, Period 1, Period 2, and Period 3. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

[6] Both height and weight captured at the Screening Visit (SV2) to calculate BMI; only weight captured at all other indicated visits.

[7] Vital signs will be assessed at the Screening Visit (SV2) and End of Study (EOS); TV1 to TV9 and during Period 1, 2 and 3 at t = 0 minutes (just prior to dosing), 15, 45 and 60 minutes. Blood pressure to be measured supine and standing (measured within 3 minutes of standing) at all timepoints.

[8] Suggested Sequence of Assessments at Pre-Dose: ECG – PK – Vitals – Efficacy. Sequence of Assessments after dosing (where applicable): MDS-UPDRS Part III - Subject "OFF"/"ON" status – ECG – PK – Vitals.

[9] 12-lead ECG (Triplicate; Holter): Period 1: Obtain three (3) sets of triplicate ECGs over approximately 1-hour (prior to dosing) as the baseline assessment; and obtain triplicate ECG at t = 15, 30, 45, 60 minutes and 2, 3, 4, 8, 12, 24 hours after dosing. Period 2 and Period 3: Obtain triplicate ECG at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes and 2, 3, 4, 8, 12, 24 hours after dosing.

[10] 12-lead ECG (Single; Resting): Obtain at the Screening Visit in triplicate (SV2). TV1 to TV9: ECG at t = 0 (just prior to dosing) and 45 minutes after dosing. Period 1, Period 2 and Period 3 at 60 minutes after dosing. EOS: A triplicate ECG will be obtained. ECGs will be assessed by the Investigator at each visit.

[11] Blood and urine collection for clinical laboratory tests will occur at Screening Visit (SV2) and at the End of Study Visit (EOS). In addition, serum pregnancy test will be performed on all females of childbearing potential.

[12] PK will be assessed for APL-130277 and placebo dosing days at t = 0 (just prior to dosing), 30, 45, 60 minutes and 2, 4 hours after dosing. PK will be assessed on the moxifloxacin dosing day at t = 0 (just prior to dosing), 30, 60 minutes and 2, 3, 4, 6, 8 hours after dosing.

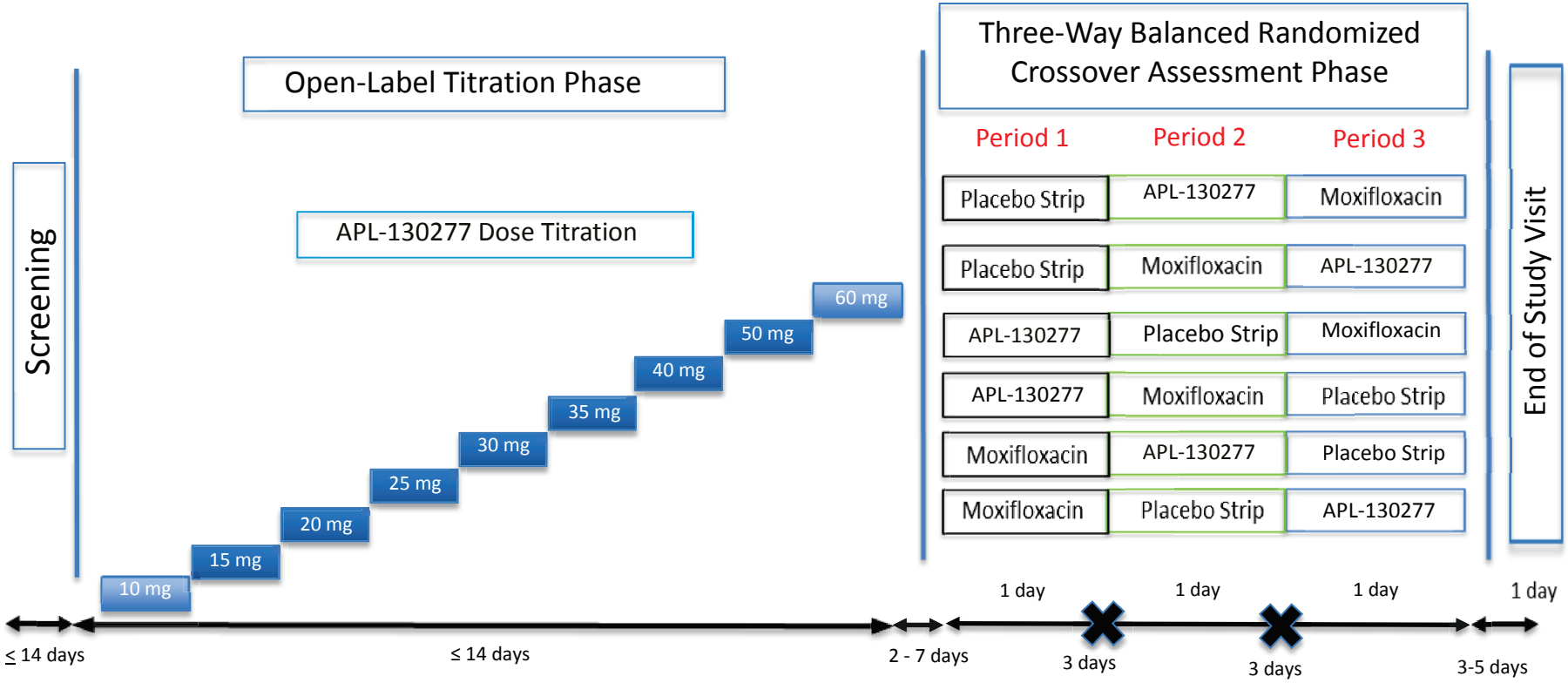
[13] MDS-UPDRS Part III (Motor Function) to be assessed at t = 0 (just prior to dosing), 30, 60 and 90 minutes after L-Dopa administration at the second Screening Visit (SV2); the modified Hoehn and Yahr will be used during the Screening Visit (SV2). Assessments during the Titration Phase at t = 0 (just prior to dosing), 30, 60 and 90 minutes after dosing; these assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.

[14] "Screening" scale to be used at the Screening Visit (SV2); "Since Last Visit" to be used at all other visits.

[15] Optional Dosing Regimen: For TV3, TV4, TV5 and TV6 only subjects can be dosed with the next highest dose of study medication within 4 hours of the previous dose, as long as the subject achieves another "OFF" state that day.

[16] Following completion of the Dose Titration Phase of the study, Sponsor approval is required prior to randomization in the Three-Way Balanced Crossover Phase. Additional details are available in the Enrollment and Randomization Adjudication Process, which is contained in a separate document.

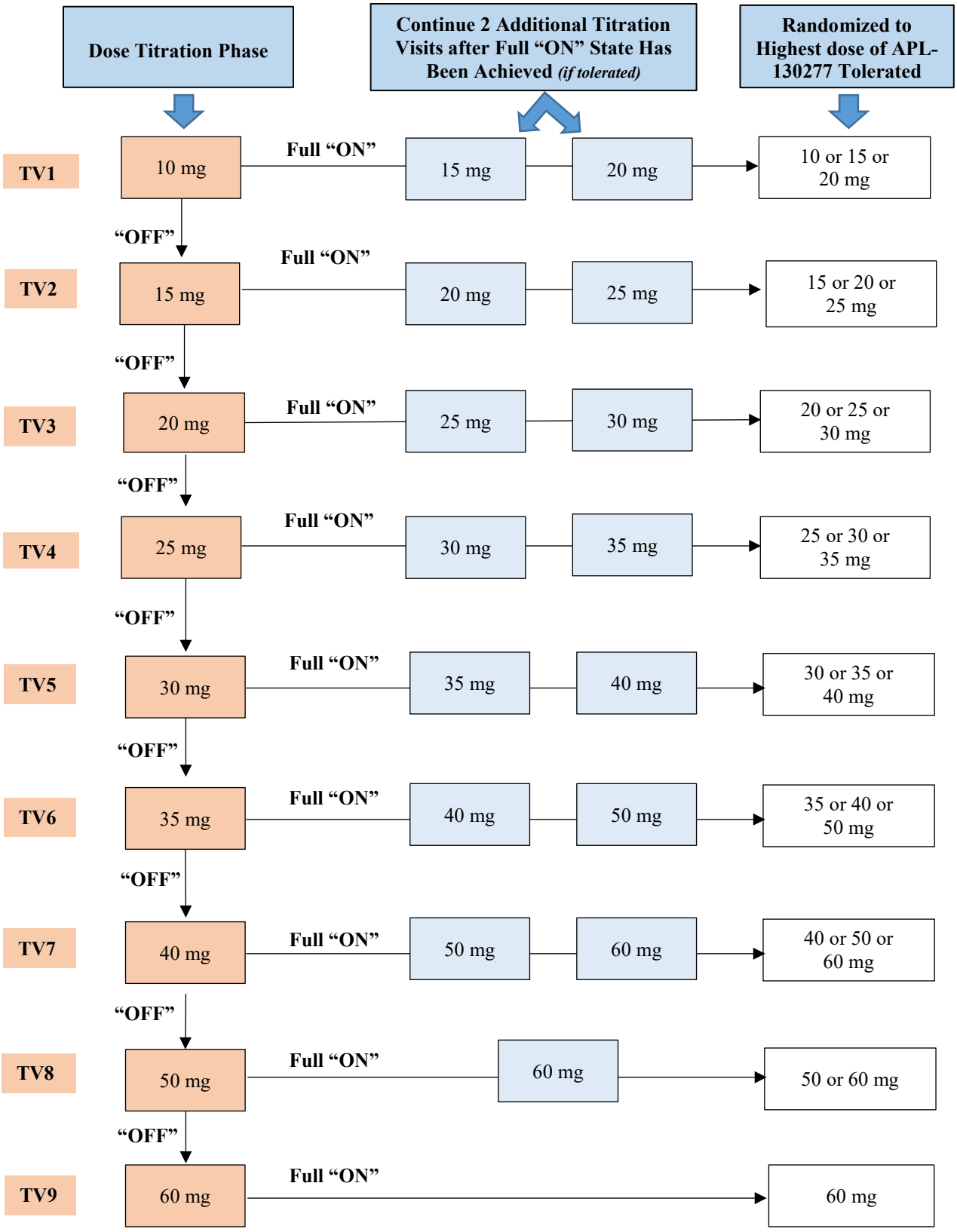
4.2 Study Design



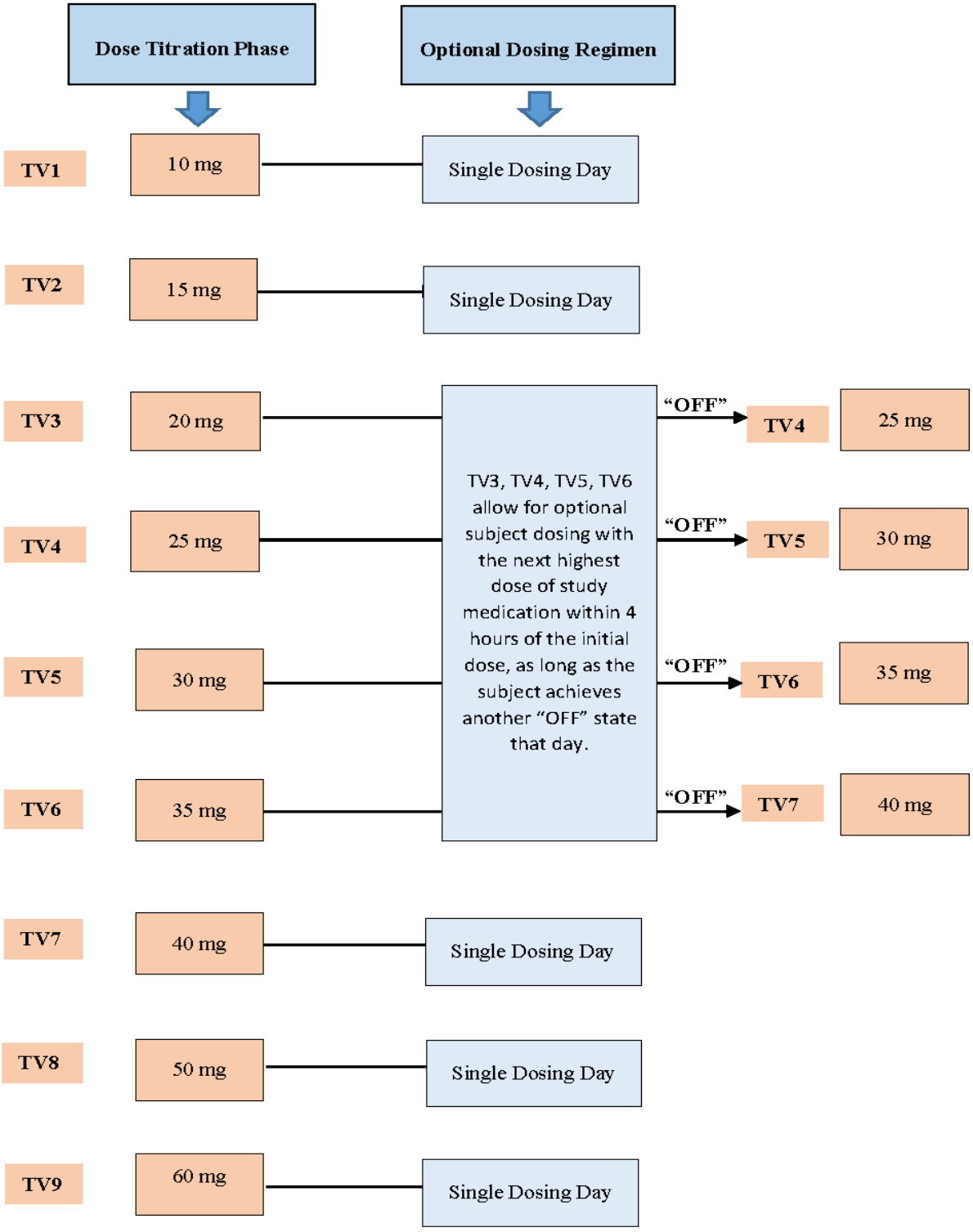
Forced Titration Until "ON" is Achieved and then Two Additional Doses if Tolerated

Randomized to Highest APL-130277 Dose Tolerated

4.3 Titration Phase Dosing Paradigm



4.4 Titration Phase Optional Dosing Regimen



5 TABLE OF CONTENTS

6 LIST OF ABBREVIATIONS

$5HT_3$	5-hydroxy tryptophan (serotonin)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APO-go®	apomorphine hydrochloride injection
APOKYN®	apomorphine hydrochloride injection
API	active pharmaceutical ingredients
AUC_{last}	area under the concentration-time curve from time zero to the last measurable plasma concentration-time curve using the linear up log down trapezoidal rule.
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity using the linear up log down trapezoidal rule.
AST	aspartate aminotransferase
b.i.d.	twice daily
BLQ	Below the limit of quantification
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
COMT	Catechol O-methyltransferase
CR	chronic release
CRA	Clinical Research Associate
CRF	case report form
CSA	clinical study agreement
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	coefficient of variation
EAC	enrollment adjudication committee
ECG	electrocardiogram
EDC	electronic data capture
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
L-Dopa	L-3,4-dihydroxyphenylalanine or Levodopa
LC-MS/MS	liquid chromatography-tandem mass spectrometry
λz	terminal-phase rate constant
MAO-B	monoamine oxidase B
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measurements
MRT	mean residence time
MMSE	Mini-Mental State Examination
NYHA	New York Heart Association
OH	Orthostatic Hypotension
PD	Parkinson's disease
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PMAP	pharmacokinetic modeling analysis plan
QTc	Corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
RR	respiratory rate
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SOP	Standard Operating Procedure
Sunovion	Sunovion Pharmaceuticals Inc.
$t_{½}$	Terminal-phase half-life
TdP	Torsades de Pointes
TEAE	treatment emergent adverse events
Temp	temperature
t.i.d.	three times daily
T_{max}	observed time of the maximum concentration
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

7 INTRODUCTION

7.1 Background

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. PD has a prevalence of approximately 0.5% to 1% among persons 65 to 69 years of age, rising to 1% to 3% among persons 80 years of age and older.[1] The disease is characterized by progressive degeneration of the dopaminergic nigrostriatal system and depletion of dopamine, which results in the core motor symptoms of bradykinesia, rigidity, tremor, and postural instability.[2] During the early stages of the disease, motor symptoms are well controlled with L-Dopa plus a dopamine decarboxylase inhibitors, dopamine agonists or MAO-B inhibitors. However, as the disease progresses, PD subjects develop motor complications which consist of dyskinesia and motor fluctuations. Motor fluctuations represent periods of "OFF" time and include wearing-"OFF", delayed "ON" (if with first morning dose termed morning akinesia), unexpected "OFF" or "ON"/"OFF" fluctuations. These motor fluctuations can be either predictable or unpredictable. The mechanisms by which response fluctuations occur are only partially understood but are thought to include presynaptic neuronal degeneration leading to a lack of buffering of released L-Dopa, postsynaptic changes in dopamine receptor sensitivity and number, and pharmacokinetic and pharmacodynamic influences of exogenously administered dopaminergic agents.[3,4] Fluctuations in plasma levels of L-Dopa occur due to the short half-life of L-Dopa and the unpredictable variability of gastric emptying. In general, approximately 40% of subjects with PD experience motor fluctuations and/or dyskinesias after 4 to 6 years of L-Dopa therapy, with close to 90% of subjects experiencing these symptoms after 9 or more years of treatment.[5]

Predictable motor fluctuations (i.e. wearing-"OFF") can be treated by increasing the dose or frequency of L-Dopa or by adding adjunctive PD medications (Catechol O-methyltransferase [COMT] inhibitors, MAO-B inhibitors, dopamine agonists). However, over time this becomes less effective. Treatment of unpredictable motor fluctuations (i.e. delayed "ON", sudden "OFF", "ON"/"OFF" fluctuations) is limited. Some subjects take oral L-Dopa immediate release as needed but this is of limited value as higher doses of L-Dopa can result in dyskinesia and perpetuates the development of further motor complications. The only approved treatment for acute management of "OFF" episodes in North America, Europe and Asia is apomorphine delivered subcutaneously (s.c.). Although efficacious, s.c. apomorphine has limited use due to its parenteral administration and since it may be difficult for a PD patient to deliver. There remains a huge unmet medical need for easy to administer, rapid, safe, effective and reliable rescue medications for the treatment of these "OFF" episodes in PD subjects. APL-130277, sublingually administered apomorphine, provides a more patient-friendly, easy to administer medication for the management of both predictable and unpredictable "OFF" episodes.

