A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy, Safety and Tolerability of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

PROTOCOL NUMBER:	CTH-300
IND:	110955
PROTOCOL DATE:	06 May 2015
SPONSORED BY:	Cynapsus Therapeutics Inc.

1 SIGNATURES OF AGREEMENT FOR PROTOCOL

[redacted] Medical Monitor
Vice President, Medical Affairs
Cynapsus Therapeutics
[redacted]

May-6-2015
Date

[redacted]
Chief Medical Officer,
Cynapsus Therapeutics
[redacted]

MAy 6. 2015.
Date

2 EMERGENCY CONTACT INFORMATION

[redacted] Medical Monitor

Vice President, Medical Affairs

Cynapsus Therapeutics Inc.

[redacted]

[redacted]

[redacted]

Clinical Project Leader

Cynapsus Therapeutics Inc.,

[redacted]

[redacted]

3 INVESTIGATOR APPROVAL STATEMENT

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all Sub-Investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Cynapsus Therapeutics Inc. (Cynapsus) during the study. I will adhere to all Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), and other applicable regulations and guidelines regarding clinical trials on a study drug during and after study completion.

Principal Investigator

Printed Name: _____

Signature: _____

Date: _____

PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy, Safety and Tolerability of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Protocol: 06 May 2015

Version: 2.0 FINAL

4 PROTOCOL SYNOPSIS

TITLE	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy, Safety and Tolerability of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)
STUDY PHASE	Phase 3
OBJECTIVES	The primary objective is to evaluate the efficacy and safety of APL-130277 versus placebo in patients with Parkinson's disease (PD) over a 12 week period.
NUMBER OF PATIENTS	Approximately one hundred and twenty-six (126) patients will be enrolled into the Dose Titration Phase in order to randomize approximately 114 patients into the Maintenance Treatment Phase.
PATIENT POPULATION	**Inclusion Criteria** Patients 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[1]. 3. Clinically meaningful response to Levodopa (L-Dopa) with well-defined early morning "OFF" episodes, as determined by the Investigator. 4. Receiving stable doses of L-Dopa/carbidopa (immediate or chronic release [CR]) administered at least 4 times per day OR Rytary™ administered 3 times per day, for at least 4 weeks before the initial Screening Visit (SV1). Adjunctive PD medication 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. Patients must experience at least one well defined "OFF" episode per day with a total daily "OFF" time duration of ≥ 2 hours during the waking day, based on patient self-assessment. 7. Patient and/or caregiver must be trained in performing home dosing diary assessments of the motor state and must be able to recognize "ON" and "OFF" states.

[1] Excluding the "more than one affected relative" criterion.

	8. Stage III or less on the modified Hoehn and Yahr scale in the "ON" state. 9. Mini–Mental State Examination (MMSE) score > 25. 10. If female and of childbearing potential, must agree to use one of the following methods of birth control: • 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). 11. 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 30 days after final drug administration. 12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study. 13. Able to understand the consent form, and to provide written informed consent. 14. Must be approved as a satisfactory candidate by an enrollment adjudication committee (EAC).
	Exclusion Criteria Patients will be excluded from participation in the study for any of the following reasons: 1. Atypical or secondary parkinsonism. 2. Previous treatment with any of the following: a neurosurgical procedure for PD; continuous subcutaneous (s.c.) apomorphine infusion; or Duodopa/Duopa. 3. Treatment with any form of s.c. apomorphine within 7 days prior to the initial Screening Visit (SV1). Patients that stopped s.c. apomorphine for any reason other than systemic safety concerns or lack of efficacy may be considered. 4. Contraindications to APOKYN®, or hypersensitivity to apomorphine hydrochloride or any of the ingredients of APOKYN® (notably sodium

	metabisulfite); Tigan® (trimethobenzamide hydrochloride; patients from US sites only); or domperidone (patients from non-US sites only). 5. Female who is pregnant or lactating. 6. Participation in a clinical trial within 30 days prior to the initial Screening Visit (SV1). 7. Receipt of any investigational (i.e., unapproved) medication within 30 days prior to the initial Screening Visit (SV1). 8. Currently taking selective $5HT_3$ antagonists (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (excluding quetiapine and clozapine) or dopamine depleting agents. 9. Drug or alcohol dependency in the past 12 months. 10. History of malignant melanoma. 11. Clinically significant medical, surgical, or laboratory abnormality in the opinion of the Investigator. 12. Major psychiatric disorder including, but not limited to, dementia, bipolar disorder, 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. 13. History of clinically significant hallucinations during the past 6 months. 14. History of clinically significant impulse control disorder(s). 15. Dementia that precludes providing informed consent or would interfere with participation in the study. 16. 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. 17. Donation of blood or plasma in the 30 days prior to first dosing. 18. Cankers or mouth sores within 30 days prior to the initial Screening Visit (SV1), or other clinically significant oral pathology in the opinion of the Investigator. The Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling a patient into the study.
STUDY DESIGN	This is a 12-week, prospective, multi-center, randomized, double-blind, placebo controlled, Phase 3 study in L-Dopa responsive PD patients with motor fluctuations, designed to determine the efficacy, safety and tolerability of APL-130277. This study will enroll approximately 126 patients. ***Study Procedures*** Before any study procedures are performed on any patient, informed consent must be obtained at an initial Screening Visit (SV1). Patients 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, and patient "ON"/"OFF" training will be performed. Eligible patients will be supplied with anti-nausea medication (US sites – Tigan® [trimethobenzamide hydrochloride; 300 mg t.i.d.]; non-US sites – domperidone [10 mg b.i.d.]), to be taken daily starting on Day -3. Patients will be asked to return to the clinic in the morning of Titration Visit 1 (TV1) for the Dose Titration Phase of the study, and will be instructed to take their last dose of L-Dopa and any other adjunctive PD medication no later than midnight on the evening prior. *Dose Titration Phase* On Titration Visit 1 (TV1), all patients will not take their regular morning dose of L-Dopa or any other adjunctive PD medications. Patients will present to the clinic in an "OFF" state and will be treated with 10 mg APL-130277. Efficacy (MDS-UPDRS Part III) will be performed prior to dosing, and at 15, 30, 45, 60 and 90 minutes after dosing. Safety assessments (adverse events [AEs], vital signs [including supine and standing blood pressure (BP) to assess orthostatic hypotension (OH)]) will be performed prior to dosing, and immediately after the 60 minute MDS-UPDRS Part III assessment. Electrocardiograms (ECGs) will be obtained prior to dosing and 50 minutes after dosing. Patients who respond to the 10 mg APL-130277 dose with a full "ON" response within 45 minutes at TV1, as assessed by the patient and Investigator, will be considered complete from a Dose Titration Phase perspective, and can proceed to randomization and the Maintenance Treatment Phase of the study at this dose. A full "ON", as assessed by the patient, is defined as: a period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a patient feels he/she can perform normal daily activities; AND the response is comparable to or better than their normal response to PD medications prior to enrolling in the study. A full "ON", as determined by the Investigator, is defined as: per clinical judgement, the period of time where the Investigator feels the medication is providing benefit with regard to mobility, stiffness and slowness and the patient has adequate motor function to allow them to perform their normal daily activities. Patients who do not achieve a complete and full "ON" response (as defined above) within 45 minutes with the 10 mg APL-130277 dose at TV1 will restart their normal PD medications and will be asked to return to the clinic within the next 3 days for Titration Visit 2 (TV2), to assess the next highest dose (i.e., 15 mg) in a manner identical to that on Titration Visit 1 (TV1), with identical evaluations. All patients will be asked to take their last dose of L-Dopa and any other adjunctive PD medication no later than midnight the