Apomorphine is a non-ergot dopamine agonist that binds to D1-like and D2-like receptors. First used as a treatment for PD as early as 1951, its clinical use was first reported in 1970 although its emetic properties and short half-life made oral use impractical. A later study found that combining the drug with 10 mg domperidone improved results significantly.[6-10]

APOKYN® and APO-go® (apomorphine hydrochloride injection, see APPENDIX I: APOKYN® Prescribing Information and APO-go® Summary of Product Characteristics) are prescription medicines that reverses "OFF" episodes (end-of-dose wearing-"OFF" and unpredictable "ON"-"OFF" episodes) associated with advancing PD. APOKYN®, which are indicated for the acute, intermittent treatment of hypomobility, "OFF" episodes associated with advanced PD, has been studied as an adjunct to other PD medications. Therapeutic use in PD is effective because of the drug's strong dopaminergic action. When administered subcutaneously, apomorphine is the most effective dopamine agonist. Within 3-20 minutes of injection, apomorphine demonstrates a magnitude of effect (ability to convert the patient with PD to the "ON" state) that is comparable to L-Dopa. The effects of a single s.c. injection last for 60 minutes. Apomorphine can be used in combination with L-Dopa. L-Dopa dosing may need to be readjusted (decreased) to reduce dopa-induced dyskinesias periods.[6-10]

Subcutaneous injection of apomorphine was developed to avoid first-pass metabolism as apomorphine is almost completely metabolized when delivered orally (between 1-2% of the total dose enters the bloodstream following oral administration). The total daily dose can range up to 20-25 mg/daily. Domperidone, a peripheral dopamine antagonist, may be administered to avoid emesis, bradycardia and hypotension caused by apomorphine's peripheral dopaminergic action. Subjects on chronic apomorphine treatment may be able to discontinue domperidone co-administration after about 2 months without recurrence of the dopaminergic adverse effects of apomorphine. Domperidone is not available in the US, where trimethobenzamide is used.

There is a small dose related prolongation of QTc interval with single doses of APOKYN®/APO-go® greater than 6 mg (see APPENDIX I: APOKYN® Prescribing Information and APO-go® Summary of Product Characteristics). This study will evaluate the QT interval prolongation potential of APL-130277.

7.2 Drug Substance

The active ingredient is apomorphine hydrochloride hemihydrate ($C_{17}H_{17}NO_2$•HCl •½H_2O(salt)). Apomorphine is synthesized from morphine, but it is not a narcotic, nor is it a controlled substance. Apomorphine hydrochloride appears as white or greyish-white glistening crystals or white powder. The R-enantiomer is used clinically.

The drug substance, apomorphine hydrochloride hemihydrate, is manufactured by Sanofi-Aventis. Apomorphine hydrochloride is manufactured from morphine monohydrate in the presence of orthophosphoric acid, ethyl acetate and hydrochloric acid. Purification is performed

in the presence of water, sodium chloride, sodium sulfite, ethyl acetate and silica gel.

A summary of physico-chemical data are provided below:

Active Pharmaceutical Ingredients (API) Common Name	Apomorphine Hydrochloride Hemihydrate
Production Site	Manufacturer of Active Pharmaceutical Ingredient for Clinical Batches: Sanofi Aventis (Aramon Site) SANOFI CHIMIE Route d'Avignon 30390 Aramon France
IUPAC nomenclature	4H-Dibenzo [de, g] quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl hydrochloride, hemihydrate
Synonyms, common names	Apomorphine hydrochloride, SR94013A, 6a,beta-aporphine-10,11-diol hydrochloride
CAS number	41372-20-7
Formula	$C_{17}H_{17}NO_2 \bullet HCl \bullet {}^1/_2H_2O$
Molecular weight	312.79 g/mol
Specific Rotation	-60.5^o to -63.0^o
pKa	pKa: 7.0, 8.9
pH	4.3
Water solubility	Sparingly soluble in water and alcohol; slightly soluble in chloroform

7.3 Drug Product (APL-130277 Sublingual Film)

The product under development, APL-130277, is a soluble thin film for sublingual administration. APL-130277 is designed to deliver apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing the extensive first pass metabolism associated with gastrointestinal absorption of the compound. The product is intended to be an alternative to the injectable form of apomorphine hydrochloride, which is marketed in North America as APOKYN® and in most of Europe and Asia as APO-go®.

APL-130277 is manufactured for clinical studies as a bilayer thin film with one layer containing the active ingredient, apomorphine hydrochloride, and the other layer containing a buffer, pyridoxine. Dosage units of 10, 15, 20, 25, and 30 mg are achieved from a single formulation by cutting different sized rectangular thin films from sheets of bulk film as shown in the table below. Identifying marks are printed in white ink on the buffer (pyridoxine) side of the

sublingual thin film.

APL-130277 Dose (mg)	Length (mm)	Width (mm)	Area (mm^2)	Identifying Mark
10	22	8.8	193.6	C1
15	22	13.2	290.4	C2
20	22	17.6	387.2	C3
25	22	22	484.0	C4
30	22	26.4	580.8	C5

To administer the 35 mg dose, study staff will administer the 20 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, immediately administer the 15 mg sublingual thin film for another 3 minutes (total dosing time should be 6 minutes).

To administer the 40 mg dose, study staff will administer the 20 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 20 mg dose, and staff will ensure the sublingual space is free of excess water. The second 20 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).

To administer the 50 mg dose, study staff will administer the 25 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 25 mg dose, and staff will ensure the sublingual space is free of excess water. The second 25 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).

To administer the 60 mg dose, study staff will administer the 30 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 30 mg dose, and staff will ensure the sublingual space is free of excess water. The second 30 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).

The APL-130277 finished drug product will be manufactured at ARx, LLC facilities at: 400 Seaks Run Road Glen Rock, PA 17327, USA.

The formulations for each of the dosage strengths have exactly the same proportions of active pharmaceutical ingredient and inactive excipients.

The formulation consists of pharmaceutically acceptable cellulosic film formers along with glycerin as a plasticizer; and flavor, sweetener and colour additives for patient

acceptability. Other excipients include sodium hydroxide to modify pH and sodium metabisulfite as an antioxidant/preservative. The formulation also includes pyridoxine HCL as a buffer component. The excipients used in formulating APL-130277 sublingual thin films, are compendial (USP, NF or FCC) items and/or are Generally Recognized as Safe (GRAS) and/or have precedent for use in pharmaceutical products approved in the US.

7.4 Clinical Experience

This is the twelfth planned in-man study for APL-130277. Previous studies CTH-101, CTH-102, CTH-103, CTH-104, CTH-106, CTH-107 and CTH-200 were performed in healthy volunteers in Malaysia, all at Info Kinetics. The first study completed in a PD patient population, CTH-105, was conducted at 4 sites in North America. CTH-203, CTH-300 and CTH-301, evaluating APL-130277 in a PD patient population, are being conducted and CTH-302 is planned for later this year.

The healthy volunteer studies are summarized in considerable detail in the Investigator's Brochure (IB). Adverse events were those expected to be seen with apomorphine, with the most common AEs being somnolence, dizziness and nausea. No dose limiting side effects were encountered and no subjects discontinued APL-130277 treatment due to an AE.

The healthy volunteer studies confirmed the method of administration, allowed further refinement of the formulation and confirmed PK comparability of APL-130277 to s.c. apomorphine. The CTH-103 and CTH-104 PK study results demonstrated dose proportionality of the doses of APL-130277 tested (10 mg, 15 mg, 25 mg) and that the 25 mg dose is sustained over an extended period of time (162 minutes) above the minimal efficacious plasma concentration of apomorphine (approximately 3 ng/mL), believed to be a level demonstrating symptomatic relief of "OFF" symptoms. The T_{max} for the 25 mg dose of APL-130277 was approximately 40 minutes, which was similar for the 10 mg and 15 mg doses of APL-130277. The rapid uptake of apomorphine in the APL-130277 sublingual thin film is comparable to that described in the s.c. apomorphine labels (i.e., between 10 and 60 minutes).

The PD subjects dosed in CTH-105 (19 subjects) displayed similar side effects to that seen in healthy volunteers; the most common AEs (seen in 2 or more subjects) were dizziness, somnolence, nausea, yawning, headache and hyperhidrosis. Most of these AEs were mild to moderate in severity. There was no dose-response relationship seen with the most common AEs and no subjects discontinued due to an AE. Local irritation of the oral mucosa was monitored in the study and none was noted.

The CTH-105 study demonstrated that APL-130277 provided rapid, clinically meaningful improvement in MDS-UPDRS Part III scores for PD subjects in the "OFF" state and converted most subjects from the "OFF" state to the "ON" state. Much of the benefit was sustained through 90 minutes. A range of doses were utilized but over half of the subjects responded to the two

lowest doses (10 and 15 mg).

The CTH-106 study results demonstrated that the orientation of the thin film does not have a meaningful impact on the bioavailability of apomorphine.

In CTH-107 and CTH-200, similar AEs were seen as in the previous healthy volunteer studies, and study analysis is ongoing.

7.5 Summary of Potential Risks and Benefits

APL-130277

Given that APL-130277 uses the same active pharmaceutical ingredient (API) as APOKYN® and APO-go®, and the pharmacokinetic profile is comparable between the sublingual thin film and the s.c. injection, the risks associated with the drug will be the same as those seen in the APOKYN® and APO-go® Product Inserts (see APPENDIX I: APOKYN® Prescribing Information and APO-go® Summary of Product Characteristics), except for the significant injection site reactions. It is assumed that the bioavailability of APL-130277 will be consistent in CTH-201 with that found in previous experience with APL-130277 compared with APOKYN® and APO-go®.

The buffer contained in the inactive layer of APL-130277 is designed to mitigate potential irritation of the oral mucosa seen in other buccal formulations of apomorphine as well as assist in maintaining a stable pH and optimal absorption kinetics. A preclinical hamster study demonstrated no evidence of microscopic or macroscopic irritation. No local irritation was noted in the CTH-105 study. In other ongoing clinical studies of APL-130277, non-serious AE reports of irritation of the oral mucosa have been received. Local irritation will be closely monitored throughout study participation. The goal of this development program, however, is to formulate a medication that provides the PD patient with an easier delivery system. We hypothesize that an orally available formulation will be easier to use, allow quicker control over predicted “OFF” periods, be more readily accessible to the patient when unpredicted “OFF” episodes occur during activities of daily living, and potentially be used by the milder PD patient when “OFF” episodes begin during the advancement of the disease.

Moxifloxacin

Moxifloxacin is an antibiotic belonging to the fluoroquinolones family and will be used as a reference product in this study.

Changes in cardiac electrophysiology have been observed following exposure to moxifloxacin, in the form of QT prolongation and is therefore contraindicated in patients with:

- Congenital or documented acquired QT prolongation;
- Electrolyte disturbances, particularly in uncorrected hypokalaemia;

- Clinically relevant bradycardia;
- Clinically relevant heart failure with reduced left-ventricular ejection fraction;
- Previous history of symptomatic arrhythmias.

The risk of cardiac abnormalities may increase with increased dose. There is a rare chance that patients may experience a severe, sudden allergic reaction (an anaphylactic reaction/shock) with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. Moxifloxacin may cause inflammation of the liver, diarrhea (during or after taking this type of antibiotic), and may occasionally cause pain and inflammation of tendons. Quinolone antibiotics may make the patient's skin become more sensitive to sunlight or UV light.

7.6 Rationale

This multi-center, Phase 2 study is designed to evaluate the QT interval prolongation potential of 10 mg to 60 mg doses of APL-130277 compared to placebo and the positive control, 400 mg moxifloxacin in subjects with PD who experience motor fluctuations (“OFF” episodes).

8 ETHICS

This study will be conducted in compliance with the principles established by the World Medical Assembly in the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects and all applicable amendments, the ICH Principles of Good Clinical Practice (GCP) (including archiving of essential study documents), and applicable regulatory requirements and guidelines.

A properly constituted, valid Institutional Review Board (IRB) or Research Ethics Board (REB) or Independent Ethics Committee (IEC) must review and approve the protocol, each Investigator's Informed Consent Form (ICF), and related subject information before the start of the study, and any subject recruitment material(s) before they are provided to subjects. During the Clinical Trial, any amendment or modification to the protocol should be submitted to the IRB/REB/IEC. The IRB/REB/IEC should also be informed of any event likely to affect the safety of subjects or the continued conduct of the study, in particular any changes in safety. All updates to the IB will be sent to the IRB/REB/IEC.

It is the responsibility of each Investigator to ensure that written informed consent is obtained from the subject before any study activity or procedure is undertaken.

9 OBJECTIVES AND STUDY ENDPOINTS

9.1 Objectives

The primary objective is to evaluate the effect of APL-130277 compared to placebo on QTc intervals in subjects with Parkinson's disease (PD) complicated by motor fluctuations.

The secondary objectives include the evaluation of safety and pharmacokinetics of APL-130277 and the comparison of efficacy of the highest tolerated dose level and the lowest APL-130277 dose resulting in a full "ON" during the Dose Titration Phase.

9.2 Study Endpoints

9.2.1 Primary Endpoint

1) Time-matched change from baseline in QTc, placebo-adjusted and corrected for HR based on the Fridericia correction method (QTcF) method (ΔΔQTcF). Assay sensitivity will be demonstrated by inclusion of a positive control, moxifloxacin.