	evening prior to the visit, and come to the clinic without taking their normal morning PD medications. Patients who achieve a full "ON" (as defined above) within 45 minutes of receiving the 15 mg dose will considered complete from a Dose Titration Phase perspective, and can proceed to the Maintenance Treatment Phase of the study. Patients who do not achieve a full "ON" response (as defined above) within 45 minutes of dosing at TV2 will restart their standard PD medications and be asked to return to the clinic within the next 3 days to assess the next higher dose of APL-130277. This will sequentially be 20 mg [TV3], 25 mg [TV4], 30 mg [TV5] and 35 mg [TV6], as appropriate. In each of these cases, patients will be asked to take their last dose of L-Dopa (and any other adjunctive PD medication) no later than midnight the evening prior to each visit, and come to the clinic without taking their normal morning medication. Safety and efficacy assessments will be performed at each visit exactly as described above. Patients who achieve a full "ON" response within 45 minutes at any titration visit may proceed to randomization and the Maintenance Treatment Phase of the study. At all titration visits, at the discretion of the patient and/or Investigator, the next highest dose may be evaluated at a subsequent titration visit following a full "ON" response in order to assess the potential for the next highest dose in inducing an improved full "ON" response. If this dose produces an improved "ON" response relative to the lower dose without impacting patient safety and tolerability, the higher dose will be used during the Maintenance Treatment Phase of the study. If the "ON" response is the same or worse, or this higher dose is not well-tolerated, the previous dose will be used during the Maintenance Treatment Phase of the study. During the Dose Titration Phase visits, if in the opinion of the Investigator the patient can no longer tolerate the "OFF" state at any point during the Visit, the patient may receive rescue L-Dopa (+/- other adjunctive PD medication) at their standard dosage, or at a dosage considered appropriate by the Investigator to achieve a full "ON" state. If this occurs, patients can return to the clinic on another day to resume the titration with the next highest dose. However, if the patient cannot tolerate the "OFF" state and does not respond efficaciously to a dose of APL-130277, they will be terminated from the study. In this study, the minimum titration dose is 10 mg APL-130277 and the maximum titration dose is 35 mg APL-130277. Any patients who reach 35 mg at Titration Visit 6 (TV6) and do not exhibit a full "ON" response (as defined above) within 45 minutes will be terminated from the study and will have the applicable procedures outlined in the End of Study Visit (EOS) performed. Dosing days in the Dose Titration Phase are not required to occur daily but must be completed within 21 days. Following completion of the titration phase, patients will return to clinic and be randomized to treatment with APL-130277 at the dose determined in the Dose Titration Phase, or matching placebo.

	The Data Safety Monitoring Board (DSMB) will review data on a regular basis during the study and, when 50% of patients have completed the Dose Titration Phase of the study, the DSMB will evaluate whether potential changes to the safety assessment schedule during the Dose Titration Phase can be implemented. Any changes will be outlined in a formal amendment to the study Protocol. *Maintenance Treatment Phase – In-clinic Visits* Patients who successfully completed the Dose Titration Phase of the study will be asked to return to the clinic in an untreated state on Maintenance Visit 1 (MV1). They will be randomized via the Interactive Web Response System (IWRS) to treatment with either APL-130277 or placebo (ratio 1:1) in a double-blind fashion. This visit will occur between 7 and 30 days after the final visit in the Dose Titration Phase of the study. The dose given will be the same as that determined during the Dose Titration Phase of the study (or matching placebo). Patients will be asked to take their last dose of L-Dopa (and any other adjunctive PD medications) no later than midnight the evening prior to the visit, and attend the clinic without taking their normal morning PD medications. Assessments of efficacy and safety will be performed for up to 90 minutes after dosing. Patients will be trained by clinic staff on how to remove study medication from its packaging, and how to handle the sublingual thin films using placebo sublingual thin films supplied to the site. Patients should not self-administer the placebo sublingual thin films. Patients cannot be discharged from the clinic until satisfactorily completing the training. During the Maintenance Treatment Phase of the study, patients will return to the clinic at monthly intervals (Maintenance Visit 2 [MV2], Maintenance Visit 3 [MV3], and Maintenance Visit 4 [MV4]), to be dosed with their randomized treatment (APL-130277 or placebo). Safety and efficacy performed at these visits will be similar to that performed on Maintenance Visit 1 (MV1). *Maintenance Treatment Phase – At Home Assessments* During the 12-week Maintenance Treatment Phase, patients will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their randomized treatment (APL-130277 or placebo) if they experience an “OFF” episode (e.g., morning akinesia, wearing “OFF”, dose failure, sudden “OFF”, etc.) during the day while on their current PD treatment regimen. Patients will be instructed to dose up to 5 “OFF” episodes per day. For 2 days prior to each of these in-clinic visits, patients will be requested to complete a home dosing diary that captures: • Time of randomized treatment self-administration; • Patient “ON”/”OFF” state at 30 minutes after dosing. Between each in-clinic visit, patients will be contacted at two week intervals by the site to assess patient well-being and safety. If required, patients will

	be asked to return to the clinic for additional evaluations at an unscheduled Dose Adjustment Visit. During the Maintenance Treatment Phase of the study, anti-nausea medication (i.e., Tigan® [trimethobenzamide hydrochloride] or domperidone for patients from US and non-US sites, respectively) may be discontinued at the discretion of the Investigator.
INVESTIGATIONAL DRUG	APL-130277 (10 mg, 15 mg, 20 mg, 25 mg, 30 mg and 35 mg [given as 2 sublingual thin films consisting of 15 mg and 20 mg]) For patients dosed with 35 mg, instructions will be given to place the first sublingual thin film (i.e., 20 mg) under the tongue for 3 minutes before placing the second sublingual thin film (i.e., 15 mg) under the tongue immediately and without delay.
REFERENCE PRODUCT	N/A
TREATMENT REGIMENS	Dose titration from 10 mg up to 35 mg APL-130277 in 5 mg increments, and long term outpatient treatment with dose reductions based on safety and tolerability.
CONCOMITANT AND CO-ANALGESIC TREATMENT	Patients at US-sites: Tigan® (trimethobenzamide hydrochloride; 300 mg t.i.d. orally) to overcome the potential nausea associated with administration of APL-130277. Patients at non-US sites: domperidone (10 mg b.i.d.) to overcome the potential nausea associated with administration of APL-130277. All patients: stable doses of a L-Dopa formulation and other stable adjunctive PD medications.
PROHIBITED TREATMENT	- Treatment with any form of apomorphine other than study medication. - Any selective $5HT_3$ antagonist (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron). - Dopamine antagonists (excluding quetiapine or clozapine) or depleting drugs. - Deep brain stimulation or other neurosurgical PD treatment, continuous s.c. apomorphine infusion or Duodopa/Duopa.
STUDY DURATION	Participation is anticipated to be approximately 135 days.
INVESTIGATIVE SITES OR COUNTRIES	This is a multicenter trial run at approximately 35 sites in North America.

STUDY ENDPOINTS	*Primary Endpoint* 1. Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS-UPDRS MOTOR) score at 30 minutes after dosing at the 12 week visit (MV4) of the Maintenance Treatment Phase. *Key Secondary Endpoint* 1. Percentage of patients with a patient-rated full "ON" response within 30 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase. *Other Secondary Endpoints* 1. The percentage of instances where a full "ON" response was achieved at 30 minutes after self-administration of study medication based on the home dosing diary entries. 2. Change from pre-dose in MDS-UPDRS MOTOR score at 15 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase. 3. Time (in minutes) to when study medication is starting to have an effect. 4. Percent of patients with a patient-rated full "ON" response within 30 minutes, whose duration from time when study medication begins to have an effect until their "OFF" (if applicable) lasts for at least 30 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase. 5. Clinical Global Impression of Improvement (CGI-I) post dosing. 6. Patient Global Impression of Improvement (PGI-I) post dosing. 7. Parkinson's Disease Questionnaire-39 (PDQ-39). 8. MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living 9. Evaluation of safety and tolerability data collected, including 12-lead ECGs, OH, oropharyngeal and dopaminergic AEs. *Other Patient-Reported Secondary Endpoints* 1. Change in sleep measures on the Epworth Sleepiness Scale (ESS). 2. European Quality of Life – 5 Dimensions (EQ-5D)
STATISTICAL METHODS SUMMARY	*Analysis Sets* All patients who are randomized and receive one dose of study medication will be included in the safety population. All patients who are randomized, receive at least one dose of study medication and have data from at least one post-randomization efficacy evaluation will be included in the modified intention to treat (mITT) population and will be used in the efficacy analysis. The mITT population will be used for the efficacy analysis, and patients will be grouped according to the randomized treatment group. The safety population will be used for the analysis of the safety endpoints and the patients will be grouped according to the treatment that they received. *Efficacy Analyses* The primary endpoint of the study is the change from pre-dose in MDS-