9.2.2 Secondary Endpoints

1) Pharmacokinetics of apomorphine and apomorphine metabolites;
2) Evaluation of safety and tolerability of APL-130277 as measured by adverse events, physical examination including assessment of oropharyngeal adverse events, 12-lead ECGs, vital signs including orthostatic hypotension (OH), clinical laboratory tests, and C-SSRS assessments;
3) ECG assessments including QTc with Bazett correction (QTcB), heart rate, PR interval, QRS interval, uncorrected QT interval, ECG morphology and presence of cardiac arrhythmias such as ventricular tachycardia or Torsade de Pointes (TdP);
4) MDS-UPDRS Part III change from pre-dose to 30, 60, 90 minutes after dosing during the Titration Phase at the highest tolerated APL-130277 dose level and the lowest APL-130277 dose resulting in a full "ON";
5) Time to "ON" during Titration Phase at the highest tolerated APL-130277 dose level and the lowest APL-130277 dose resulting in a full "ON";
6) Duration of "ON" during Titration Phase at the highest tolerated APL-130277 dose level and the lowest APL-130277 dose resulting in a full "ON".

10 STUDY DESIGN

This is a multi-center, phase 2, randomized, double-blind, placebo controlled, 3-period crossover, positive control, QT-evaluation study of APL-130277 in subjects with PD complicated by motor fluctuations ("OFF" episodes).

10.1 General Overview

This study will commence with initial Screening Visits, followed by an open-label Dose Titration Phase in which individual responses to single doses of APL-130277 are evaluated in order to determine the dose for the Randomized Assessment Phase. APL-130277 and placebo will be double-blinded and randomized in a balanced three-way crossover Williams design with open-label moxifloxacin treatment (Period 1, Period 2 and Period 3).[11]

10.1.1 Screening Visits

Before any study procedures are performed on any subject, informed consent must be obtained at an initial Screening Visit (SV1). Subjects recruited to participate in the study, and who have provided full consent to participate, will be asked to attend a second Screening Visit (SV2), having taken their last dose of L-Dopa and any other adjunctive PD medication no later than midnight the evening prior to the visit. Their normal morning dose of L-Dopa (***without*** adjunctive PD medication) will be administered in the clinic following confirmation of an "OFF" episode by the Investigator and subject, to ensure that they experience an "ON" response. Eligibility criteria will be assessed by the Investigator and approved by the Enrollment Authorization Committee (EAC) prior to enrollment.

Subjects will be asked to return to the clinic the morning of Titration Visit 1 (TV1) to start the Dose Titration Phase of the study.

If needed, the site will arrange subject transfers. Alternatively, subjects may be monitored in the clinic overnight to facilitate "OFF" evaluation the following morning if such facilities exist and the subject consents. These occurrences will not be considered a SAE.

10.1.2 Dose Titration Phase

Depending on the Investigator's decision, subjects will be asked to arrive at the clinic:

- after their usual morning dose of PD medications; but before taking their next dose of medication; OR
- after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior).

During the Dose Titration Phase of the study, subjects will start with a dose of 10 mg APL-130277 and increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full "ON" state. Once a full "ON" state

is achieved, dosing will continue for 2 additional visits to a maximum dose of 60 mg (i.e., if a subject experiences the first full “ON” at 10 mg, dosing will continue up until a dose of 20 mg).

For those subjects who do not achieve a full "ON" response, titration should continue until the maximum tolerated dose of APL-130277 is determined.

Note: For subjects who have previously participated in the CTH-300 or CTH-301 study, the subject will begin titration at the effective dose used in the respective previous study. Similarly dose titration of these subjects will increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full “ON” state. Once a full “ON” state is achieved, dosing will continue for 2 additional visits to a maximum dose of 60 mg (i.e., if a subject experiences the first full “ON” at 35 mg, dosing will continue up until a dose of 50 mg).

At Titration Visit 1 (TV1), once the subject's “OFF” state has been confirmed by both the Investigator and subject, the subject will be treated with 10 mg APL-130277. Subjects who tolerate the 10 mg APL-130277 will restart their normal PD medications and will be asked to return to the clinic the next business day for Titration Visit 2 (TV2), to assess the next highest dose (i.e., 15 mg) in a manner identical to that of Titration Visit 1 (TV1).

Doses of APL-130277 will increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until a full “ON” state is achieved, then dosing will continue for 2 additional visits to a maximum dose of 60 mg. This will sequentially be 20 mg (TV3), 25 mg (TV4), 30 mg (TV5), 35 mg (TV6), 40 mg (TV7), 50 mg (TV8) and 60 mg (TV9).

For Titration Visit 3 (TV3), Titration Visit 4 (TV4), Titration Visit 5 (TV5) and Titration Visit 6 (TV6) subjects should be dosed with the next highest dose of study medication within 4 hours of the dose, as long as the subject achieves another “OFF” that day. TV3 should be paired with TV4 (20 mg and 25 mg can be dosed on the same day); TV4 should be paired with TV5 (25 mg and 30 mg can be dosed on the same day), TV5 should be paired with TV6 (30 mg and 35 mg can be dosed on the same day) and TV6 should be paired with TV7 (35 mg and 40 mg can be dosed on the same day).

Should the subject be unable to tolerate either of the two additional dose levels after reaching a full “ON” state, in the Investigator’s opinion, due to adverse events commonly associated with apomorphine (e.g., orthostatic hypotension, nausea, vomiting, etc.), subjects will be randomized to the previous dose.

Dosing days in the Dose Titration Phase should be scheduled on consecutive business days and a maximum of 2 days between visits may be permitted with Medical Monitor approval. All visits in the Dose Titration Phase must be completed within 14 days.

Safety and efficacy assessments will be performed at each visit according to the protocol.

10.1.3 Three-Way Balanced Randomized Crossover Assessment Phase: Period 1, Period 2, Period 3

Subjects who successfully complete the Dose Titration Phase of the study, and are approved by the Sponsor to proceed to randomization, will be asked to return to the clinic for Period 1 Dosing Visit 1 (P1V1). This visit will occur between 2 and 7 days after the final visit in the Dose Titration Phase of the study. Depending on the Investigator's decision, subjects will be asked to arrive at the clinic:

- after their usual morning dose of PD medications; but before taking their next dose of medication; OR
- after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior).

Subjects will be randomized in equal numbers to six possible sequences of each of the three treatments being studied:

1. Treatment A: APL-130277 at the dose determined in the Dose Titration Phase,
2. Treatment B: Matched placebo APL-130277,
3. Treatment C: A single 400 mg dose of moxifloxacin.

Following confirmation by both the Investigator and subject that the subject is in the “OFF” state, the subject will be dosed according to the subject's random treatment assignment. APL-130277 and placebo APL-130277 will be administered in a double-blind fashion and moxifloxacin will be administered open-label in a three-way balanced crossover. All subjects will be exposed to all three treatments. The six possible treatment sequences are: 1) ABC; 2) ACB; 3) BCA; 4) BAC; 5) CAB; and 6) CBA.

Subjects will return to clinic 3 days after Period 1 and will be dosed for Period 2 with one of the other two treatments.

Subjects will return to clinic 3 days after Period 2 and will be dosed for Period 3 with the third and last treatment.

At the Period 1 Dosing Visit 1 (P1V1), three (3) sets of triplicate 12-Lead ECGs will be obtained using a continuous 12-lead Holter monitor over approximately 1-hour (prior to dosing) as the baseline assessment for analyses defined in Section 15.4.3.

10.1.4 Enrollment Adjudication Committee (EAC)

The Investigator must obtain approval from the EAC and Sponsor prior to enrolling any subject into the study. The EAC will determine the subject’s appropriateness for inclusion in the study, independent of the entry criteria. The EAC will consult with the Medical Monitor, and the Investigator as appropriate, to address and resolve any outstanding questions or issues.

The EAC review should be completed within 48 hours of submitting a request, and the Investigator will be informed of the decision. Following EAC/Sponsor approval, the final determination of eligibility for enrollment in the study will be made by the Investigator, who will then submit a request via the IWRS for enrollment into the Dose Titration Phase of the study. In case of refusal, the decision will be accompanied by a rationale. For additional details, please refer to the Enrollment and Randomization Adjudication Process, which is contained in a separate document.

A dedicated charter will be developed in order to address the mode of operations of the EAC to ensure the integrity of the study will be protected. The communication from the EAC, documenting review and approval of the subject, will serve as EAC documentation for inclusion into the study and must be stored in the site study file.

11 PATIENT POPULATION

11.1 Selection of Study Population

A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at each study site.

The study will require forty-two (42) subjects to complete the 3-period, single dose crossover phase. Recruitment will continue until the required number of subjects completes the study.

11.1.1 Inclusion Criteria

Subjects who meet each of the following criteria will be eligible for participation in the study:

1) Male or female ≥ 18 years of age.
2) Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria (excluding the "more than one affected relative" criterion).
3) Clinically meaningful response to Levodopa (L-Dopa). Subjects with or without well-defined "OFF" episodes, as determined by the Investigator, will be allowed.
4) Receiving stable doses of L-Dopa/carbidopa (immediate or sustained release) administered at least 3 times per day OR Rytary™ administered 3 times per day, for at least 4 weeks before the initial Screening Visit (SV1). Subjects receiving L-Dopa/carbidopa 3 times a day must also be on stable treatment with adjunctive PD medication regimens. These regimens must be maintained at a stable dose for at least 4 weeks prior to the initial Screening Visit (SV1) with the exception that MAO-B inhibitors must be maintained at a stable level for at least 8 weeks prior to the initial Screening Visit (SV1).
5) No planned medication change(s) or surgical intervention anticipated during the course of study.
6) The subject must be able to have a drug withdrawal induced "OFF" episode.
7) Stage III or less on the modified Hoehn and Yahr scale in the "ON" state.
8) Mini–Mental State Examination (MMSE) score > 21.
9) If female and of childbearing potential, must agree to use one of the following methods of birth control throughout the study and until at least 30 days after final drug administration:
    - Oral contraceptive;
    - Contraceptive patch;
    - Barrier (diaphragm, sponge or condom) plus spermicidal preparations;

- Intrauterine contraceptive system;
- Levonorgestrel implant;
- Medroxyprogesterone acetate contraceptive injection;
- Complete abstinence from sexual intercourse;
- Hormonal vaginal contraceptive ring; or
- Surgical sterilization or partner sterile (must have documented proof).

10) Male subjects must be either surgically sterile, agree to be sexually abstinent or use a barrier method of birth control (e.g., condom) from first study drug administration until at least 30 days after final drug administration.
11) Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.
12) Able to understand the consent form, and to provide written informed consent.
13) Must be approved as a satisfactory candidate by the Enrollment Authorization Committee (EAC) and the Sponsor.

11.1.2 Exclusion Criteria

Subjects will be excluded from participation in the study for any of the following reasons:

1) Atypical or secondary parkinsonism.
2) Nausea associated with the use of dopamine agonists that requires treatment with an anti-emetic.
3) Previous treatment with any of the following: a neurosurgical procedure for PD; continuous subcutaneous (s.c.) apomorphine infusion; or Duodopa/Duopa.
4) Treatment with any form of s.c. apomorphine within 7 days prior to the initial Screening Visit (SV1). Subjects that stopped s.c. apomorphine for any reason other than systemic safety concerns or lack of efficacy may be considered.
5) Contraindications to moxifloxacin or APOKYN®, or hypersensitivity to apomorphine hydrochloride or any macrolide antibiotic or any of the ingredients of APOKYN® (notably sodium metabisulfite).
6) Female who is pregnant or lactating.
7) Participation in a clinical trial within 30 days prior to the initial Screening Visit (SV1), with the exception of clinical studies related to APL-130277.
8) Receipt of any investigational (i.e., unapproved) medication within 30 days prior to the initial Screening Visit (SV1), with the exception of APL-130277.

9) Any selective $5HT_3$ antagonists (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (including Tigan [trimethobenzamide] and domperidone, but excluding quetiapine or clozapine) or dopamine depleting agents within 30 days prior to initial Screening Visit (SV1).
10) Drug or alcohol dependency in the past 12 months.
11) Subject has a history of malignancy within 5 years prior to SV1, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Pituitary tumors of any duration are excluded.
12) Documented abnormalities with ECGs including, arrhythmias, clinically meaningful interval irregularities, structural heart abnormalities, myocardial infarction, presence or history of a pacemaker, or any abnormality of the ECG, that in the opinion of the Investigator, would interfere with the ability to measure the QT interval, or correct the QT interval for heart rate.
13) Male subjects with a screening corrected QT interval using Fridericia's formula (QTcF) of ≥ 450 ms; female subjects with a screening QT interval ≥ 470 ms. Eligibility will be based on the core laboratory ECG interpretation report.
14) HR at screening < 45 bpm or > 100 bpm.
15) QRS duration at screening > 120 ms.
16) PR interval at screening > 200 ms.
17) Subjects with a history of cataplexy, unexplained syncope or seizures.
18) Family history of sudden cardiac death.
19) Heart failure (NYHA Class II or greater) and/or a myocardial infarction.
20) Current use of any concomitant mediations that prolong the QT/QTc interval. Refer to https://crediblemeds.org for listing.
21) History of additional risk factors for TdP (i.e., heart failure, hypokalemia, family history of Long QT Syndrome).
22) Clinically significant medical, surgical, or laboratory abnormality in the opinion of the Investigator.
23) Subject has a positive screening laboratory test result for human immunodeficiency virus (HIV).
24) Subject has a positive screening laboratory test result for hepatitis B surface antigen or hepatitis C antibodies and has liver function test results at screening above the ULN for the reference laboratory.

25) Major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis (including Parkinson's disease psychosis), or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.

26) History of clinically significant impulse control disorder(s).

27) Dementia that precludes providing informed consent or would interfere with participation in the study.

28) Current suicidal ideation within one year prior to the second Screening Visit (SV2) as evidenced by answering "yes" to Questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or attempted suicide within the last 5 years.

29) Donation of blood or plasma in the 30 days prior to first dosing.

11.2 Prior and Concomitant Treatments

11.2.1 Prohibited Treatments

The following concomitant treatments will not be allowed during the course of this study:

- Any form of s.c. apomorphine from 7 days prior to the initial Screening Visit (SV1) until study completion.
- Any selective $5HT_3$ antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron) from 30 days prior to the initial Screening Visit (SV1) until study completion.
- Dopamine antagonists (including Tigan [trimethobenzamide] and domperidone, but excluding quetiapine or clozapine) or dopamine depleting drugs.
- Deep brain stimulation or other neurosurgical procedure for the treatment of PD, continuous s.c. apomorphine infusion, or Duodopa/Duopa.
- Any medication that can prolong QT. Refer to https://crediblemeds.org for listing.

11.2.2 Permitted Treatments

The following concomitant treatments will be allowed during the course of the study:

- Stable doses of an L-Dopa formulation with or without other stable adjunctive PD therapies (from at least 4 weeks prior to the initial Screening Visit (SV1), with no planned medication changes during the study).
- Any other medication other than those identified in Section 11.2.1 are allowed, provided they are stable, with no planned medication changes scheduled during the study. Other therapies should only be administered as necessary for the treatment of the subject, at the

discretion of the Investigator. All concomitant medications must be recorded in the appropriate Case Report Form (CRF) for the subject.

11.3 Subject Withdrawal from the Study

Subjects may be withdrawn from participating in this study for the following:

1) If QT/QTc is > 500 ms and is an increase from screening of > 60 ms (to be confirmed by triplicate ECG). If a subject experiences an adverse event suggestive of torsade de pointes (TdP) the immediate management of TdP will be according to standard medical care as directed by the Investigator/primary care physician;
2) In order to protect their safety and/or well-being;
3) If they are unwilling or unable to comply with required study procedures;
4) If they withdraw their consent to participate in the study;
5) If the study is prematurely terminated by the Sponsor or Regulatory Authorities;
6) If they no longer meet the inclusion/exclusion criteria within the study.

Subjects will be advised that they are free to withdraw from the study at any time, for any reason, and without prejudice. Every reasonable and appropriate effort should be made by the Investigator to keep subjects in the study. However, subjects must be withdrawn from the study if the subject withdraws his or her consent to participate. In the event of subject withdrawal, the Investigator should attempt to determine the reason for the subject's withdrawal.

The reason for discontinuation and the date of withdrawal from the study will be recorded in the appropriate CRF. The Investigator should make at least 3 documented attempts to contact a subject who is lost to follow-up, with at least 1 attempt made by a certified letter. Documentation of contact attempts must be made in the subject's record.

Neither subjects withdrawing from the study nor those removed by the Investigator or Sponsor will be replaced. Subjects who are withdrawn from this study may not re-enter the study at a later date. The screening number for a withdrawn subject will not be reassigned to another subject.

If a subject is removed or withdraws from the study, the procedures outlined in the EOS Visit will be performed, where possible.

12 STUDY PROCEDURES

This study will consist of the following:

1) Screening Visits (SV1 and SV2)
2) Dose Titration Phase
    a. Titration Visit 1 (TV1)
    b. Titration Visit 2 (TV2)
    c. Titration Visit 3 (TV3)
    d. Titration Visit 4 (TV4)
    e. Titration Visit 5 (TV5)
    f. Titration Visit 6 (TV6)
    g. Titration Visit 7 (TV7)
    h. Titration Visit 8 (TV8)
    i. Titration Visit 9 (TV9)
3) Three-Way Balanced Randomized Crossover Assessment Phase
    a. Period 1 Dosing Visit (P1V1)
    b. Period 2 Dosing Visit (P2V2)
    c. Period 3 Dosing Visit (P3V3)
4) End of Study Visit (EOS)

12.1 Screening Visits (SV1 and SV2)

Subjects must sign an ICF before any screening-related procedures are performed at an initial Screening Visit (SV1). Following receipt of subject consent, the subject will be asked to return to the clinic for the second Screening Visit (SV2). All screening assessments must be performed within 14 days before Titration Visit 1 (TV1).

If required by the Investigator, and following receipt of subject consent, the Investigator may review the subject's medical history, BMI, height, weight, vital signs, ECGs and perform a complete physical examination at SV1 to determine if the subject may be eligible for study participation. If these assessments are done at SV1, the remaining procedures outlined below for SV2, including the assessment of L-Dopa responsiveness, will only be performed.

The following procedures will be performed by study staff at SV2:

- Reconfirm consent.

- Review inclusion/exclusion criteria.
- Record demographics and detailed medical history, including review of medications taken within 6 months prior to the initial Screening Visit (SV1), current treatment regimens, drug, alcohol and smoking history.
- Perform a complete physical examination, including an oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure height and weight; calculate BMI.
- Obtain a 12-lead ECG in triplicate using a resting ECG device for eligibility. Triplicate ECG should be completed within 5 minutes. ECGs will be centrally reviewed by the ECG laboratory and the result provided for eligibility.
- Record vital signs (BP, HR, RR and Temp), after the subject has been in a supine position for 5 minutes. Subject BP to be measured both supine and standing (within 3 minutes of standing).
- Collect blood and urine sample for clinical laboratory tests (hematology, chemistry, urinalysis and serology). Serum pregnancy test for females of child-bearing potential only.
- Assess suicidal ideation using C-SSRS (see APPENDIX V: Columbia Suicide Severity Rating Scale (C-SSRS)). The "Screening" scale should be used at this visit.
- Perform a MMSE.
- Assess subject using the Modified Hoehn and Yahr scale (see APPENDIX III: Modified Hoehn and Yahr Scale).
- Assess subject motor function using MDS-UPDRS Part III at t = 0 (just prior to L-Dopa administration), 30, 60 and 90 minutes after L-Dopa administration (see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS). These assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.
- Perform subject training in order to distinguish "OFF' versus "ON" episodes (see Section 12.6.3.1).
- Investigator confirmation of "OFF" or "ON". The subject must be in an "OFF" state prior to dosing to ensure they experience an "ON" response.
- Subject confirmation of "OFF" or "ON".

- Confirm L-Dopa responsiveness. Subjects will take their normal dose of L-Dopa without their normal adjunctive PD medication.
- Record any AEs/SAEs that have occurred after the informed consent was obtained.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- Subject inclusion into the study to be approved by the EAC.

The Investigator will review all information obtained from the screening procedures. If the subject is not eligible, the subject will be a screening failure and will not attend any other visits. Subjects who fulfill all entry criteria will be found eligible to participate in the trial and an appointment for Titration Visit 1 (TV1) will be made.

Eligible subjects will be asked to return to the clinic the morning of Titration Visit 1 (TV1) to start the Dose Titration Phase of the study.

12.2 Dose Titration Phase (TV1 to TV9)

Depending on the Investigator's decision, subjects will be asked to arrive at the clinic:

- after their usual morning dose of PD medications; but before taking their next dose of medication; OR
- after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior).

Once the subject's “OFF” state has been confirmed by both the Investigator and subject, the subject will be treated with 10 mg APL-130277 (TV1). Subjects who tolerate the 10 mg APL-130277 will restart their normal PD medication and will be asked to return to the clinic the next business day for Titration Visit 2 (TV2) to assess the next highest dose in a manner identical to that of TV1.

During the Dose Titration Phase of the study, subjects will start with 10 mg and increase in 5 mg increments up to 40 mg and in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full “ON” state. Once a full “ON” state is achieved, dosing will continue for 2 additional visits to a maximum dose of 60 mg (e.g., if a subject experiences the first full “ON” at 10 mg, dosing will continue up until a dose of 20 mg). Dosing days in the Dose Titration Phase should be scheduled the next business day after the previous visit and must be completed within 14 days.

- Titration Visit 1 (TV1) – 10 mg APL-130277;
- Titration Visit 2 (TV2) – 15 mg APL-130277;
- Titration Visit 3 (TV3) – 20 mg APL-130277;

- Titration Visit 4 (TV4) – 25 mg APL-130277;
- Titration Visit 5 (TV5) – 30 mg APL-130277;
- Titration Visit 6 (TV6) – 35 mg APL-130277 (20 mg sublingual thin film under the tongue for 3 minutes before placing the second 15 mg sublingual thin film, sequentially for another 3 minutes [total dosing time should be 6 minutes]);
- Titration Visit 7 (TV7) - 40 mg APL-130277 (20 mg sublingual thin film under the tongue for 3 minutes before placing the second 20 mg sublingual thin film, sequentially for another 3 minutes [total dosing time should be 6 minutes]);
- Titration Visit 8 (TV8) - 50 mg APL-130277 (25 mg sublingual thin film under the tongue for 3 minutes before placing the second 25 mg sublingual thin film, sequentially for another 3 minutes [total dosing time should be 6 minutes]);
- Titration Visit 9 (TV9) - 60 mg APL-130277 (30 mg sublingual thin film under the tongue for 3 minutes before placing the second 30 mg sublingual thin film, sequentially for another 3 minutes [total dosing time should be 6 minutes]).

For Titration Visit 3 (TV3), Titration Visit 4 (TV4), Titration Visit 5 (TV5) and Titration Visit 6 (TV6) **only**, subjects can be dosed with the next highest dose of study medication within 4 hours of the initial dose, as long as the subject achieves another "OFF" state that day.

- TV3 should be paired with TV4 (20 mg and 25 mg can be dosed on the same day);
- TV4 should be paired with TV5 (25 mg and 30 mg can be dosed on the same day)
- TV5 should be paired with TV6 (30 mg and 35 mg can be dosed on the same day).
- TV6 should be paired with TV7 (35 mg and 40 mg can be dosed on the same day).

After reaching a full "ON" state, the subject will continue with the next two Titration Visits. Should the subject be unable to tolerate one of the two additional dose levels after reaching a full "ON" state, in the Investigator's opinion, due to adverse events commonly associated with apomorphine (e.g., orthostatic hypotension, nausea, vomiting, etc.), subjects will be randomized to the previous dose.

Study staff will perform the following procedures at each Titration Visit:

- Reconfirm consent.
- Review restriction criteria.
- Perform an abbreviated physical examination, including oropharyngeal examination at t = 0 (just prior to dosing) and 120 minutes after dosing at TV1 to TV9. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the

tongue.

- Single 12-lead ECG will be obtained using a resting ECG device at t = 0 (just prior to dosing) and 45 minutes after dosing as a safety evaluation; assessment by the Investigator/ECG qualified person to be completed at the visit.
- Record vital signs (BP, HR, RR and Temp) at t = 0 minutes (just prior to dosing), 15, 45 and 60 minutes after dosing. Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Assess subject motor function using MDS-UPDRS Part III at t = 0 (just prior to dosing), 30, 60 and 90 minutes after dosing (see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)). These assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.
- Investigator confirmation of "OFF" or "ON". The subject must be in an "OFF" state prior to dosing in order to proceed with dosing. Investigator will assess "OFF"/"ON" state as part of the MDS-UPDRS Part III assessments.
- Subject confirmation of "OFF" or "ON". The subject must be in an "OFF" state prior to dosing in order to proceed with dosing.
- When subject is in the "OFF" state, dose with APL-130277.
- Subject will report the time when they turned to a full "ON" (if applicable) and report the time when they turned "OFF" following dosing (if it occurs within 90 minutes of dosing).
- Record any AEs/SAEs that have occurred since the last visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- Assess suicidal ideation using C-SSRS (see APPENDIX V: Columbia Suicide Severity Rating Scale (C-SSRS)). The "Since Last Visit" scale should be used at this visit.
- Subject inclusion into the Crossover Phase to be approved by Sponsor prior to Randomization.

If in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. Where possible, administration of rescue L-Dopa should be delayed until after the 60 minute efficacy assessments are complete.

If the subject receives rescue L-Dopa (± other adjunctive PD medication) as described above, subjects can return to the clinic on another day to resume the titration with the next highest dose.

12.3 Three-Way Balanced Randomized Crossover Assessment Phase: Period 1, Period 2, Period 3

Subjects who successfully completed the Dose Titration Phase will be asked to return to the clinic for Period 1 Dosing Visit 1 (P1V1). This visit will occur between 2 and 7 days after the final visit in the Dose Titration Phase of the study. Depending on the Investigator's decision, subjects will be asked to arrive at the clinic:

- after their usual morning dose of PD medications; but before taking their next dose of medication; OR
- after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior).

Following confirmation by both the Investigator and subject that the subject is in the “OFF” state, the subject will be randomized using the Williams design. Subjects will be randomized in equal numbers to six possible sequences of each of the three treatments being studied:

1. Treatment A: APL-130277 at the dose determined in the Dose Titration Phase,
2. Treatment B: Matched placebo APL-130277,
3. Treatment C: A single 400 mg dose of moxifloxacin.

APL-130277 and placebo will be administered in a double-blind fashion and moxifloxacin will be administered open-label in a three-way balanced crossover. All subjects will be exposed to all three treatments. The six possible treatment sequences are: 1) ABC; 2) ACB; 3) BCA; 4) BAC; 5) CAB; and 6) CBA. In Period 1, regardless of the randomized treatment assignment, the baseline ECG will be obtained over approximately 1-hour (prior to dosing) using a Holter monitor device. Three (3) sets of triplicate 12-lead ECGs will be used as the baseline assessment for analyses as defined in Section 15.4.3. Triplicate 12-lead ECGs will also be obtained at t = 15, 30, 45, 60 minutes after dosing and at 2, 3, 4, 8, 12, 24 hours after dosing.

Subjects will return to clinic 3 days after Period 1 and will be dosed for Period 2 with one of the other two treatments.

Subjects will return to clinic 3 days after Period 2 and will be dosed for Period 3 with the third and last treatment.

12.3.1 Double-Blind APL-130277 and Placebo Treatment Periods

The following procedures will take place at these visits except where explicitly noted:

- Reconfirm consent.
- Review restriction criteria.
- Perform an abbreviated physical examination, including oropharyngeal examination at

t = 0 (just prior to dosing) and 120 minutes after dosing. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

- Measure body weight.
- Triplicate 12-lead ECG will be obtained using a Holter monitor device at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes after dosing and at 2, 3, 4, 8, 12, 24 hours after dosing. If the treatment is administered in Period 1, t = 0 will be omitted and replaced by the baseline ECG baseline assessment described above in Section 12.3.
- A single 12-lead ECG will be obtained using a resting ECG device 60 minutes after dosing as a safety evaluation; assessment by the Investigator/ECG qualified person to be completed at the visit.
- Record vital signs (BP, HR, RR and Temp) at t = 0 minutes (just prior to dosing), and at 15, 45 and 60 minutes after dosing. Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Collection and processing of blood samples for PK assessment will occur at the following time points: t = 0 (just prior to dosing), 30, 45, 60 minutes after dosing and at 2, 4 hours after dosing.
- Investigator confirmation of “OFF” or “ON”. The subject must be in an “OFF” state prior to dosing in order to proceed with dosing.
- Subject confirmation of “OFF” or “ON”. The subject must be in an “OFF” state prior to dosing in order to proceed with dosing.
- When subject is in the “OFF” state, proceed with dosing according to the randomization scheme.
- Record any AEs/SAEs that have occurred since the last visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- Assess suicidal ideation using C-SSRS (see APPENDIX V: Columbia Suicide Severity Rating Scale (C-SSRS)). The “Since Last Visit” scale should be used at this visit.

If in the opinion of the Investigator the subject can no longer tolerate the “OFF” state at any point during the visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full “ON” state. Where possible, administration of rescue L-Dopa should be delayed until 120 minutes after dosing.

12.3.2 Open-Label Moxifloxacin Treatment Period

The following procedures will be conducted at this visit except where explicitly noted:

- Reconfirm consent.
- Review restriction criteria.
- Perform an abbreviated physical examination, including oropharyngeal examination at t = 0 (just prior to dosing) and 120 minutes after dosing. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure body weight.
- Triplicate 12-lead ECG will be obtained using a Holter monitor device at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes after dosing and at 2, 3, 4, 8, 12, 24 hours after dosing. If the treatment is administered in Period 1, t = 0 will be omitted and replaced by the baseline ECG baseline assessment described above in Section 12.3.
- A single 12-lead ECG will be obtained using a resting ECG device 60 minutes after dosing as a safety evaluation; assessment by the Investigator/ECG qualified person to be completed at the visit.
- Record vital signs (BP, HR, RR and Temp) at t = 0 minutes (just prior to dosing), 15, 45 and 60 minutes after dosing. Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Collection and processing of blood samples for PK assessment will occur at the following time points: t = 0 (just prior to dosing), 30, 60 minutes after dosing and at 2, 3, 4, 6, 8 hours after dosing.
- Investigator confirmation of “OFF” or “ON”. The subject must be in an “OFF” state prior to dosing in order to proceed with dosing.
- Subject confirmation of “OFF” or “ON”. The subject must be in an “OFF” state prior to dosing in order to proceed with dosing.
- When subject is in the “OFF” state, dose with 400 mg moxifloxacin.
- Record any AEs/SAEs that have occurred since the last visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- Assess suicidal ideation using C-SSRS (see APPENDIX V: Columbia Suicide Severity Rating Scale (C-SSRS)). The “Since Last Visit” scale should be used at this visit.

If in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. Where possible, administration of rescue L-Dopa should be delayed until 120 minutes after dosing.

12.4 End of Study Visit

Approximately 7 days following the completion of the study (after P3V3), subjects will be asked to return to the clinic for a final safety assessment visit. The following procedures will take place at this visit:

- Reconfirm consent.
- Perform a complete physical examination, including an oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure body weight.
- Triplicate 12-lead ECG will be obtained using a resting ECG device. Triplicate ECG should be completed within 5 minutes; assessment by the Investigator/ECG qualified person to be completed at the visit.
- Record vital signs (BP, HR, RR and Temp), after the subject has been in a supine position for 5 minutes. Subject BP to be measured both supine and standing (within 3 minutes of standing).
- Collect blood and urine sample for clinical laboratory tests (hematology, chemistry, urinalysis). Serum pregnancy test for females of child-bearing potential only.
- Assess suicidal ideation using C-SSRS (see APPENDIX V: Columbia Suicide Severity Rating Scale (C-SSRS)). The "Since Last Visit" scale should be used at this visit.
- Record any AEs/SAEs that have occurred since the last visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.5 Duration of Treatment

Subject participation in this study from Screening until final study completion is anticipated to be a maximum of 46 days.

12.6 Assessments

12.6.1 Order of Assessments

The following summarizes the suggested sequence of assessments prior to dosing during SV2, Dose Titration Phase and Periods 1, 2, and 3 of the study:

ECG – PK – Vitals – Efficacy

The following summarizes the suggested sequence of assessments after dosing during Dose Titration Phase and Periods 1, 2, and 3 of the study:

MDS-UPDRS Part III - Subject "OFF"/"ON" status – ECG – PK – Vitals

In the event the completion of the MDS-UPDRS Part III at a previous timepoint conflicts with other assessments that are scheduled, priority should be given to completing the MDS-UPDRS Part III first before conducting the remaining assessments.