	UPDRS MOTOR score after 30 minutes at 12 weeks (Maintenance Visit 4, MV4). The difference between APL-130277 and placebo at MV4 will be estimated using a Mixed Model for Repeated Measurements (MMRM). The model will include the observed change from pre-dose MDS-UPDRS MOTOR score values after 30 minutes at Maintenance Visit 1 (MV1), Maintenance Visit 2 (MV2), Maintenance Visit 3 (MV3) and Maintenance Visit 4 (MV4) as the response values, i.e. no imputation will be done. The treatment difference at 12 weeks will be estimated using contrasts. The MMRM model will include the treatment group (APL-130277 or placebo), visit (MV1, MV2, MV3 and MV4), the stratification variables (if any) and the interaction between the treatment group and visit as fixed factors. The change from pre-dose in MDS-UPDRS MOTOR score after 30 minutes at the final Titration visit will be used as a covariate in the model. The sensitivity analyses of the primary endpoint will be specified in the Statistical Analysis Plan. Sensitivity analysis will include a method to handle missing data (e.g., Analysis of Covariance with last observation carried forward or pattern mixture models using multiple imputation), definition of analysis population (e.g., patients completing the study) and statistical method (e.g., Analysis of Covariance models separately for each visit). The primary and secondary endpoints will be tested using a hierarchical approach. The primary endpoint will be tested first and the difference will be declared statistically significant if the nominal two-sided p-value is less than 0.05. In case the primary objective is statistically significant, the secondary endpoint ranked first will be tested using a nominal significance level of 0.05 based on two-sided tests. The testing will continue in a hierarchical manner as long as the previously ranked endpoint was statistically significant. The continuous secondary endpoints will be analyzed using a MMRM model similar to the one used for the primary endpoint. The categorical endpoints will be analyzed using Cochran-Mantel-Haenszel test stratified by the stratification variables, if any. The time-to-event endpoints will be described using the Kaplan-Meier method along with group comparisons analyzed using the Cox proportional hazards model. For categorical and time-to-event endpoints, each visit will be tested separately. In case of missing data, the last value will be carried forward for the categorical and time-to-event endpoints. *Safety Analyses* The analysis of the safety data will focus on the comparison of APL-130277 and placebo during the Maintenance Treatment Phase. In addition, all safety data will be reported separately for the Dose Titration Phase. Adverse events will be tabulated by treatment group 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. For vital signs and ECG parameters, the changes from pre-dose to post-dose assessments of the corresponding day will be calculated and compared between the treatment groups using

	descriptive statistics. In addition, the changes from baseline in the pre-dose values will be compared between the treatment groups. The changes in laboratory values and C-SSRS from baseline to subsequent visits will be compared as well.
SAMPLE SIZE CALCULATION	The study intends to show the superiority of sublingual apomorphine compared with placebo. Assuming a treatment difference of 7 points and standard deviation of 10 points, a sample size of 44 patients per group or 88 patients for two groups will provide ≥ 90% power to detect a statistically significant difference at the 0.05 level (2-sided), using a two-sample t-test. Taking into consideration a 10% dropout rate during the titration phase and a 15% dropout rate during the maintenance phase, the study plans to enroll approximately 126 patients into the Dose Titration Phase and to randomize approximately 114 patients into the Maintenance Treatment Phase.

5 STUDY DESIGN FLOW CHART

5.1 Schedule of Events Table

				Dose Titration Phase[1]						Maintenance Treatment Phase								
Procedures	**Screening Visits[2]**		**Telephone Call[3]**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**	**Maintenance Visit 1[1]**	**Telephone Call**	**Maintenance Visit 2**	**Telephone Call**	**Maintenance Visit 3**	**Telephone Call**	**Maintenance Visit 4**	**End of Study Visit[20]**	**Dose Adjustment Visit**
Study Visit	**SV1**	**SV2**	**T1**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**MV1**	**T2**	**MV2**	**T3**	**MV3**	**T4**	**MV4**	**EOS**	**N/A**
Day (+/- 2 days)	**-28 to -3**		**-4**	**1**	**4**	**7**	**10**	**13**	**16**	**23**	**37**	**51**	**55**	**79**	**93**	**100**	**107**	**N/A**
Outpatient Visit[4]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	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	X	X	X
Review Entry Criteria	X	X																
Review Restriction Criteria				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Medical History/Demographics		X[2]																
Complete Physical Exam, including Oropharyngeal Exam[5]		X[2]								X		X		X		X	X	
Abbreviated Physical Exam, including Oropharyngeal Exam[6]				X	X	X	X	X	X									
Anti-nausea Medication (starts on Day-3)[7]		X	X[3]	X	X	X	X	X	X	X		X		X				
BMI, weight and height[8]		X[2]								X		X		X		X	X	
Vital Signs (BP, HR, RR and Temp) [9, 10]		X[2]		X	X	X	X	X	X	X		X		X		X	X	X
12-Lead ECG[10, 11]		X[2]		X	X	X	X	X	X	X		X		X		X	X	
Clinical Laboratory Tests		X															X	
MMSE		X																
Modified Hoehn and Yahr		X																
MDS-UPDRS Parts I, II and IV		X														X		
MDS-UPDRS Part III[10, 12]		X		X	X	X	X	X	X	X		X		X		X		

				Dose Titration Phase[1]						Maintenance Treatment Phase								
Procedures	**Screening Visits[2]**		**Telephone Call[3]**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**	**Maintenance Visit 1[1]**	**Telephone Call**	**Maintenance Visit 2**	**Telephone Call**	**Maintenance Visit 3**	**Telephone Call**	**Maintenance Visit 4**	**End of Study Visit[20]**	**Dose Adjustment Visit**
Study Visit	**SV1**	**SV2**	**T1**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**MV1**	**T2**	**MV2**	**T3**	**MV3**	**T4**	**MV4**	**EOS**	**N/A**
Day (+/- 2 days)	**-28 to -3**		**-4**	**1**	**4**	**7**	**10**	**13**	**16**	**23**	**37**	**51**	**55**	**79**	**93**	**100**	**107**	**N/A**
Confirmation of L-Dopa Responsiveness		**X**																
Clinical Confirmation of "OFF" or full "ON"[13]		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**		**X**		
Patient Confirmation of "OFF" or full "ON"[13]		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**		**X**		
Randomization										**X**								
In-Clinic Dosing[14]				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**		**X**		
Dispense Study Medication for Outpatient Dosing										**X**		**X**		**X**				**X**
Collect Study Medication												**X**		**X**		**X**	**X[21]**	**X**
Provide Patient Dosing Diary[15]				**X[16]**						**X**		**X**		**X**				**X**
Collect Patient Dosing Diary[15]										**X**		**X**		**X**		**X**		**X**
Patient "OFF" versus "ON" Training		**X[17]**																
Treatment Compliance												**X**		**X**		**X**	**X[21]**	**X**
C-SSRS[18]		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**		**X**	**X**	
PDQ-39		**X**								**X**		**X**		**X**		**X**	**X[21]**	
PGI[19]										**X**		**X**		**X**		**X**	**X[21]**	
CGI[19]										**X**		**X**		**X**		**X**	**X[21]**	
Epworth Sleepiness Scale		**X**								**X**		**X**		**X**		**X**	**X[21]**	
Caregiver Burden (Zarit Burden Interview [ZBI])[22]		**X**								**X**		**X**		**X**		**X**	**X[21]**	