12.6.2 Clinical Safety Assessments

12.6.2.1 Physical Examinations

Complete physical examinations at all scheduled timepoints must include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including the oral cavity (and oropharyngeal cavity examination); musculoskeletal system; central and peripheral nervous system; and skin; to be done at the second Screening Visit (SV2) and End of Study (EOS) Visit.

Abbreviated physical examinations at all scheduled timepoints must include head-eyes-ears-nose and throat; heart, lungs; abdomen; oropharyngeal cavity examination; and skin; to be done at t = 0 (just prior to dosing) and 120 minutes after dosing at visits TV1 to TV9, Period 1, Period 2, and Period 3.

All physical examinations performed in this study, whether complete or abbreviated, will include an oropharyngeal cavity examination by the Investigator (or designate trained to perform this examination) and will include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue. Each location within the oropharyngeal examination will be scored and graded as follows:

- Finding
    - None
    - Focal reddening
    - Multiple foci of reddening
    - Edema
    - Ulceration

- Grade
    - Mild
    - Moderate
    - Severe

All abnormal findings at baseline will be recorded on the Medical History/Concomitant Diagnoses page (or equivalent) of the CRF. New abnormal findings or a worsening of baseline conditions detected at follow-up physical examinations will be recorded as AEs on the CRF.

The Investigator (or designate) should evaluate each finding against AE criteria and complete the AE CRF, as appropriate. Photographs for reference may be taken by the Investigator (or designate) provided the subject provides consent to do so.

12.6.2.2 Vital Signs

Vital signs (HR, RR, BP and body temperature) will be measured at various timepoints after the subject has been in a supine position for 5 minutes. Vital signs will be measured at t = 0 (just prior to dosing), 15, 45, 60 minutes after dosing at all scheduled study visits. Vital signs (BP only) will also be measured within three minutes of standing at all timepoints. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.

Study personnel will carefully monitor subjects for signs of OH; defined as:

- a systolic BP decrease of ≥ 20 mmHg within three minutes of standing up from a supine position; and/or
- a diastolic BP decrease of ≥ 10 mmHg within three minutes of standing up from a supine position.

12.6.2.3 12-Lead ECG

12-lead ECGs will be performed as outlined in the protocol using two modalities, a continuous Holter monitor and a resting ECG device. Detailed instructions will be provided to study staff and subjects.

12-lead Holter Monitor: At the Period 1 Dosing Visit 1 (P1V1), three (3) sets of triplicate 12-lead ECGs will be obtained over approximately 1-hour (prior to dosing) as the baseline assessment for analyses defined in Section 15.4.3. Triplicate 12-lead ECGs will also be obtained at t = 15, 30, 45, 60 minutes after dosing and at 2, 3, 4, 8, 12, 24 hours after dosing. In Period 2 and Period 3, triplicate 12-lead ECG will be obtained at t = 0, 15, 30, 45, 60 minutes and at 2, 3, 4, 8, 12, 24 hours after dosing. **At each ECG extraction time points the subject must have rested in the supine position for 10 minutes prior to the nominal timepoint and 10 minutes**

after.

ECGs obtained using the continuous Holter monitor will be sent directly to the central core ECG laboratory contracted by the Sponsor and/or its designate. The Holter monitor results will not be provided to the site.

Resting ECG Device: At Screening Visit 2 (SV2) a triplicate 12-lead ECG will be obtained. Triplicate ECG should be completed with 5 minutes. The screening ECG will be centrally reviewed by the ECG Laboratory and the result provided for eligibility.

At each Titration Visit, a single 12-lead ECG will be performed at t = 0 (just prior to dosing) and 45 minutes after dosing. In Period 1, Period 2 and Period 3, a single ECG will be performed at t = 60 minutes after dosing. At the End of Study Visit (EOS), a triplicate 12-lead ECG will be obtained.

ECGs obtained using a resting ECG device will be used as a safety evaluation and assessed by the Investigator/ECG qualified person at each visit.

The following parameters will be reported in the CRF based on the safety ECGs:

- Heart rate
- PR interval
- QRS interval
- RR interval
- QT interval
- QTc Interval (Fridericia's correction)
- QTc Interval (Bazett's correction)

All safety ECGs should be assessed by the Investigator and deemed "Normal", "Abnormal, not clinically significant" or "Abnormal, clinically significant". Abnormal readings that, in the opinion of the Investigator are deemed clinically significant should be reported as AEs on the appropriate CRF page.

12.6.2.4 Modified Hoehn and Yahr

The Modified Hoehn and Yahr scale will be administered at the second Screening Visit (SV2) to verify subjects meet the eligibility criteria for this study. This will be conducted in the "ON" state.

12.6.2.5 Mini-Mental State Examination

Mini-Mental State Examination (MMSE) is used to evaluate a person's cognitive and mental function and will be administered at the second Screening Visit (SV2) to verify subjects meet the

eligibility criteria for this study.

12.6.2.6 Clinical Laboratory Tests

The following clinical laboratory test samples will be collected where documented:

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelet count (or estimate), white blood cell (WBC) count including differential.
Serum Chemistry:	albumin, total bilirubin, total protein, alkaline phosphatase, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea, creatinine, glucose, sodium, potassium, uric acid, globulin, vitamin B6. Serum pregnancy test will be performed on all females of child-bearing potential only.
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones.
Serology (at the Screening Visit only):	Human immunodeficiency virus (HIV), Hepatitis B surface antigen, Hepatitis C antibodies.

12.6.2.7 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all personnel involved in the drawing of blood and the handling of specimens in both the clinic and laboratory settings.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples may be outlined in the study Laboratory Manual. It is the responsibility of the Investigator to ensure all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

Blood and urine samples for hematology, serum chemistry, urinalysis, and serology will be sent to a central laboratory for analyses. Please see the Laboratory Manual for details.

12.6.2.8 C-SSRS

Formal assessments of subject suicidal ideation and behavior will be assessed at the second Screening Visit (SV2) and all following visits through to the End of Study (EOS). A final assessment will be performed at the time of termination, regardless if it is scheduled (i.e., at EOS) or an early termination/withdrawal.

At SV2 the C-SSRS 'Screening' assessment tool will be used. Subjects who answer 'Yes' to Questions 4 and 5 at this Visit should be excluded from participation in the study. All subsequent evaluations will utilize the C-SSRS 'Since Last Visit' assessment.

12.6.2.9 Medical History

At the Screening Visit (SV2), the Investigator (or designate) will review the subject's medical history in order to ascertain the subject's eligibility. The medical history should assess the subject's current PD medications, including medication name, dose, number of tablets per dose (if applicable), dosage units and frequency per day.

The medical history assessment will include a detailed assessment of the subjects PD history, including, but not limited to:

- Year of Diagnosis;
- Presence of a rest tremor at the time of diagnosis;
- Year when motor fluctuations began;
- Type of "OFF" episodes experienced (e.g., morning akinesia, wearing-"OFF", delayed "ON", dose failure, sudden "OFF");
- Number of "OFF" episodes per day;
- Typical length of "OFF" episodes.
- PD medications previously or currently taken, including:
    - Dopamine agonists;
    - MAO-B inhibitors;
    - COMT inhibitors;
    - Amantadine;
    - Anti-cholinergics.

12.6.3 Efficacy Assessments

12.6.3.1 Confirmation of "OFF" or "ON" Episodes

<u>"OFF" and "ON" Training of Subjects at SV2</u>

At Screening Visit 2 (SV2), subjects will present to the clinic having taken their last dose of L-Dopa and any other adjunctive PD medication no later than midnight the evening prior to the visit. Their normal morning dose of L-Dopa (**without** adjunctive PD medication) will be administered in the clinic. Prior to administration of their L-Dopa dose, subjects will be examined by the Investigator in order to verify that they are in the "OFF" state. If they are in the "OFF" state, the Investigator will educate the subject that this is an "OFF" period or "OFF"

episode. The Investigator should clearly explain to the subject that this "OFF" time is when their medication has worn off, and does not provide benefits in terms of mobility, slowness and stiffness.

Subjects will then take their next scheduled dose of L-Dopa. Once the Investigator determines that the subject is experiencing an "ON" state, they should educate the subject that this is an "ON" state. The Investigator should clearly explain to the subject that an "ON" episode is the period of time where their medication is providing benefit with regard to mobility, slowness and stiffness, and they feel they can perform normal daily activities. Once the subject has demonstrated understanding of the "OFF" and "ON" state, the training is complete. Successful completion and understanding of this training should be noted in the appropriate CRF.

Any subject who cannot differentiate between an "ON" and "OFF" state will be deemed a screen failure.

Definitions of Full "ON" and "OFF"

The following definitions will be used in this study:

"OFF" – defined as:

- A period of time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness;
- Confirmed by the Investigator using their clinical judgement as "OFF".
- Confirmed by the subject as "OFF".

Full "ON" as assessed by the subject – defined as:

- A period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a subject feels he/she can perform normal daily activities.
- A response comparable to or better than their normal response to PD medications prior to enrolling in the study.

Full "ON" as assessed by the Investigator – defined as:

- Based on clinical judgment, it is the period of time where the Investigator feels the medication is providing benefit with regard to mobility, stiffness and slowness and the subject has adequate motor function to allow them to perform their normal daily activities.

Clinical confirmation of the "OFF" state must occur prior to dosing a subject with study medication (or their standard L-Dopa dose at the second Screening Visit (SV2)). The same assessor should be utilized for each subject throughout the study.

Subjects must confirm they are in an "OFF" state prior to dosing with study medication (or their

standard L-Dopa dose at the second Screening Visit (SV2)).

The Investigator will assess “OFF”/” ON” state as part of the MDS-UPDRS Part III assessments.

At each Dose Titration, the subject will report the time when they turned to full “ON” (if applicable) and will report the time when they turned “OFF” following dosing (if it occurs within 90 minutes of dosing). The timing of this should begin when the subject is dosed with the study medication, APL-130277, and recorded with a suitable timing device. These times are to be documented on the appropriate form of the CRF.

12.6.3.2 MDS-UPDRS Part III

The Motor Function section (Part III) of the MDS-UPDRS will be administered at all visits where it is indicated.

Administration will be performed at t = 0 (just prior to dosing), 30, 60 and 90 minutes after dosing at the second Screening Visit (SV2) and during the Dose Titration Phase.

These assessments will exclude the “Dyskinesia Impact on Part III Ratings” and the Hoehn and Yahr staging. The modified Hoehn and Yahr will be used during the Screening Visit (SV2).

The MDS-UPDRS can only be performed by the Principal Investigator or Sub-Investigator who has been trained to perform this evaluation. In specific cases, another appropriately experienced and certified study staff member can perform the assessment if approved by the Sponsor.

12.6.3.3 Pharmacokinetic (PK) Evaluation

Blood draws for PK analyses on APL-130277 and placebo treatment days will occur at t = 0 (just prior to dosing), 30, 45, 60 minutes after dosing and at 2, 4 hours after dosing. On the moxifloxacin treatment day, blood draws will occur at t = 0 (just prior to dosing), 30, 60 minutes after dosing and at 2, 3, 4, 6, 8 hours after dosing. Sampling should occur as close as possible to the target time.

Instructions specific to PK draws will be outlined in the PK lab manual.

13 ADVERSE EVENTS

Adverse events will be recorded from the time of signing of the ICF by the subject through to 30 days after study completion or earlier, if warranted by a subject discontinuation.

13.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject (or patient) or clinical investigation subject (or patient) administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition.

13.1.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening;
- Requires in-subject hospitalization (being admitted) or prolongation of existing hospitalization;
- Results in permanent (persistent) disability/incapacity;
- Is a congenital anomaly;
- Is an important medical event.

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as **important medical events** that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject (or patient) or may require intervention to prevent another of the outcomes listed in the definition above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the investigational drug, or a hospital admission for a diagnostic evaluation of an AE, **does not** qualify the condition or event as an SAE.

A spontaneous abortion or congenital anomaly in an infant born to a mother who was exposed to

the investigational drug during pregnancy **is** an SAE. Because the effect of APL-130277 or apomorphine on human male reproduction has not been determined, all pregnancies (in the subject or the subject's partner) will be documented on the Pregnancy Reporting Form with expressed consent.

Due to the nature of subjects being enrolled in this study, and the given study objectives, subjects who are hospitalized for their titration and Period 1, 2 and 3 visit "OFF" episodes will not be considered a SAE.

13.1.3 Definition of Severity

The clinical "severity" of an AE will be classified as:

Mild:	Causes no limitation of usual activities.
Moderate:	Causes some limitation of usual activities.
Severe:	Prevents or severely limits usual activities.

13.1.4 Definition of Start Date, Stop Date, and Duration

Start Date:	The date at which the AE is first noted.
Stop Date:	The date at which the AE is known to be resolved. If it is not known to have stopped, then indicate "ongoing".
Duration:	A time in days, hours or minutes (this is optional).

13.1.5 Action(s) Taken

Actions taken may consist of:

None:	No actions taken.
Discontinued Investigational Drug:	Investigational drug was permanently discontinued because of the AE.
Change Investigational Drug:	Investigational drug was given at a lower dose, at a longer interval between doses, or was temporarily withheld because of the AE.

Treatment:	Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure.
Others:	Other actions, such as an operative procedure, were required because of the AE.

13.1.6 Definition of Expectedness

An expected AE is an AE for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected AE is an AE for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and (b) hepatitis with a first occurrence of fulminate hepatitis.

13.1.7 Adverse Events of Special Interest

Adverse events of special interest (AESI) for APL-130277 pertaining to irritation of the oral mucosa require immediate reporting (see Section 13.1.14) no matter if the event is serious or non-serious. These AESIs include, but are not limited to:

- Stomatitis
- Oral Ulcers

Note: Per their discretion, Investigators may use other terminology and/or descriptors pertaining to irritation of the oral mucosa.

Other AESIs for APL-130277 should be immediately reported only if they meet the serious criteria or lead to the discontinuation of the subject from the study. These AESIs include:

- Changes in QT.
- Orthostatic Hypotension.

13.1.8 Definition of Relationship to Investigational Drug(s)

The categories for classifying the Investigator's opinion regarding the relationship of an AE to investigational drug(s) are listed below:

Certain:	An AE occurring in a plausible time relationship to investigational drug administration and which cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.
Probable (likely):	An AE with a reasonable time sequence to administration of the investigational drug and which is unlikely to be attributed to concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.
Possible:	An AE with a reasonable time sequence to administration of the investigational drug, but which could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Unlikely:	An AE, including laboratory test abnormality, with a temporal relationship to investigational drug administration that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Not related:	An AE with sufficient evidence to accept that there is no causal relationship to investigational drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven; etc.).

13.1.9 Definition of Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Resolved;
- Resolved with sequelae;
- Ongoing;
- Death;

- Unknown.

Death should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for the AE attributed as the cause of death in the death certificate or summary.

13.1.10 Documentation of Adverse Events

The Investigator will monitor and/or ask about or evaluate AEs using non-leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term;
- When the AE first occurred (start date);
- When the AE stopped (stop date), or an indication of "ongoing";
- How long the AE persisted (optional);
- Severity of the AE;
- Seriousness;
- Actions taken;
- Outcome;
- Investigator opinion regarding the relationship of AE to the investigational drug(s).

13.1.11 Follow-up of Subjects With an Adverse Event

Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record.

13.1.12 Special Procedures for Managing AEs/SAEs and Need for Unblinding

If AEs occur in a subject which are not tolerable, or for which continued administration of investigational drug is not reasonable in view of the potential benefit to subject, the Investigator must decide whether to stop investigational treatment and/or treat the subject. Subject withdrawal should be avoided, if possible. If discontinuation of treatment occurs, every attempt should be made to restart study drug if medically appropriate, whatever the duration of discontinuation.

13.1.13 Notification of Serious Adverse Events

The Investigator must report all SAEs and pregnancies promptly to Sunovion or its designee, by completing the SAE form and submit by email (or fax) within 24 hours of first becoming aware of

the event. Email: sunovionsafety@druginfo.com or Fax: 1-855-278-6344.

The Investigator will be able to contact the study medical monitors. The North American Medical Monitor is Dr. Poonam Hundal (mobile: +1 (919) 592-1802 or email: Poonam.Hundal@increscarch.com) and the European Union Medical Monitor is Dr. Souad-Amel Kechairi (mobile: +33 (0) 6 13 56 67 03 or email: Souad-Amel.Kechairi@increscarch.com).

If a SAE is reported via telephone, the Investigator must follow up the initial telephone notification by completing the SAE form and submit by email (or fax).

At the time of the first notification of an SAE, the clinical site should provide the following information to the contact person, if available:

- Subject's study number and initials;
- Subject's date of birth;
- Subject's gender;
- Date of first dose of investigational drug(s);
- Date of last dose of investigational drug(s), if applicable;
- AE term;
- Time and date of occurrence of the event;
- A brief description of the event, outcome to date, and any actions taken;
- The seriousness criteria(on) that were met;
- Concomitant medication at onset of the event;
- Relevant medical history information;
- Relevant laboratory test findings;
- Investigator's opinion of the relationship to investigational drug(s);
- Whether and when the Investigator was unblinded as to the subject's treatment assignment.

Any missing or additional relevant information concerning the SAE should be provided in a written follow-up report.

The Sponsor or designee will promptly notify all clinical sites and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB), Research Ethics Board (REB), or Independent Ethics Committee (IEC) by the

Investigator or the appropriate person at the clinical site if required per IRB/REB/IEC guidelines.

13.1.14 Notification of Adverse Events of Special Interest

All AESIs pertaining to irritation of the oral mucosa (Section 13.1.7) must be reported immediately to the Sponsor regardless of seriousness or presumed relationship to study drug. All AESIs pertaining to irritation of the oral mucosa are considered immediately reportable events and must be reported within 1 business day of the Investigator or study center staff becoming aware of the event.

Similarly, any AESI related to:

- Changes in QT
- Orthostatic Hypotension

that meet the serious criteria or leads to the discontinuation of the subject from the study (Section 13.1.7), regardless of presumed relationship to study drug, must be reported to the Sponsor within 1 business day of the Investigator or study center staff becoming aware of the event.

AESIs that require immediate reporting should be submitted via Email: sunovionsafety@druginfo.com or by Fax: 1-855-278-6344.

14 TREATMENTS

14.1 Treatments Administered

APL-130277 is a near square bilayer film containing apomorphine hydrochloride. APL-130277 is intended for fast sublingual absorption for use in rescue therapy for acute intermittent "OFF" episodes experienced by PD subjects. APL-130277 bilayer is composed of 2 layers laminated together: a first layer is composed of cellulose-ether based film, containing drug substance, stabilizers and plasticizers; a second layer contains a pH-modifier (pyridoxine hydrochloride) contained within a similar cellulosic film base, flavor agents and a permeation enhancer. Buffer layer will be on the side of the sublingual film that has an alphanumeric printing.

APL-130277 sublingual thin films will be provided in 5 strengths: 10 mg, 15 mg, 20 mg, 25 mg and 30 mg. Two sublingual thin films will be administered sequentially to form the 35 mg dose, 40 mg dose, 50 mg dose and 60 mg dose (as described below). In this study, placebo sublingual thin films will be prepared, which will be identical in appearance, size and colour, but contain no active ingredient (i.e., apomorphine).

Moxifloxacin 400 mg tablets will be provided to the site for oral administration.

14.2 Administration of Study Medication

During all phases of this study; subjects will be dosed by study staff.

Dose Administration for APL-130277 and Placebo:

Before dosing, the study staff will read out to subjects:

"The product is a film. It will be placed against the bottom of the tongue. After the dose is placed in the mouth, close your mouth naturally. Let your tongue take a natural position. Do not move the tongue around to try to taste the drug or change its position. Just let it slowly dissolve in place. It will dissolve in 3 to 4 minutes. During that time try not to swallow saliva or the film. When the film is dissolved, raise your hand to let the clinical staff know. We will ask that you open your mouth to show us."

Subjects will be instructed to consume a glass of water immediately prior to dosing, and staff will ensure the sublingual space is free of excess water.

Using gloved hands, or a single-use plastic disposable tweezers, staff will place the product beneath the tongue, with the drug side facing up and placed against the bottom of the tongue (i.e., the side of the film that does not have an alphanumeric printing), and ask subjects to close their mouth naturally. Subjects should not swallow the medication and should also try not to swallow their saliva for at least 3 minutes. If, upon inspection at the 3 minute mark, the film is not completely dissolved, subjects should be instructed to close their mouth and hold the study medication under their tongue for another minute (i.e., maximum of 4 minutes in total).

If the subject feels the film has fully dissolved prior to the 3 minute mark, they should indicate this to staff by raising their hand, who will then verify. If upon inspection, the film is not completely dissolved, subjects should be instructed to close their mouth again and hold the study medication under their tongue. Staff may verify at regular intervals, as appropriate, for a duration maximum of 4 minutes in total.

To administer the 35 mg dose, study staff will administer the 20 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, immediately administer the 15 mg sublingual thin film for another 3 minutes (total dosing time should be 6 minutes).

To administer the 40 mg dose, study staff will administer the 20 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 20 mg dose, and staff will ensure the sublingual space is free of excess water. The second 20 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).

To administer the 50 mg dose, study staff will administer the 25 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 25 mg dose, and staff will ensure the sublingual space is free of excess water. The second 25 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).

To administer the 60 mg dose, study staff will administer the 30 mg sublingual thin film under the tongue first, and then after 3 minutes has elapsed, subjects will be instructed to consume approximately 1 teaspoon of water immediately prior to dosing the second 30 mg dose, and staff will ensure the sublingual space is free of excess water. The second 30 mg sublingual thin film will be administered under the tongue for another 3 minutes (total dosing time should be 6 minutes).

Dose Administration for Moxifloxacin:

A single dose of 400 mg of moxifloxacin tablet will be administered orally to the subjects by study staff. The tablet should be swallowed whole with plenty of water; do not crush or chew the tablet.

14.3 Storage

The Investigator is responsible for ensuring the proper storage of study medication according to procedures agreed in advance. Each Investigator is required to keep investigational drug product in a locked cabinet or other secure storage contained with limited access to personnel. Temperature logs must be maintained for the storage room.

APL-130277/Placebo: Unit dose pouches must be stored at controlled room temperature: 68-77°F (20-25°C).

Moxifloxacin: Tablets must be stored at controlled room temperature 59-86°F (15-30°C). Avoid freezing. Store in the original package to protect from moisture.

The Investigator must maintain accurate and adequate records including expiry dates, lot number, and quantities received, individual usage, etc. At the end of the study, the Investigator must also return unused supplies to the Sponsor giving an account of usage in a trial whether or not the trial is completed or terminated. At the time of return to the Sponsor, the Investigator must verify that all unused or partially used drug supplies have been returned and that no remaining supplies are in the Investigator's possession. Certificates of delivery and returns must be signed and filed in the clinical site file.

14.4 Packaging and Labeling

Investigational drug product will be administered in the clinic.

APL-130277 and Placebo:

Each package of investigational drug product and matched placebo APL-130277 will be labeled with study specific information meeting all the applicable regulatory requirements, including specifying the dose of APL-130277.

Individual sublingual thin films of APL-130277 and matched placebo APL-130277 will be supplied packed in individual unit dose pouches.

Moxifloxacin 400 mg Tablets:

Moxifloxacin film-coated tablets will be packaged according to the market authorization holder and labeled with study specific information meeting all the applicable regulatory requirements.

14.5 Drug Accountability

Drug supplies, which will be provided by Sunovion or a CRO appointed by Sunovion, must be kept in a secure, limited access storage area.

The Investigator, pharmacist, and/or investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the return to Sunovion of unused product(s). These records will include dates, quantities, batch/serial numbers, expiry dates, and the unique code numbers assigned to the investigational product(s) and trial subjects. The Investigator, pharmacist, and/or investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the clinical trial protocol and reconcile all investigational product(s) received from Sunovion. At the time of return to Sunovion, the Investigator or site designate must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining

supplies are in the Investigator's possession.

Note: If any of the investigational drug is not dispensed; is lost, stolen, spilled, unusable; or arrives at the clinical site in a damaged container, this information must be documented and reported to Sunovion and appropriate regulatory agencies as required. The investigational drug will only be administered to subjects participating in this study. Only authorized clinical site personnel may supply or administer the investigational drug.

14.6 Method of Assigning Subjects to Treatment Groups

In the Dose Titration Phase, all subjects will be assigned open-label APL-130277 treatment using an IWRS system.

In the Three-Way Balanced Randomized Crossover Assessment Phase (Period 1, Period 2, Period 3) subjects will be randomized using the Williams Design such that subjects are randomized in equal numbers to six possible sequences of each of the three treatments being studied:

1) APL-130277 at the dose determined in the Dose Titration Phase,

2) Matched placebo APL-130277,

3) A single 400 mg dose of moxifloxacin.

APL-130277 and placebo will be administered in a double-blind fashion and moxifloxacin will be administered open-label in a three-way balanced crossover. The strength of APL-130277 or placebo (i.e., 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg) to be given will be determined based on safety/tolerability during the Dose Titration Phase of the study.

14.7 ECG Methodology: Central Laboratory

ECGs obtained digitally using a continuous 12-lead Holter device will undergo central review. ECGs to be used in the analysis will be selected/extracted at predetermined time points and will be read centrally using a high-resolution manual on-screen caliper semiautomatic method with annotations. Triplicate (3) 12-lead ECGs at each timepoint specified will be downloaded from the continuous recording approximately one minute apart. The digital ECGs will undergo a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist also blinded to the study treatment.

Digital ECGs will be processed via the central core laboratory's validated data management system, EXPERT. Interval duration measurements will be collected using computer assisted caliper placements on three consecutive beats. Trained analysts will review all ECGs for correct lead and beat placement and adjudicate the pre-placed algorithm calipers as necessary using a proprietary validated electronic caliper system applied on a computer screen (manual adjudication methodology). A cardiologist will then verify the interval durations and perform the

morphology analysis. The ECG interval duration measurements will be performed in Lead II and when Lead II is not analyzable in Lead V5, when Lead V5 is not analyzable in Lead V2, followed by the most appropriate lead, if necessary.

On-screen measurements of the RR, PR, QRS, and QT interval durations will be performed and heart rate, QTcF and QTcB will be derived by the following process:

Interval measurements will be obtained by the following method:

- Three (3) R-R mean R-R Interval is reported
- Three (3) PR mean PR Interval is reported
- Three (3) QRS mean QRS Width is reported
- Three (3) QT mean QT Interval is reported

The following calculations will be made from the interval measurements:

Three (3) QTcF measurements—QTc correction by the Fridericia's formula

- $QTcF1 = QT1/\sqrt[3]{RR1}$
- $QTcF2 = QT2/\sqrt[3]{RR2}$
- $QTcF3 = QT3/\sqrt[3]{RR3}$
- Mean QTcF = (QTcF1 + QTcF2 + QTcF3)/3

Three (3) QTcB measurements- QTc correction by the Bazett's formula

- $QTcB1 = QT1/\sqrt{RR1}$
- $QTcB2 = QT2/\sqrt{RR2}$
- $QTcB3 = QT3/\sqrt{RR3}$
- Mean QTcB = (QTcB1 + QTcB2 + QTcB3)/3

Three (3) Heart Rate measurements

- HR1 = 60 / RR1
- HR2 = 60 / RR2
- HR3 = 60 / RR3
- Mean HR = (HR1 + HR2 + HR3)/3

Each fiducial point (onset of P wave, onset of Q wave, offset of S wave, and offset of T wave) will be marked. The original ECG waveform and such annotations will be saved separately in XML format for independent review.

14.8 Randomization

At Screening, the IWRS will assign a unique subject identification number to the subject known as the Screening Number. This number will be associated with the subject throughout the study. Every subject that signs an ICF must be entered into the IWRS regardless of eligibility in order to obtain a Screening Number. This 7-digit number will consist of a 4-digit site ID followed by a 3-digit number assigned sequentially within each site starting at 001.

Following Sponsor approval (additional details are available in the Enrollment and Randomization Adjudication Process, which is contained in a separate document), subjects will be randomized centrally at a study level after the Dose Titration Phase has been completed (prior to Period 1 Dosing Visit 1) to one of the six randomization sequences using the Williams design:

1. APL-130277 – Placebo – Moxifloxacin
2. APL-130277 – Moxifloxacin – Placebo
3. Placebo – Moxifloxacin – APL-130277
4. Placebo – APL-130277 – Moxifloxacin
5. Moxifloxacin – Placebo – APL-130277
6. Moxifloxacin – APL-130277 – Placebo

No stratification factors will be used. The randomization scheme will be designed by the study statistician. Once designed, an independent randomization expert will execute the randomization in the IWRS. The 5-digit randomization number is used to identify the treatment sequence (APL-130277, placebo, moxifloxacin) of the kits that will be assigned to the subject during the Period 1, Period 2 and Period 3 of the Crossover Phase.

A randomization number can only be assigned to one subject and cannot be reused once assigned.

14.9 Blinding

This study will be open-label during the Dose Titration Phase and for moxifloxacin dosing during the Crossover Assessment Phase.

APL-130277 and Placebo Dosing Visits will be double-blinded.

An IWRS will allocate treatment for Period 1, Period 2 and Period 3 Dosing Visits based on a pre-specified randomization list, generated by the IWRS provider.

For blinded Dosing Visits active and placebo study medication will be provided to each site participating in the study. For each dose, study medication and placebo packaging will be identical in size, shape, color and appearance. Investigators will not have access to the randomization (treatment) code except in case of a SAE. In this case, the code may be broken

only in exceptional circumstances when knowledge of the study medication is essential for treating the subject. Subjects and study staff members will be blinded to treatment assignments until the completion of the study.

A list of treatment kit numbers for each treatment sequence is generated centrally by the vendor selected by the Sponsor to perform this function, and the treatment kits are prepared in accordance with this list. Numbers will not be reused regardless of the status of the use of the corresponding study drug.

15 STATISTICAL ANALYSES

15.1 Statistical Analysis Plan

Full statistical considerations and complete analysis of data collected in this study will be specified in a formal Statistical Analysis Plan (SAP). This section of the protocol prospectively outlines the analysis methods. The final SAP will be finalized prior to locking the database and prior to unblinding any study data. The SAP will serve as a complement to the study protocol and supersedes it in case of differences. In case of major differences between the study protocol and SAP (e.g. changes in the analysis related to the primary endpoint), a protocol amendment will be considered.

15.2 Analysis Populations

15.2.1 Safety Analysis Set

All subjects who receive at least one dose of study medication will be included in the safety analysis set. The safety analysis set will be used for the analysis of the safety endpoints and the subjects will be grouped according to the treatment that they received.

15.2.2 PK Analysis Set

The PK analysis set includes all subjects with at least one PK evaluation and will be used for the analysis of the PK data.

15.2.3 Efficacy Analysis Set

The efficacy analysis set includes subjects who have efficacy assessments at the lowest or highest dose level resulting in a full "ON". The efficacy analysis set will be used for the analysis of the efficacy data collected during the Dose Titration Phase.

15.2.4 ECG and PK-PD Analysis Sets

The analysis populations for the ECG and pharmacokinetic-pharmacodynamic (PK-PD) analyses (Evaluable Population) will be comprised of all subjects who are randomized, receive at least one dose of study medication, and have at least one evaluable pre-dose ECG and one evaluable on-treatment post-dose ECG within the same Treatment Period. Additionally, for the PK-PD analysis (placebo corrected change in QTc vs. plasma concentration), a time-matched plasma concentration would also be necessary.

15.3 Sample Size Calculation

The study is powered to detect a mean difference in the change in QTcF between APL-130277 and placebo (ΔΔQTcF) of 7 ms, assuming that the true difference between APL-130277 and placebo can be up to 3 ms, adding up to the predefined threshold of 10 ms. The standard deviation of ΔΔQTcF is assumed to be 14 ms.[12] Assuming a one-sided significance level of 0.05,

42 subjects are required for the 3x3 cross-over phase to achieve approximately 80% power.