				Dose Titration Phase[1]						Maintenance Treatment Phase								
Procedures	**Screening Visits[2]**		**Telephone Call[3]**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**	**Maintenance Visit 1[1]**	**Telephone Call**	**Maintenance Visit 2**	**Telephone Call**	**Maintenance Visit 3**	**Telephone Call**	**Maintenance Visit 4**	**End of Study Visit[20]**	**Dose Adjustment Visit**
Study Visit	**SV1**	**SV2**	**T1**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**MV1**	**T2**	**MV2**	**T3**	**MV3**	**T4**	**MV4**	**EOS**	**N/A**
Day (+/- 2 days)	**-28 to -3**		**-4**	**1**	**4**	**7**	**10**	**13**	**16**	**23**	**37**	**51**	**55**	**79**	**93**	**100**	**107**	**N/A**
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS)		**X**								**X**		**X**		**X**		**X**	**X[21]**	
European Quality of Life – 5 Dimensions (EQ-5D)		**X**								**X**		**X**		**X**		**X**	**X[21]**	
Outpatient Self-Administration Training										**X**								
AEs/Serious AEs (SAEs)		**X**	**X**	**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**	**X**	**X**	**X**
Record Reason(s) for Dose Adjustment																		**X**

[1] Dosing during the Titration Phase must be completed within 21 days. The initial Maintenance Visit (MV1) must occur between 7 and 30 days after the final Dose Titration Phase visit.

[2] All screening procedures to be conducted within 28 days prior to Titration Visit 1 (TV1). If required by the Investigator, and following receipt of patient consent, the Investigator may review the patients' medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the patient may be eligible for study participation. Procedures performed on SV1 will not be repeated at SV2.

[3] Reminder phone call to patient to start their anti-nausea medication on the morning of Day -3.

[4] Patients may be monitored in the clinic overnight before Dose Titration Visits if such facilities exist and the patient consents.

[5] 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.

[6] 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 post dosing at TV1 to TV6. 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.

[7] May be discontinued in the Maintenance Treatment Phase, at the discretion of the Investigator.

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

[9] Vital signs will be assessed at the Screening Visit (SV2), all Dose Adjustment Visits and EOS; TV1 to TV6 and MV1 to MV4 at t = 0 minutes (just prior to dosing) and immediately after the 60 minute MDS-UPDRS Part III assessment. Blood pressure to be measured supine and standing (measured within 3 minutes of standing) at all timepoints.

[10] Suggested Sequence of Assessments at Pre-Dose: ECG – Vitals – Patient "OFF"/"ON" status - MDS-UPDRS Part III
Suggested Sequence of Assessments Post-Dose where conflict arises: MDS-UPDRS Part III - Patient "OFF"/"ON" status - ECG – Vitals.
If a previously scheduled MDS-UPDRS assessment is not complete prior to performing these assessments, it must be completed prior to performing any scheduled ECG and/or Vitals.

[11] Triplicate 12-lead ECG at the Screening Visit (SV2); single ECGs at t = 0 (just prior to dosing) and 50 minutes post dosing at TV1 to TV6 and MV1 to MV4; single ECG at EOS.

[12] MDS-UPDRS Part III (Motor Function) to be assessed at t = 0 (just prior to dosing), 15, 30, 45, 60 and 90 minutes post dosing at the Screening Visit (SV2), TV1 to TV6, and MV1 to MV4. These assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging. During the Dose Titration Phase only, these assessments may cease if the patient does not experience a full "ON" response within 45 minutes of dosing.

[13] Investigator/patient confirmation of "OFF" or "ON" at SV2.

At TV1 to TV6 and MV1 to MV4, the Investigator will assess "OFF/"ON" state as part of the MDS-UPDRS Part III assessments. During the Dose Titration Phase, these assessments may cease if the patient does not experience a full "ON" response within 45 minutes of dosing.

At TV1 to TV6 and MV1 to MV4, the patient should report: "OFF"/"ON" state at 0, 15, 30, 45, 60 and 90 minutes after dosing, time to when the study medication is starting to have an effect (if applicable), and time to "OFF" following dosing (if it occurs within 90 minutes of dosing). Patients will also be asked if they attained a full "ON" state anytime within 30 minutes of dosing. During the Dose Titration Phase only, these assessments may cease if the patient does not experience a full "ON" response within 45 minutes of dosing.

[14] Dosing in clinic from outpatient supplies (excluding MV4).

[15] Sites will call each patient 3 days before an in-clinic visit during the Maintenance Treatment Phase to remind patients to complete the Patient Dosing Diary. Diary will record: time when patient self-administers a dose; patient "ON"/"OFF" status at 30 minutes following dosing.

[16] Patient Dosing Diary provided on TV1 will be provided for training purposes only. During this phase, patients should be instructed to use their scheduled PD medication administration as the reference point. If needed, patients will be retrained on MV1 in the use of the home dosing diary.

[17] Patient "OFF" versus "ON" Training will occur as part of the L-Dopa challenge at SV2.

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

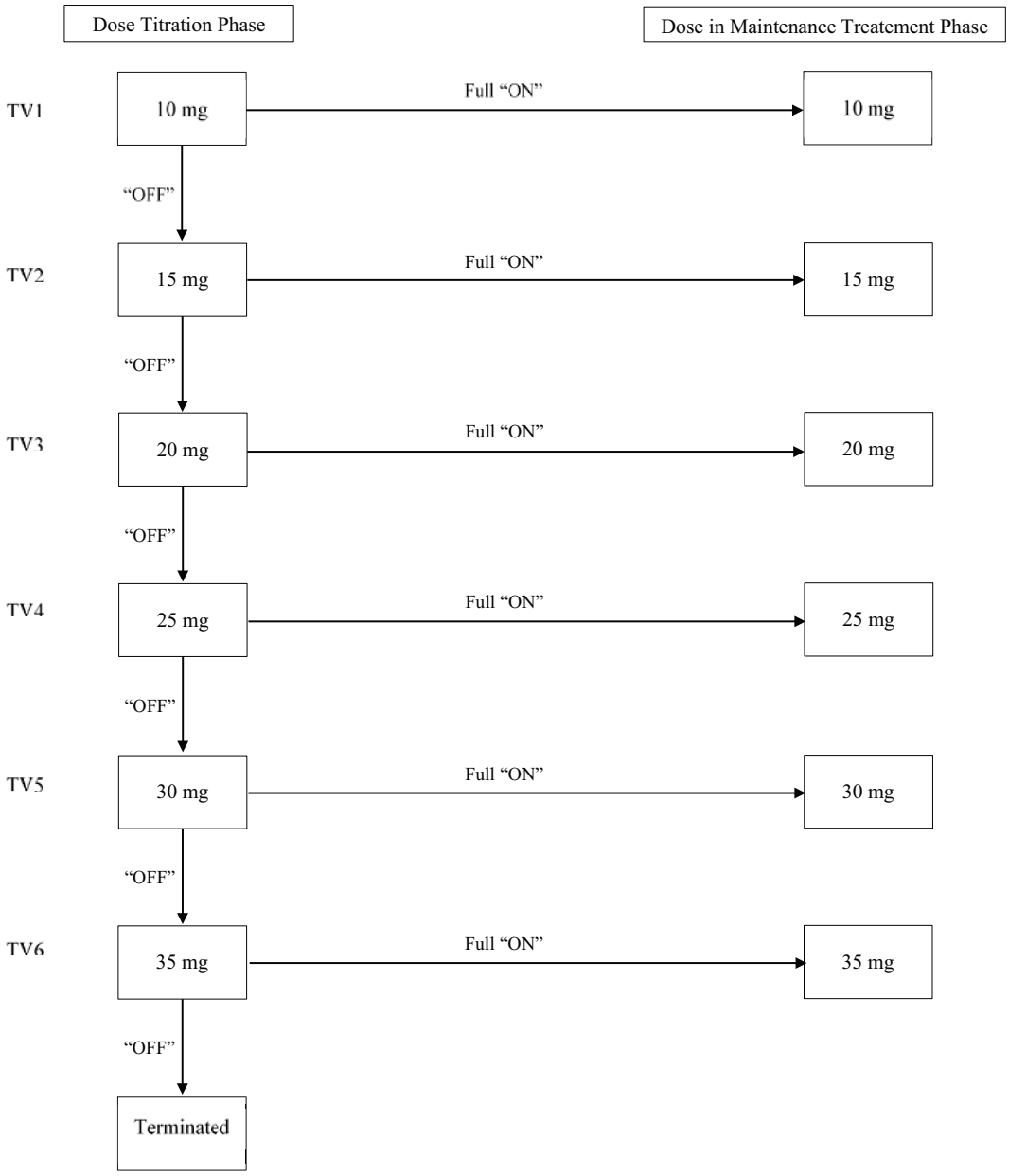
[19] –S to be used at first visit, -I to be used at all subsequent visits.