15.4 ECG and Concentration-QTc Effect Analysis

15.4.1 Primary Endpoint

The primary endpoint for this trial will be the time-matched change from baseline in QTc, placebo-adjusted and corrected for HR based on the Fridericia correction method (QTcF) method (ΔΔQTcF).

15.4.2 Secondary Endpoints

Secondary endpoints will include:

- QTc with Bazett correction (QTcB);
- Heart rate;
- PR interval;
- QRS interval;
- Uncorrected QT interval;
- ECG morphology.

15.4.3 Central Tendency Analyses

The primary analysis for the QT/QTc data in this study is based on the time-matched analysis for each treatment group. This time-matched analysis will be based upon the endpoint "change from baseline in the QTcF interval, placebo-adjusted – ΔΔQTc." Baseline is defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (P1V1). Note that the measurements from the three ECGs collected at a time point are averaged to produce a single value for each ECG interval for that time point. These baseline and Day 1 post-dose ECG data, for each Treatment Period, will then be subjected to a mixed effects model (using the SAS Procedure PROC MIXED) with the following covariates: time (categorical), treatment, time by treatment interaction, region, gender, and the baseline value of the parameter. Since this is a crossover design, period and sequence terms will necessarily also be included in the model. Subject will be included as a random effect. Gender and region effects will be investigated as specified below. Should a significant treatment by gender/region interaction be observed, it will also be included in the model. The estimates of the ΔΔQTc at each time point and its confidence intervals (CI) will be performed using a LSMEAN statement within PROC MIXED and a diff option. For this analysis a 90% two-sided confidence interval will be calculated. Hypotheses will be based upon the Intersection-Union test. Since the Intersection-Union test can be applied here, no multiple endpoint adjustment is needed. Based on the ICH E14 guidance, the hypothesis will be evaluated by observing if any of the time points have a two-sided 90% upper confidence bound (i.e. one-

sided 95%) which is equal to, or exceeds, 10 ms.

The upper limit of the two-sided 90% CI on treatment will be compared to the 10 ms bound only for APL-130277 versus placebo. If the upper limit of the two-sided 90% CI for APL-130277 versus placebo falls below 10 ms, it will be concluded that APL-130277 does not prolong the QTc interval to a clinically significant degree.

The 7 time points to be evaluated for the primary analysis include 15, 30, 45 60 minutes and 2, 3, and 4 hours post-dose. If only 1 or 2 of the 7 timepoints for APL-130277 just exceeded 10 ms, a determination of whether this is a false positive response relied on all of the study findings with special emphasis on the PK-PD model described below.

The analysis also will be presented in a graphical manner: for each comparison of interest all CI's (corresponding to the number of post-baseline time points) will be presented superimposed in one graph showing moxifloxacin and APL-130277, all of which have been placebo-adjusted. A similar analysis will be conducted for QTcB.

15.4.4 Establishment of Assay Sensitivity

To establish assay sensitivity, there should be at least one time point where the lower confidence bound of the mean difference of moxifloxacin and placebo is greater than 5 ms. The same model as described for the time-matched analyses will be used for this analysis.

The hypothesis of assay sensitivity will be rejected if the lower limit of the one-sided (Bonferroni corrected) 95% confidence interval is never above 5 ms. However, detecting the positive control's effect will establish the ability of the study to detect such an effect of the study drug.

For purposes of determining assay sensitivity, 4 time points (i.e., hours 1, 2, 3, and 4) will be utilized for calculating the one-sided 95% (i.e. two-sided 90%) confidence limits. In this case, since the alternative hypothesis is that at least one of the time points is greater than or equal to 5 ms, a multiplicity adjustment is necessary. Therefore, the confidence intervals will be calculated using Bonferroni adjustment, specifically an adjusted alpha error level of $0.05/4 = 0.0125$. Note that although only these time points will be used to assess assay sensitivity, the calculated upper and lower confidence bounds (Bonferroni-corrected) for the entire moxifloxacin profile will be displayed.

15.4.5 Outlier Analyses

An outlier or categorical analysis supplements the central tendency analysis by determining if there were subjects who had an exaggerated effect on any ECG interval that would not be revealed in a mean change from baseline central tendency analysis. Each subject would be considered having an outlier value based on the most extreme value across all of the time points.

The following criteria ("study endpoints") are defined for this analysis:

- Heart rate: A value for a subject is considered to be an outlier at a pre-determined post-dose time point if the heart rate measurement at that time point is < 50 bpm and the measure is at least a 25% decrease from the subject's baseline mean heart rate (i.e., a bradycardic event) or if the heart rate measurement at the pre-determined post-dose time point is > 100 bpm and the measure is at least a 25% increase from the baseline mean heart rate (i.e., a tachycardic event).
- PR interval: A value for a subject is considered to be an outlier at a pre-determined post-dose time point if the PR interval at that follow-up time point is > 200 ms and it is at least a 25% increase from the subject's baseline mean PR interval.
- QRS interval: A value for a subject is considered to be an outlier at a pre-determined post-dose time point if the QRS interval at that follow-up time point is > 100 ms and it is at least a 25% increase from the subject's baseline mean QRS interval.
- QT interval: A value for a subject is considered to be an outlier at a pre-determined post-dose time point if the QT interval at that follow-up time point is > 500 ms and the subject's baseline mean QT interval is ≤ 500 ms.
- QTcF: A value for a subject is considered to be an outlier at a pre-determined post-dose time point if the QTcF interval at that follow-up time point is > 500 ms and the subject's baseline mean QTcF interval is ≤ 500 ms. Outlier values will also be presented if the QTcF interval at a pre-determined post-dose time point is > 480 ms when the subject's baseline mean QTcF interval is ≤ 480 ms and when a pre-determined post-dose time point is > 450 ms when the subject's baseline mean QTcF interval is ≤ 450 ms. In addition, the proportion of subjects with changes from baseline in > 30-60 ms and > 60 ms will be reported.
- QTcB: A value for a subject is considered to be an outlier at a pre-determined post-dose time point if the QTcB interval at that follow-up time point is > 500 ms and the subject's baseline mean QTcB interval is ≤ 500 ms. Outlier values will also be presented if the QTcB interval at a pre-determined post-dose time point is > 480 ms when the subject's baseline mean QTcB interval is ≤ 480 ms and when a pre-determined post-dose time point is > 450 ms when the subject's baseline mean QTcB interval is ≤ 450 ms. In addition, the proportion of subjects with changes from baseline in > 30-60 ms and > 60 ms will be reported.

15.4.6 Morphologic Analyses

Morphological analyses will be performed with regard to the ECG waveform interpretation as defined by the central ECG laboratory's cardiologist. Changes from baseline to on-treatment will be evaluated.

All findings will be presented in the ECG listings. New onset findings will be presented as the percentage of subjects meeting the "new" criteria within each Treatment Period ("new" means not present on any baseline ECG and becomes present on at least one on-treatment ECG) for the following variables:

- Second degree heart block;
- Third degree heart block;
- Atrial fibrillation or atrial flutter;
- Complete right bundle branch block;
- Complete left bundle branch block;
- ST segment change (elevation and depression separately);
- T wave abnormalities (negative T waves only);
- Myocardial infarction pattern; and
- Any new abnormal U waves.

15.4.7 Pharmacokinetic-Pharmacodynamic Analyses

A concentration-QTc analysis will be conducted to evaluate the relationship between the placebo-corrected (placebo-adjusted) change from baseline in QTc intervals (QTcF and QTcB and plasma concentrations of APL-130277). The analysis will be done as a separate standalone analysis and a detailed PK modeling analysis plan (PMAP) will be generated to describe the planned evaluation.

15.4.8 Safety Analysis

Disposition

The number of subjects who failed the screening will be summarized along with the reason for exclusion. The premature discontinuation will be summarized by study phase and treatment group/dose level along with the reason for the discontinuation.

Adverse events

The adverse event data will be summarized for the overall APL-130277 treatment and further classified by the dose level at the time of the onset of the event. In addition, the adverse events starting during the placebo and moxifloxacin treatment will be summarized. Adverse events will be tabulated by treatment group and dose level according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be summarized by body system and preferred term. Descriptive statistics will be used to compare the overall incidence of TEAEs between the treatment groups.

Safety laboratory variables

The changes in safety laboratory variables from Screening to the end of the study will be summarized with descriptive statistics or listed only.

Vital signs

The vital signs, including orthostatic blood pressure will be summarized with descriptive statistics as changes from pre-dose to post dose time points by treatment group/dose level.

Oral irritation

The data on oral irritation will be summarized with descriptive statistics.

The full details of the safety analysis will be provided in the SAP.

15.5 Pharmacokinetic Analysis

The stand-alone non-compartmental PK analysis of the plasma PK concentration data will be described in details in a separate PK analysis plan (PKAP).

Apomorphine levels and metabolites (norapomorphine and apomorphine sulphate) will be measured in plasma using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Pharmacokinetic parameters will be derived using noncompartmental methods employing a validated installation of Phoenix WinNonlin® version 6.3 or higher (Pharsight, St Louis, MO) software.

The following PK parameters will be estimated or calculated using plasma apomorphine, norapomorphine and apomorphine sulphate concentration-time data. Other PK parameter may be calculated as appropriate. Actual elapsed time from dosing will be used to determine all individual PK parameters.

C_{max}	Maximum drug concentration in plasma, determined directly from the concentration-time profile.
T_{max}	Time of C_{max} in plasma, determined directly from the concentration-time profile.
AUC_{0-t}	Area under the plasma concentration vs. time curve from time of dosing to last measurable concentration, calculated using the linear up, log down trapezoidal rule.
AUC_{inf}	AUC extrapolated to infinity (AUC_{last} + last quantifiable concentration/λ_z), calculated using the linear-up/log-down trapezoidal rule.
λ_z	The terminal phase rate constant; estimated by linear regression through the

terminal phase of the log concentration-time profile, using at least 3 data points.

$t_{½}$ The terminal phase half-life calculated as:

$$t½ = \frac{\ln(2)}{\lambda z}$$

CL/F Plasma clearance, calculated as Dose/AUC_{inf} after single dose (apomorphine only).

MRT Mean residence time calculated using the following equation: MRT = $AUMC_{inf}/AUC_{inf}$. $AUMC_{inf}$ is the area under the first moment curve.

M/P Ratio Metabolite to Parent exposure ratio (C_{max} and AUC).

Linear and semi-log plots of the concentration-time data for apomorphine and metabolites will be presented by subject and treatment.

Plasma apomorphine and metabolites (norapomorphine and apomorphine sulphate) concentrations will be summarized using descriptive statistics (including N, mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum). Concentrations below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics and for construction of mean concentration-time profiles.

Actual elapsed time from dosing will be used to determine all individual PK parameters. Plasma PK parameters will be tabulated by dose level, and summary statistics that are presented will include the arithmetic and geometric mean, geometric CV%, SD of the arithmetic mean, median, minimum, maximum, and N.

15.6 Efficacy Analysis

The main efficacy endpoint of this study is the change in MDS-UPDRS Part III at 30 minutes. The MDS-UPDRS Part III will be analyzed using a Mixed Model for Repeated Measures with data from the lowest dose level resulting in a full "ON" and at the highest tolerated dose level during the Titration Phase as response variables. The baseline (SV2) value will be included as a covariate and the day (1 = assessment at the lowest dose level resulting in a full "ON", 2 = assessment at the highest tolerated dose level) and dose level (10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg) as fixed factors in the model. Separate models will be used for each time point (30, 60 and 90 minutes).

The other efficacy endpoints will be analyzed with similar principles. These analyses will be defined in the SAP.

16 STUDY CONDUCT

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate clinical site, review of protocol procedures with the Investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

16.1 Regulations and Guidelines

By signing this study protocol, the Investigator agrees to conduct this study in accordance with all laws, regulations and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 GCP and in agreement with the Declaration of Helsinki (including all applicable amendments). While delegation of certain aspects of the study to Sub-Investigators and study coordinators is appropriate, the Principal Investigator (PI) will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The PI is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., Sub-Investigators and study coordinators) and their specific study related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, investigational drugs, and their specific duties within the context of the study. Investigators are responsible for providing Sunovion with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by Sunovion and the relevant governing authorities.

See APPENDIX II: Regulations and Guidelines for additional information.

16.2 Study Initiation

Clinical study staff may not screen or enroll subjects into the study until receiving notification from Sunovion or its designee that the study can be initiated at the clinical site. The clinical site will not be authorized for study initiation until:

- The Sponsor has received the appropriate Regulatory Authority/Agency approval for the protocol and ICF;
- The clinical site has received the appropriate IRB/REB/IEC approval for the protocol and the IRB/REB/IEC-approved ICF;
- The clinical site has a Clinical Trial Agreement in place;
- The clinical site personnel, including the Investigator, have participated in a study initiation meeting.

16.3 Study Documentation

16.3.1 Investigator's Regulatory Documents

The regulatory documents listed below must be received from the Investigator and reviewed and approved by Sunovion or its designee before the clinical site can initiate the study and before Sunovion will authorize shipment of investigational drug to the clinical site. Copies of the Investigator's regulatory documents must be retained at the clinical site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the APL-130277 IB, copies of regulatory references, copies of IRB/REB/IEC correspondence, and investigational drug accountability records must be retained as part of the Investigator's regulatory documents. It is the Investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

Documents Required for Regulatory Packet:

Confidentiality Agreement	Signed Clinical Trial Agreement
Final Protocol	PI CV
Final Protocol Amendments (if any)	PI Medical License
Protocol Signature Pages	Sub-Investigator CV
Protocol Amendment Signature Pages (if any)	Sub-Investigator License
APL-130277 IB	IRB Approvals
Signed Financial Disclosure	IRB Membership List / Assurance Statement
Regulatory Agency Approval	Approved Informed Consent Template(s)

Additional documentation requirements may be communicated by Sunovion staff (or it's designate).

16.3.2 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all subjects who sign an ICF.

The vendor selected to perform CRF design will be responsible for drafting CRFs for the study, which Sunovion will review and approve before implementation. An electronic CRF may be used instead of paper CRFs, and the term CRF is synonymous for both types of CRFs.

CRFs are considered confidential documents and should be handled and stored accordingly. Sunovion or its designee will provide the necessary training on the use of the specific CRF system used during the study to ensure that the information is captured accurately and appropriately.

In order to ensure data accuracy, CRF data for individual subject visits should be completed as soon as possible following the visit in accordance with the site Clinical Trial Agreement in place. CRFs will be reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRA will verify data recorded with source documents.

A copy of all the CRFs will be sent securely to Sunovion at the end of the study.

If the study is managed using an Electronic Data Capture (EDC) system, the Investigator agrees to maintain accurate CRFs/EDC modules and source documentation as part of the case histories for all subjects who sign an ICF.

CRFs/EDC modules are considered confidential documents and should be handled and stored accordingly. Sunovion or its designee will provide the necessary training on the use of the specific EDC system used during the study to ensure that the information is captured accurately and appropriately.

In order to ensure data accuracy, EDC module data for individual subject visits should be completed as soon as possible following the visit and in accordance with the site Clinical Trial Agreement in place. EDC data will be reviewed by the CRA during monitoring visits. The CRA will verify data recorded with source documents.

All corrections or changes requested to the study data must be made as soon as possible by the study site, and verified by the Investigator. When all incorrect and/or inconsistent data has been accounted for, EDC data will be considered complete.

The site is expected to notify the Study Medical Monitor before breaking the study blind, unless it is in the subject's best interest if the blind is broken immediately. All corrections or changes made to any study data must be appropriately tracked in an audit trail. When all incorrect and/or inconsistent data has been accounted for, CRFs will be considered complete.

16.3.3 Source Documents

All information recorded in the CRF must be supported by corresponding source documentation. Examples of acceptable source documentation include but are not limited to hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. If available, source documents for at least the 2 years prior to screening will be reviewed by the CRA to verify the subject's eligibility for the study.

Original versions of the laboratory reports and ECG tracings will be retained at the clinical site

with the subject's source documents.

16.4 Data Quality Assurance

Sunovion and its designees will perform quality control and assurance checks on all clinical studies that it sponsors. Sunovion, or its designee, will be responsible for additional data quality assurance related to the clinical data being generated, entered and maintained as part of this clinical study.

16.4.1 Monitoring the Study

Clinical monitors will conduct site visits to the study facilities to monitor the study. The Investigator agrees to allow these monitors and other authorized Sunovion personnel access. The clinical site will be monitored by Sunovion and/or it's designate to ensure compliance with the protocol, GCP, and applicable regulations and guidelines. As representatives of Sunovion, CRAs are responsible for following the study protocol closely and notifying project management of any noted deviations. The assigned CRA(s) will visit the Investigator and clinical site at periodic intervals and maintain periodic communication. The CRA(s) will maintain current knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. While on site, the CRA(s) will review regulatory documents, compare entries in the source documents, and review investigational drug accountability records. The CRA will ask for clarification and/or correction of any noted inconsistencies.

By signing the protocol, the Investigator agrees to meet with the CRA during clinical site visits, to ensure that study staff is available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation and medical records, to the clinical supplies dispensing and storage area, and agrees to assist the monitors in their activities, if requested. The Investigator also agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

16.4.2 Routine Data Collection

CRFs will be reviewed by the CRA during monitoring visits. The CRA will verify data with source documents. If the CRA's comparison of the original CRF data with source documents reveals data discrepancies or omissions that require study staff to make corrections, corrections will be made. After the CRF data have been monitored and all corrections have been made, the Investigator must appropriately document within the data system his/her agreement with the data contained therein. If corrections are required subsequent to the Investigator's signature, the Investigator must document his/her agreement with the CRF data to confirm the accuracy of the changed data. A copy of all CRF data will be retained at the clinical site. If corrections are required after all data have been electronically transferred, corrections that have been made must be verified in writing by the Investigator, and new data provided to Sunovion.

Should an EDC system be implemented, the CRA will verify data with source documents. If the CRA's comparison of the original EDC module data with source documents reveals data discrepancies or omissions that require study staff to make corrections, the corrections will be made as outlined in the Study Monitoring Plan. After the EDC module data have been monitored and all corrections have been made, the Investigator must appropriately document within the data system his/her agreement with the data contained therein. If corrections are required subsequent to the Investigator's signature, the Investigator must document his/her agreement with the EDC module data to confirm the accuracy of the changed data. A copy of all EDC module data will be retained at the clinical site. If corrections are required after all data have been electronically transferred, the corrections must be made as instructed in site training.

16.4.3 Expedited Data Collection

Monitoring of selected CRF data may occur following the CRF submission, using data from the data system and source documents as necessary. Any post submission/transfer corrections of CRF data must be verified in writing by the Investigator, and new data provided to Sunovion.

16.4.4 Data Management

A vendor contracted by Sunovion will provide the data management system and data management services for the study. An EDC system may be implemented.

Clinical site personnel will be responsible for providing resolutions to all data queries. The Investigator will be required to review and document data to ensure the accuracy of the corrected and/or clarified data. If an EDC system is implemented, this documentation will be electronic. Query forms or documentation must be generated and filed by the site.

16.4.5 Study Termination

The study may be terminated at Sunovion's discretion at any time for any reason. If Sunovion discovers conditions that warrant early termination of the study, the Investigator will be notified by Sunovion or its designee. Examples of conditions that may warrant premature termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study; and
- The decision on the part of Sunovion to suspend or discontinue testing, evaluation, or development of the investigational product.

16.4.6 Clinical Site Closure

On termination of the study, all screening and ongoing study related procedures conducted at the clinical site will be closed. Sunovion may terminate participation of the clinical site at any time. Examples of conditions that may warrant premature termination of a clinical site include, but are not limited to the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines;
- Inadequate subject enrollment;
- Administrative reasons.

17 GENERAL CONSIDERATIONS

17.1 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Sunovion. The protocol amendment must be signed by the Investigator and approved by the IRB/REB/IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

17.2 Use of Information and Publication

All information concerning APL-130277, Sunovion's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Sunovion to the Investigator and not previously published, is considered confidential and remains the sole property of Sunovion. The CRFs also remain the property of Sunovion. The Investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Sunovion in connection with the continued development of APL-130277 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Publication or other public presentation of APL-130277 data resulting from this study requires prior review and written approval of Sunovion, which will not be unreasonably withheld. Abstracts, manuscripts, and presentation materials should be provided to Sunovion for review at least 30 days prior to the relevant submission deadline.

After publication of the results of the multi-center study or 24 months after the clinical study report has been finalized, whichever comes first, the Sponsor acknowledges the Investigator's rights to publish results from this study. Any such scientific paper, presentation, communication, or other information concerning the study described in this protocol must be submitted to the Sponsor for review prior to submission for publication/presentation.

17.3 Records Retention

The Investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (1) 2 years after the last marketing authorization for the investigational drug has been approved or Sunovion has discontinued its research with respect to such drug; or (2) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify Sunovion in writing of its intent to destroy all such material. Sunovion shall have 30 days to respond to the Investigator's notice, and Sunovion shall have a further opportunity to retain such materials at Sunovion's expense.

17.4 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the study team has determined that specimens are no longer needed and the decision has been made that there are no samples to be re-assayed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

17.5 Subject Injury

In general, specific to provisions in the clinical trial agreement, if a subject is injured as a direct result of a test article and the site, its staff and Investigators have followed the protocol and all documentation supporting the proper running of the trial, Sunovion will pay for reasonable and necessary medical treatment for the injury. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, Sunovion shall comply with such laws or regulations. Where applicable, Sunovion has taken specific national insurance.

18 REFERENCES

1) Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. *Neurol Clin.* 1996;14:317-35.

2) Hornykiewicz O. Basic research on dopamine in Parkinson's disease and the discovery of the nigrostriatal dopamine pathway: the view of an eyewitness. *Neurodegener Dis.* 2008;5:114–7.

3) Mouradian MM, Heuser IJ, Baronti F, et al. Pathogenesis of dyskinesias in Parkinson's disease. *Ann Neurol.* 1989;25(5):523-6.

4) Stocchi F, Vacca L, Ruggieri S, et al. Intermittent vs. continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. *Arch Neurol.* 2005;62(6):905-10.

5) Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord*. 2001;16(3):448-58.

6) APOMORPHINE treatment for morphine addiction. *Br J Addict Alcohol Other Drugs*. 1949;46(2):93-101.

7) Cotzias GC, Papavasiliou PS, Fehling C, Kaufman B, Mena I. Similarities between neurologic effects of L-dipa and of apomorphine. *N Engl J Med.* 1970;282(1):31-3.

8) Corsini GU, Del Zompo M, Gessa GL, Mangoni A. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. *Lancet.* 1979;1(8123):954-6.

9) Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. *J Pharmacol Exp Ther.* 2002;303(2):791-804.

10) Schwab RS, Amador LV, Lettvin JY. Apomorphine in Parkinson's disease. *Trans Am Neurol Assoc.* 1951;56: 251–3.

11) Wang BS, Wang XJ, Gong, LK. The Construction of a Williams Design and Randomization in a Cross-Over Clinical Trials Using SAS. *J Stat Softw.* 2009;29(1):1-10.

12) Mendzelevski B, Sprenger CR, Spiegelstein O, Rabinovich-Guilatt L. Cardiac safety of rasagiline, a selective monoamine oxidase type B inhibitor for the treatment of Parkinson's disease: a thorough QT/QTc study. Int J Clin Pharmacol Ther. 2014 Mar;52(3):192-201.

19 APPENDICES

19.1 APPENDIX I: APOKYN® Prescribing Information and APO-go® Summary of Product Characteristics

https://www.apokyn.com/sites/all/themes/apokyn/content/resources/Apokyn_PI.pdf

https://www.medicines.org.uk/emc/medicine/12941

19.2 APPENDIX II: Regulations and Guidelines

19.2.1 Declaration of Helsinki

The Policy of the World Medical Association is available at URL: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

19.2.2 Approval by an IRB/REB/IEC

This protocol must be reviewed and approved by a valid IRB/REB/IEC prior to initiation of the study. Written notification of approval is to be submitted by the Investigator to Sunovion monitor prior to shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval will consist of a completed Institutional Review Board Approval form or Research Ethics Board Approval form, or written documentation from the IRB or REB containing the same information.

Until written approval by the IRB/REB/IEC has been received by the Investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB/REB/IEC. Written approval from the IRB/REB/IEC, or a designee, must be received by Sunovion, before implementation. This written approval will consist of a completed approval form, or written documentation from the IRB/REB/IEC containing the same information.

19.2.3 Regulatory Authority/Agency

For Investigational New Drug (IND) studies, the minimum standards of study conduct and requirements for informed consent are defined in the applicable regulations of the country in which the study is conducted.

This protocol must be reviewed and approved by the country specific Regulatory Authority/Agency prior to initiation of the study. The Sponsor or authorized delegate will be responsible for the submission.

19.3 APPENDIX III: Modified Hoehn and Yahr Scale

Modified Hoehn & Yahr

0: Asymptomatic.

1: Unilateral involvement only.

1.5: Unilateral and axial involvement

2: Bilateral involvement without impairment of balance.

2.5: Mild bilateral disease with recovery on pull test.

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.

19.4 APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

MDS-UPDRS Permissions

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

Continue to p. 2 to view the MDS-UPDRS

MDS-UPDRS

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

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

The authors of this new version are:

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

Contact person: Christopher G. Goetz, MD
Rush University Medical Center
1725 W. Harrison Street, Suite 755
Chicago, IL USA 60612

Telephone 312-942-8016
Email: cgoetz@rush.edu

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:

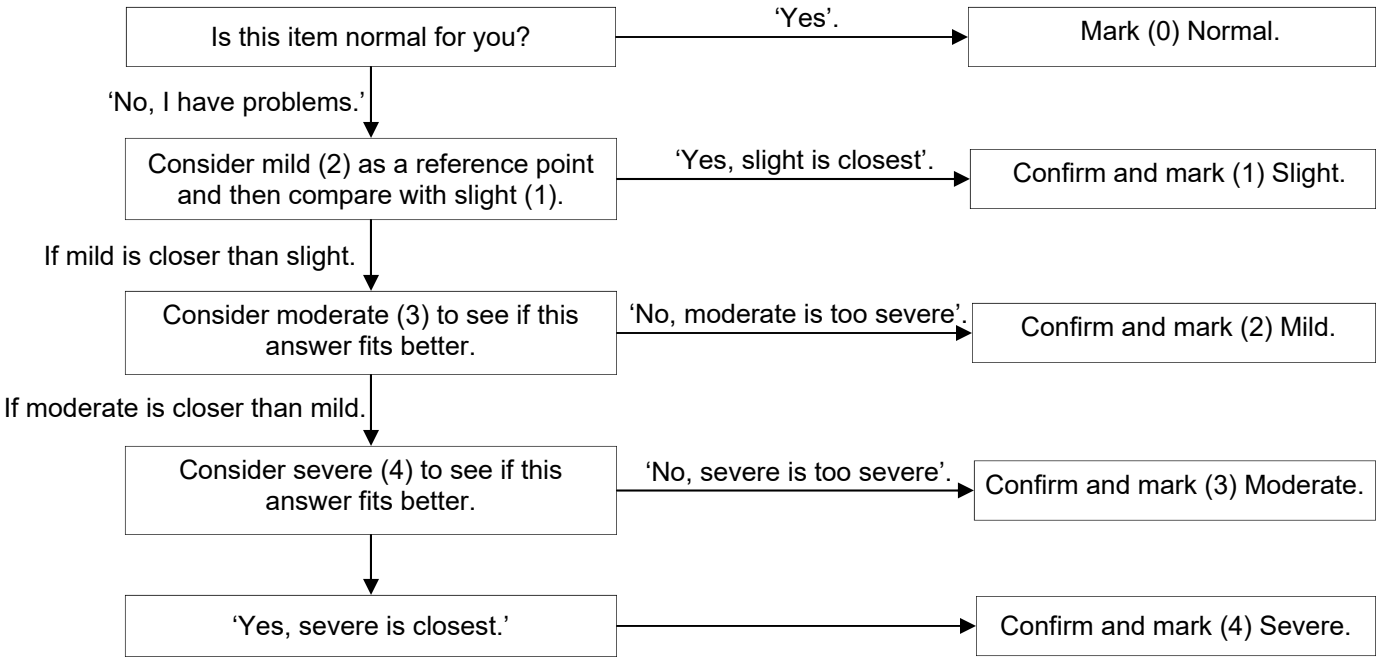
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating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

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



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

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

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

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

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

1.1 COGNITIVE IMPAIRMENT — **SCORE**

Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver.

Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information]

0: Normal:	No cognitive impairment.	
1: Slight:	Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions.	☐
2: Mild:	Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.	
3: Moderate:	Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.	
4: Severe:	Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	

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

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

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

SCORE

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

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

0: Normal: No problems present.

1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver.

2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life.

3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life.

4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.

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

Patient Questionnaire:

Instructions:

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

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

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

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

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

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

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

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

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

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

SCORE

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.

☐

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 not part of being sleepy or sad

0: Normal: No fatigue.

1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people.

2: Mild: Fatigue causes me some troubles doing things or being with people.

3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything.

4: Severe: Fatigue stops me from doing things or being with people.

☐

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

2.1 SPEECH

Over the past week, have you had problems with your speech?

0: Normal: Not at all (no problems).

1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself.

2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday.

3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood.

4: Severe: Most or all of my speech cannot be understood.

☐

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

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

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

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

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another persons to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor. 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

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

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

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

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

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

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

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

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

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

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

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

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

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

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

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

SCORE

3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

- 0: Normal: No rigidity.
- 1: Slight: Rigidity only detected with activation maneuver.
- 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.
- 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.
- 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

- 0: Normal: No problems.
- 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
- 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
- 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
- 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

SCORE

3.5 HAND MOVEMENTS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problem.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

SCORE

3.7 TOE TAPPING

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problem.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

SCORE

3.9 ARISING FROM CHAIR

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13

0: Normal:	No problems. Able to arise quickly without hesitation.
1: Slight:	Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.
2: Mild:	Pushes self up from arms of chair without difficulty.
3: Moderate:	Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.
4: Severe:	Unable to arise without help.

☐

3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for “freezing of gait” (next item 3.11) while patient is walking. Observe posture for item 3.13

0: Normal:	No problems.
1: Slight:	Independent walking with minor gait impairment.
2: Mild:	Independent walking but with substantial gait impairment.
3: Moderate:	Requires an assistance device for safe walking (walking stick, walker) but not a person.
4: Severe:	Cannot walk at all or only with another person’s assistance.

☐

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

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

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.

☐ RUE

☐ LUE

☐ RLE

☐ LLE

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.

☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR

SCORE

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal: No tremor.

1: Slight: Tremor at rest is present < 25% of the entire examination period.

2: Mild: Tremor at rest is present 26-50% of the entire examination period.

3: Moderate: Tremor at rest is present 51-75% of the entire examination period.

4: Severe: Tremor at rest is present > 75% of the entire examination period.

☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

☐

Part IV: Motor Complications

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

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

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

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

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

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

A . DYSKINESIAS [exclusive of OFF-state dystonia]

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 calculation).

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): _____

SCORE

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

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

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

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

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

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

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

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

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

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

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

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

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

0: Normal: No dystonia OR NO OFF TIME.

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

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

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

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

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

Summary statement to patient: READ TO PATIENT

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

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

MDS UPDRS Score Sheet

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

July 1, 2008

19.5 APPENDIX V: Columbia Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

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.

Past X Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

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.
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). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

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

Most Severe

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

____

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

____

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

____

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

____

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

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Past X Years or Lifetime

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 ☐

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

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

____

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:

Enter Code: _____

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

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).

Enter Code: _____

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

19.6 APPENDIX VI: United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria

Step 1 - Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 - Exclusion criteria for PD

- History of repeated strokes with stepwise progression of Parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communication hydrocephalus on imaging study
- Negative response to large doses of L-Dopa in absence of malabsorption
- MPTP exposure

Step 3 - Supportive prospective positive criteria for PD

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to L-Dopa
- Severe L-Dopa-induced chorea
- L-Dopa response for 5 years or more
- Clinical course of ten years or more

Reference: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55(3):181-4.