[20] Patients whose participation is terminated during the Dose Titration Phase or Maintenance Treatment Phase will have the procedures/assessments outlined in the EOS visit completed.

[21] Assessments will not be performed on patients whose participation is terminated during the Dose Titration Phase of the study.

[22] Assessment optional; to be completed if caregiver is present and consent is provided.

5.2 Dose Titration Phase Dosing Paradigm



At all titration visits, at the discretion of the patient and/or Investigator, the next highest dose may be evaluated at a subsequent titration visit following a full "ON" response in order to assess the potential for the next highest dose in inducing an improved full "ON" response. If this dose produces an improved "ON" response relative to the lower dose without impacting patient safety and tolerability, the higher dose will be used during the Maintenance Treatment Phase of the study. If the "ON" response is the same or worse, or this higher dose is not well-tolerated, the previous dose will be used during the Maintenance Treatment Phase of the study.

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7 LIST OF ABBREVIATIONS

$5HT_3$	5-hydroxy tryptophan (serotonin)
AE	adverse event
ALT	alanine aminotransferase
APOKYN®	apomorphine hydrochloride injection
API	active pharmaceutical ingredients
AST	aspartate aminotransferase
b.i.d.	twice daily
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
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
Cynapsus	Cynapsus Therapeutics Inc.
DSMB	Data Safety Monitoring Board
EAC	enrollment adjudication committee
ECG	electrocardiogram
EDC	electronic data capture
EQ-5D	European Quality of Life – 5 Dimensions
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
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
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measurements
MMSE	Mini-mental State Examination
OH	Orthostatic Hypotension
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire
PGI	Patient Global Impression
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBC	red blood cell
REB	Research Ethics Board
RR	respiratory rate
SAE	serious adverse event
s.c.	subcutaneous
SOP	Standard Operating Procedure
TEAE	treatment emergent adverse events
Temp	temperature
t.i.d.	three times daily
US	United States
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
ZBI	Zarit Burden Interview

8 INTRODUCTION

8.1 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 patients 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 patients with PD experience motor fluctuations and/or dyskinesias after 4 to 6 years of L-Dopa therapy, with close to 90% of patients 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 Parkinson's disease 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 patients 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 the United States is apomorphine injected s.c.. This product is not approved in Canada. 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 patients. 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.[6-11]

APOKYN® (apomorphine hydrochloride injection, see APPENDIX I: APOKYN® Prescribing Information) is the first and only prescription medicine that reverses "OFF" episodes (end-of-dose wearing-"OFF" and unpredictable "ON"-"OFF" episodes) associated with advancing PD. APOKYN®, which is 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 subcutaneous (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.[6-11]

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. Patients 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.

8.2 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 minute, 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° to -63.0°
pKa	pKa: 7.0, 8.9
pH	4.3
Water solubility	Sparingly soluble in water and alcohol; slightly soluble in chloroform

8.3 Drug Product (APL-130277 Sublingual Thin 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 as APOKYN®.

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.

Apomorphine Hydrochloride Loading (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

The 35 mg dose will be administered by dosing with the 20 mg sublingual thin film, and after 3 minutes have elapsed, followed by dosing with a 15 mg sublingual thin film.

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 color 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.

8.4 Clinical Experience

This is the sixth planned in-man study for APL-130277. Previous studies, CTH-101, CTH-102, CTH-103 and CTH-104 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. Another study in healthy volunteers is currently being conducted in Malaysia.

The healthy volunteer studies are summarized in considerable detail in the Investigator 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 AE.

The healthy volunteer studies confirmed the method of administration, allowed further refinement of the formulation and confirmed PK comparability of APL-130277 to APOKYN®. 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 APOKYN® label (i.e., between 10 and 60 minutes).

The PD patients dosed in CTH-105 (19 patients) displayed similar side effects to that seen in healthy volunteers; the most common AEs (seen in 2 or more patients) 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 patients discontinued due to AE.

The CTH-105 study demonstrated that APL-130277 provided rapid, clinically meaningful improvement in MDS-UPDRS Part III scores for PD patients in the "OFF" state and converted most patients 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 patients responded to the two lowest doses of (10 and 15 mg).

8.5 Summary of Potential Risks and Benefits

Given that APL-130277 uses the same API as APOKYN®, and that 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® Prescribing Information (see APPENDIX I: APOKYN® Prescribing Information), except for the significant injection site reactions. It is assumed that the bioavailability of APL-130277 will be consistent in CTH-300 with that found in previous experience with APL-130277 compared with APOKYN®.

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 and there have been no reports of local irritation in any of the human studies to date. There is still a risk of local irritation however, and the study will closely monitor this potential AE. The goal of this development program, however, is to formulate a medication that provides the PD patient with an easier delivery system. It is hypothesized 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.

8.6 Rationale

This a multi-center, Phase III, study is designed to evaluate the efficacy, safety and tolerability of

multiple treatments of APL-130277 in patients with PD who experience motor fluctuations ("OFF" episodes). "OFF" episodes are frequently seen in PD patients who receive chronic treatment with L-Dopa, and can be a source of disability. Additional doses of L-Dopa may not be effective because of a long-duration to benefit, or no response at all. A treatment that rapidly and reliably turns patients "ON" is an important unmet medical need in PD.

Single doses of APL-130277 for the treatment of "OFF" episodes experienced by patients with PD have been previously investigated in both a healthy and PD population, however, a well powered study testing multiple treatments of APL-130277 in both an in-clinic and outpatient setting has not been performed. Such a study will provide information on the effect of APL-130277 on "OFF" episodes based on physician and patient assessment in a controlled clinical setting, and based on patient evaluations in an outpatient setting. This study will provide information on treating "OFF" episodes in a PD patient population, assessing the drug in a manner in which it will be recommended for regular clinical use. The study is thus designed to primarily investigate the efficacy of APL-130277 in treating "OFF" episodes (e.g., morning akinesia, wearing "OFF", dose failure, sudden "OFF") when compared with placebo over a 3 month treatment period in both an in-clinic and at-home environment.

9 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 patient information and recruitment materials before the start of the study. During the Clinical Trial, any amendment or modification to the protocol should be submitted to the IRB/REB/IEC. It should also be informed of any event likely to affect the safety of patients 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 patient before any study activity or procedure is undertaken.

10 OBJECTIVES AND STUDY ENDPOINTS

10.1 Objectives

The primary objective is to evaluate the efficacy and safety of APL-130277 versus placebo in patients with PD over a 12 week period.

10.2 Study Endpoints

10.2.1 Primary Endpoint

1) Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS-UPDRS MOTOR) score at 30 minutes after dosing at the 12 week visit (MV4) of the Maintenance Treatment Phase.

10.2.2 Key Secondary Endpoint

1) Percentage of patients with a patient-rated full "ON" response within 30 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase.

10.2.3 Other Secondary Endpoints

1) The percentage of instances where a full "ON" response was achieved at 30 minutes after self-administration of study medication based on the home dosing diary entries.
2) Change from pre-dose in MDS-UPDRS MOTOR score at 15 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase.
3) Time (in minutes) to when study medication is starting to have an effect.
4) Percent of patients with a patient-rated full "ON" response within 30 minutes, whose duration from time when study medication begins to have an effect until their "OFF" (if applicable) lasts for at least 30 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase.
5) CGI-I post dosing.
6) PGI-I post dosing.
7) PDQ-39.
8) MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living.
9) Evaluation of safety and tolerability data collected, including 12-lead ECGs, OH, oropharyngeal and dopaminergic AEs.

10.2.4 Other Patient-Reported Secondary Endpoints

1) Change in sleep measures on the ESS.
2) EQ-5D.

11 STUDY DESIGN

This is a 12-week, prospective, multi-center, randomized, double-blind, placebo controlled, Phase 3 study in L-Dopa responsive PD patients with motor fluctuations, designed to determine the efficacy, safety and tolerability of APL-130277. This study will enroll approximately 126 patients.

11.1 General Overview

This study will be a randomized, placebo-controlled efficacy study, with initial Screening Visits, followed by an initial Dose Titration Phase in which individual responses to single doses of APL-130277 are evaluated in order to determine the initial starting dose for treating "OFF" episodes in an outpatient setting. Once complete, patients will be randomized to either the APL-130277 or placebo (ratio 1:1) and move to the Maintenance Treatment Phase of the study, where they will self-administer study medication in up to 5 "OFF" episodes per day for 12 weeks in the at-home portion of the study. Patients will return to the clinic at regular intervals for safety and efficacy assessments (including the primary endpoint in-office assessments). Overall duration of participation will be approximately 135 days.

11.1.1 Screening Visits

Before any study procedures are performed on any patient, informed consent must be obtained at an initial Screening Visit (SV1). If required by the Investigator, and following receipt of patient consent, the Investigator may review the patients' medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the patient may be eligible for study participation and continuation onto the second Screening Visit (SV2). Patients recruited to participate in the study, and who have provided full consent to participate, will be asked to attend the 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, and patient "ON"/"OFF" training will be performed (see Section 13.6.3.1). Eligible patients will be supplied with anti-nausea medication (US sites - Tigan® [trimethobenzamide hydrochloride; 300 mg t.i.d.]; non-US sites – domperidone [10 mg b.i.d.]), to be taken daily starting on Day -3.

Patients will be asked to return to the clinic in the morning of Titration Visit 1 (TV1) for the Dose Titration Phase of the study, and will be instructed to take their last dose of L-Dopa and any other adjunctive PD medication no later than midnight on the evening prior.

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

11.1.2 Dose Titration Phase

On Titration Visit 1 (TV1), patients will arrive at the clinic in the practically defined "OFF" state having not taken their regular morning dose of L-Dopa or any other adjunctive PD medications, as well as having taken their last dose of L-Dopa and any other adjunctive PD medications no later than midnight the night before. Patients in an "OFF" state, as determined by both the Investigator and patient, will be treated with 10 mg APL-130277. Efficacy (MDS-UPDRS Part III) will be performed prior to dosing, and at 15, 30, 45, 60 and 90 minutes after dosing. Safety assessments (AE, vital signs [including supine and standing BP to assess OH) will be performed prior to dosing, and immediately after the 60 minute MDS-UPDRS Part III assessment. Electrocardiograms (ECGs) will be obtained prior to dosing and 50 minutes after dosing.

Patients who respond to the APL-130277 10 mg dose with a full "ON" response within 45 minutes at TV1, as assessed by the patient and Investigator, will be considered complete from a Dose Titration Phase perspective, and can proceed to randomization and the Maintenance Treatment Phase of the study at this dose. A full "ON", as assessed by the patient, is defined as: a period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a patient feels he/she can perform normal daily activities; AND the response is comparable to or better than their normal response to PD medications prior to enrolling in the study (refer to Section 13.6.3.1). A full "ON", as determined by the Investigator is defined as: the period of time where the Investigator feels the medication is providing benefit with regard to mobility, stiffness and slowness and the patient has adequate motor function to allow them to perform their normal daily activities (refer to Section 13.6.3.1).

Patients who do not achieve a complete and full "ON" response (as defined in Section 13.6.3.1) within 45 minutes with the 10 mg APL-130277 dose at TV1 will restart their normal PD medications and will be asked to return to the clinic within the next 3 days for Titration Visit 2 (TV2), to assess the next highest dose (i.e., 15 mg) in a manner identical to that on Titration Visit 1 (TV1), with identical evaluations. All patients will be asked to take their last dose of L-Dopa and any other adjunctive PD medication no later than midnight the evening prior to the visit, and come to the clinic without taking their normal morning PD medications. Patients who achieve a full "ON" (as defined in Section 13.6.3.1) within 45 minutes of receiving the 15 mg dose will be considered complete from a Dose Titration Phase perspective, and can proceed to randomization and the Maintenance Treatment Phase of the study. Patients who do not achieve a full "ON" response (as defined in Section 13.6.3.1) within 45 minutes of dosing at TV2 will restart their standard PD medications and be asked to return to the clinic within the next 3 days to assess the next higher dose of APL-130277. This will sequentially be 20 mg [TV3], 25 mg [TV4], 30 mg [TV5] and 35 mg [TV6], as appropriate. In each of these cases, patients will be asked to take their last dose of L-Dopa (and any other adjunctive PD medication) no later than midnight the evening prior to each visit, and come to the clinic without taking their normal morning PD medications. For patients dosed with 35 mg, instructions will be given to place the first sublingual thin film (i.e.,

20 mg) under the tongue for 3 minutes before placing the second sublingual thin film (i.e., 15 mg) under the tongue immediately after and without delay. For each visit in the Dose Titration Phase, the site will arrange patient transfers, if needed. Alternatively, patients may be monitored in the clinic overnight if such facilities exist and the patient consents. These occurrences will not be considered a SAE. Safety and efficacy assessments will be performed at each visit exactly as described above. Patients who achieve a full "ON" response within 45 minutes at any titration visit may proceed to randomization and the Maintenance Treatment Phase of the study.

At all titration visits, at the discretion of the patient and/or Investigator, the next highest dose may be evaluated at a subsequent titration visit following a full "ON" response in order to assess the potential for the next highest dose in inducing an improved full "ON" response. If this dose produces an improved "ON" response relative to the lower dose without impacting patient safety and tolerability, the higher dose will be used during the Maintenance Treatment Phase of the study. If the "ON" response is the same or worse, or this higher dose is not well-tolerated, the previous dose will be used during the Maintenance Treatment Phase of the study.

During the Dose Titration Phase visits, if in the opinion of the Investigator the patient can no longer tolerate the "OFF" state at any point during the Visit, the patient may receive rescue L-Dopa (+/- other adjunctive PD medication) at their standard dosage, or at a dosage considered appropriate by the Investigator to achieve a full "ON" state. If this occurs, patients can return to the clinic on another day to resume the titration with the next highest dose. However, if the patient cannot tolerate the "OFF" state and does not respond efficaciously to a dose of APL-130277, they will be terminated from the study.

In this study, the minimum titration dose is 10 mg APL-130277 and the maximum titration dose is 35 mg APL-130277. Any patients who reach 35 mg at Titration Visit 6 (TV6) and do not exhibit a full "ON" response (as defined in Section 13.6.3.1) within 45 minutes will be terminated from the study and will have the applicable procedures outlined in the EOS Visit performed.

Dosing days in the Dose Titration Phase are not required to occur daily, but must be completed within 21 days. Following completion of the titration phase, patients will return to clinic and be randomized to treatment with APL-130277 at the dose determined in the Dose Titration Phase, or matching placebo.

The DSMB will review data on a regular basis during the study and, when 50% of patients have completed the Dose Titration Phase of the study, the DSMB will evaluate whether potential changes to the safety assessment schedule during the Dose Titration Phase can be implemented. Any changes will be outlined in a formal amendment to the study Protocol.

11.1.3 Maintenance Treatment Phase – In-clinic Visits

Patients who successfully completed the Dose Titration Phase of the study will be asked to return to the clinic on Maintenance Visit 1 (MV1). They will be randomized via the IWRS to treatment

with either APL-130277 or placebo (ratio 1:1) in a double-blind fashion. This visit will occur between 7 and 30 days after the final visit in the Dose Titration Phase of the study. The dose given will be the same as that determined during the Dose Titration Phase of the study (or matching placebo). Patients will be asked to take their last dose of L-Dopa (and any other adjunctive PD medications) no later than midnight the evening prior to the visit, and attend the clinic without taking their normal morning PD medications. Assessments of efficacy and safety will be performed for up to 90 minutes after dosing. Patients will be trained by clinic staff on how to remove study medication from its packaging, and how to handle the sublingual thin films using placebo sublingual thin films supplied to the site. Patients **should not** self-administer the placebo sublingual thin films. Patients cannot be discharged from the clinic until satisfactorily completing the training.

At the in-clinic visits, patients will be instructed to place the sublingual thin film under their tongue (see Section 15.2 for full dosing details). Patients will be asked to follow the same process of study drug administration (excluding staff confirmation) during the at-home portion of the study.

During the Maintenance Treatment Phase of the study, patients will return to the clinic at monthly intervals (Maintenance Visit 2 [MV2], Maintenance Visit 3 [MV3], and Maintenance Visit 4 [MV4]), to be dosed with their randomized treatment (APL-130277 or placebo). Safety and efficacy performed at these visits will be similar to that performed on Maintenance Visit 1 (MV1).

11.1.4 Maintenance Treatment Phase – At Home Assessments

For the duration of the Maintenance Treatment Phase, patients will be instructed that for the next 12 weeks, they should continue with their regular PD medication regimen(s), but should dose themselves with their randomized treatment (APL-130277 or placebo) if they experience an "OFF" episode (e.g., morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) during the day while on their current treatment regimen. Patients will be instructed to dose up to 5 "OFF" episodes per day.

For 2 days prior to each of these in-clinic visits, patients will be requested to complete a home dosing diary that captures:

- Time of randomized treatment self-administration;
- Patient "ON"/"OFF" state at 30 minutes after dosing.

Between each in-clinic visit, patients will be contacted at two week intervals by the site to assess patient well-being and safety. If required, patients will be asked to return to the clinic for additional evaluations at an unscheduled Dose Adjustment Visit. These visits will be classified as unscheduled visits.

During the Maintenance Treatment Phase of the study, anti-nausea medication (i.e., Tigan®

[trimethobenzamide hydrochloride] or domperidone for patients from US and non-US sites, respectively) may be discontinued at the discretion of the Investigator. All other PD medications must remain stable during the Maintenance Treatment Phase of the study, with the exception of modifications needed for safety reasons, which must be discussed with the Medical Monitor.

11.2 Blinding

An IWRS will allocate treatment during the Maintenance Treatment Phase based on a pre-specified randomization list, generated by the IWRS provider.

Active and placebo study medication for the Maintenance Treatment Phase will be provided to each site participating in the study. For each dose, study medication and packaging will be identical in size, shape, colour 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 patient. Patients and clinical staff members will be blinded to treatment assignments until the completion of the study.

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

11.3 Data Safety Monitoring Board

This study will be conducted in a double-blind fashion in which patients, Investigators and their study staff, and the Sponsor are blinded with respect to treatment allocation. A DSMB will be convened during the course of the study in order to:

- On a regular basis, review the safety data including SAEs;
- Respond to special requests from regulatory authorities and/or IRB/IEC/REBs;
- Evaluate results of an analysis performed after 50% patients have completed the Dose Titration Phase to determine if it is safe and appropriate to reduce the extent of safety evaluations during titration, and to make recommendations for amending the protocol.

The full responsibilities and purview of the DSMB will be outlined in the DSMB Charter, which will be approved by the Sponsor prior to the initiation of the first patient into the Dose Titration Phase of the study.

11.4 Enrollment Adjudication Committee (EAC)

The Investigator must obtain approval from the EAC prior to enrolling any patient into the study.

The EAC will be comprised of a committee of two neurologists who will determine the patient's appropriateness for inclusion in the study, independent of the entry criteria (see APPENDIX XV: Enrollment Adjudication Committee Form). 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 in writing (e.g., via e-mail) of the decision. Following EAC 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.

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 patient, will serve as EAC documentation for inclusion into the study and must be stored in the site study file.

12 PATIENT POPULATION

12.1 Selection of Study Population

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

Approximately one hundred and twenty-six (126) patients will be enrolled into the Dose Titration Phase in order to randomize approximately 114 patients into the Maintenance Treatment Phase.

12.1.1 Inclusion Criteria

A patient will be eligible for study entry if all of the following inclusion criteria are met:

1) Male or female ≥ 18 years of age.
2) Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria[2] (see APPENDIX XIV: United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria).
3) Clinically meaningful response to L-Dopa with well-defined early morning "OFF" episodes, as determined by the Investigator.
4) Receiving stable doses of L-Dopa/carbidopa (immediate or CR) administered at least 4 times per day OR Rytary™ administered 3 times per day, for at least 4 weeks before the initial Screening Visit (SV1). Adjunctive PD medication 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) Patients must experience at least one well defined "OFF" episode per day with a total daily "OFF" time duration of ≥ 2 hours during the waking day, based on patient self-assessment.
7) Patient and/or caregiver must be trained in performing home dosing diary assessments of the motor state and must be able to recognize "ON" and "OFF" states.
8) Stage III or less on the modified Hoehn and Yahr scale in the "ON" state.
9) MMSE score > 25.
10) If female and of childbearing potential, must agree to use one of the following methods of birth control:
    - Oral contraceptive;

[2] Excluding the "more than one affected relative" criterion.

- 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).

11) 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 30 days after final drug administration.

12) Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.

13) Able to understand the consent form, and to provide written informed consent.

14) Must be approved as a satisfactory candidate by an EAC.

12.1.2 Exclusion Criteria

A patient will not be eligible for study entry if any of the following exclusion criteria are met:

1) Atypical or secondary parkinsonism.

2) Previous treatment with any of the following: a neurosurgical procedure for PD; continuous s.c. apomorphine infusion; or Duodopa/Duopa.

3) Treatment with any form of s.c. apomorphine within 7 days prior to the initial Screening Visit (SV1). Patients that stopped s.c. apomorphine for any reason other than systemic safety concerns or lack of efficacy may be considered.

4) Contraindications to APOKYN®, or hypersensitivity to apomorphine hydrochloride or any of the ingredients of APOKYN® (notably sodium metabisulfite); Tigan® (trimethobenzamide hydrochloride; patients from US sites only); or domperidone (patients from non-US sites only).

5) Female who is pregnant or lactating.

6) Participation in a clinical trial within 30 days prior to the initial Screening Visit (SV1).

7) Receipt of any investigational (i.e., unapproved) medication within 30 days prior to the initial Screening Visit (SV1).

8) Currently taking selective $5HT_3$ antagonists (i.e., ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (excluding quetiapine or clozapine) or dopamine depleting agents.
9) Drug or alcohol dependency in the past 12 months.
10) History of malignant melanoma.
11) Clinically significant medical, surgical, or laboratory abnormality in the opinion of the Investigator.
12) Major psychiatric disorder including, but not limited to, dementia, bipolar disorder, 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.
13) History of clinically significant hallucinations during the past 6 months.
14) History of clinically significant impulse control disorder(s).
15) Dementia that precludes providing informed consent or would interfere with participation in the study.
16) 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 C-SSRS or attempted suicide within the last 5 years.
17) Donation of blood or plasma in the 30 days prior to first dosing.
18) Cankers or mouth sores within 30 days prior to the initial Screening Visit (SV1), or other clinically significant oral pathology in the opinion of the Investigator. The Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling a patient into the study.

12.2 Prior and Concomitant Treatments

12.2.1 Prohibited Treatments

The following prior and/or 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 (e.g., ondansetron, granisetron, dolasetron, palonosetron, alosetron) from 30 days prior to the initial Screening Visit (SV1) until study completion.

- Any dopamine antagonists or dopamine depleting drugs excluding anticholinergics and/or antihistamines with anticholinergic effects. Examples include, but are not limited to:
    - **Antipsychotics -** Both typical and atypical antipsychotics (except quetiapine and clozapine), including but not limited to: aripiprazole, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, olanzapine, risperidone, ziprasidone, depot neuroleptics;
    - Cinnarizine;
    - Flunarizine;
    - Prochlorperazine;
    - Promethazine;
    - Tetrabenazine;
    - Lithium;
    - Metoclopropamide;
    - Reserpine.
- Deep brain stimulation or other neurosurgical procedure for the treatment of PD.
- Continuous s.c. apomorphine infusion.
- Duodopa/Duopa.
- Cisapride.
- Dronedarone.

12.2.2 Permitted Treatments

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

- Domperidone (10 mg b.i.d.; non-US sites) or Tigan® (trimethobenzamide hydrochloride; 300 mg t.i.d.; US sites) to overcome the potential nausea associated with apomorphine administration. Use of anti-nausea medication will be required during the Dose Titration Phase of the study, however may be discontinued during the Maintenance Treatment Phase, at the discretion of the Investigator.
- 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). MAO-B inhibitors will be allowed but must be stable for at least 8 weeks prior to the initial Screening Visit (SV1).

- Any other medication other than those identified in Section 12.2.1 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 patient, at the discretion of the Investigator. All concomitant medications must be recorded in the appropriate Case Report Form (CRF) for the patient.

12.3 Patient Withdrawal from the Study

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

1) In order to protect their safety and/or well-being;
2) If they, or their caregiver, are unwilling or unable to comply with required study procedures;
3) If they withdraw their consent to participate in the study;
4) If the study is prematurely terminated by the Sponsor or Regulatory Authorities;
5) If they no longer meet the inclusion/exclusion criteria within the study.

Patients 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 patients in the study. However, patients must be withdrawn from the study if the patient withdraws his or her consent to participate. In the event of patient withdrawal, the Investigator should attempt to determine the reason for the patient'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 patient 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 patient's record.

Neither randomized patients withdrawing from the study nor those removed by the Investigator or Sponsor will be replaced. Randomized patients who are withdrawn from this study may not re-enter the study at a later date. The patient number/randomization number for a withdrawn patient will not be reassigned to another patient.

If a patient is removed or withdraws from the study, the procedures outlined in the EOS Visit will be performed, where possible. Patients withdrawn/terminated during the Dose Titration Phase will have fewer assessments performed than those withdrawn/terminated during the Maintenance Treatment Phase (refer to Section 5 and Section 13.4.5 for additional details on the procedures to be performed).

13 STUDY PROCEDURES

This study will consist of the following:

1) Screening Visits (SV1 and SV2)
2) Telephone Call (T1)
3) 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)
4) Maintenance Treatment Phase
    a. Maintenance Visit 1 (MV1)
    b. Maintenance Visit 2 (MV2)
    c. Maintenance Visit 3 (MV3)
    d. Maintenance Visit 4 (MV4)
    e. Telephone Call (T2 to T4)
    f. End of Study Visit (EOS)
    g. Unscheduled Dose Adjustment Visits

13.1 Screening Visits (SV1 and SV2; Day -28 to -3)

Patients must sign an ICF before any screening-related procedures are performed at an initial Screening Visit (SV1). Following receipt of patient consent, the patient will be asked to return to the clinic for the second Screening Visit (SV2). All screening assessments must be performed within 28 days before Titration Visit 1 (TV1).

If required by the Investigator, and following receipt of patient consent, the Investigator may review the patients' medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the patient 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:

- 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 lower lip, the surface of the tongue, and under the tongue.
- Provide patient with anti-nausea medication (to begin on Day -3).
- Measure height and weight; calculate BMI.
- Record vital signs (BP, HR, RR and Temp), after the patient has been in a supine position for 5 minutes. Patient BP to be measured both supine and standing (within 3 minutes of standing).
- Perform a standard 12-lead ECG in triplicate.
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, urinalysis and serology). Serum pregnancy for females of child-bearing potential only. The total volume of blood collected will not exceed 25 mL.
- Perform a MMSE.
- Assess patient using the Modified Hoehn and Yahr scale (see APPENDIX III: Modified Hoehn and Yahr Scale).
- Assess patient using MDS-UPDRS Parts I, II and IV (see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)).
- Assess patient motor function using MDS-UPDRS Part III at t = 0 (just prior to L-Dopa administration), 15, 30, 45, 60 and 90 minutes after L-Dopa administration (see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)).
- Confirm L-Dopa responsiveness. Patients will take their normal morning dose of L-Dopa ***without*** their normal adjunctive PD medication.
- Investigator confirmation of "OFF" or "ON".
- Patient confirmation of "OFF" or "ON".
- Perform patient training in order to distinguish "OFF" versus "ON" episodes (see Section 13.6.3.1).

- Assess suicidal ideation using C-SSRS (see APPENDIX VI: Columbia Suicide Severity Rating Scale (C-SSRS)). The "Screening" scale should be used at this visit.
- Provide the patient with the PDQ-39 to complete (see APPENDIX VII: PDQ-39).
- Assess using the ESS (see APPENDIX X: ESS).
- Assess caregiver burden using the ZBI (see APPENDIX XI: ZBI).
- Complete the QUIP-RS (see APPENDIX XII: QUIP-RS).
- Provide the patient with the EQ-5D (see APPENDIX XIII: EQ-5D).
- Record any AEs/SAEs that have occurred since the last patient visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.

The Investigator will review all information obtained from the screening procedures. If the patient is not eligible, the patient will be a screening failure and will not attend any other visits. Patients 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.

13.2 Telephone Call (T1)

Approximately 4 days prior to the scheduled Titration Visit 1 (TV1) of the Dose Titration Phase, site staff will call the potential patient to remind them to initiate their anti-nausea medication regimen on Day -3. Any questions pertaining to the study and/or study procedures should be addressed during this telephone contact. Staff should enquire and record any AEs/SAEs that have occurred since the last patient visit, and any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.

13.3 Dose Titration Phase (TV1 to TV6)

13.3.1 TV1 to TV6

The evening prior to these visits, patients will be asked to take their last dose of L-Dopa and other adjunctive PD medication ***no later than midnight*** and to return to the clinic in the morning having not taken their normal morning PD medications. If needed, the site will arrange patient transfers. Alternatively, patients may be monitored in the clinic overnight if such facilities exist and the patient consents. These occurrences will not be considered a SAE.

Doses of APL-130277 will be administered as follows during the Dose Titration Phase:

- 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 (administered as a 20 mg sublingual thin film and 15 mg sublingual thin film, sequentially).

Site staff will perform the following procedures on each Titration Visit:

- Reconfirm consent.
- Review restriction criteria.
- Perform an abbreviated physical examination, including oropharyngeal examination, prior to dosing and 2 hours post 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.
- Record supine vital signs (BP, HR, RR and Temp) prior to dosing and after the 60 minute MDS-UPDRS Part III assessment. Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Perform a standard 12-lead ECG prior to dosing and 50 minutes after dosing.
- Assess patient motor function using MDS-UPDRS Part III at t = 0 (just prior to dosing), 15, 30, 45, 60 and 90 minutes after dosing (see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)). During the Dose Titration Phase only, these assessments may cease if the patient does not experience a full "ON" response within 45 minutes of dosing.
- If patients are in the "OFF" state, dose with APL-130277.
- Investigator confirmation of "OFF" or "ON". Investigator will assess "OFF"/"ON" state as part of the MDS-UPDRS Part III assessments. The patient must be in an "OFF" state prior to dosing in order to proceed with dosing. During the Dose Titration Phase only, these assessments may cease if the patient does not experience a full "ON" response within 45 minutes of dosing.
- Patient confirmation of "OFF" or "ON". Patient should report: "OFF"/"ON" state at t = 0, 15, 30, 45, 60 and 90 minutes after dosing, time to when the study medication is starting to have an effect (if applicable), and time to "OFF" following dosing (if it occurs within 90 minutes of dosing). Patients will also be asked if they attained a full "ON" state anytime within 30 minutes. During the Dose Titration Phase only, these assessments may cease if the patient does not experience a full "ON" response within

45 minutes of dosing. The patient must be in an "OFF" state prior to dosing in order to proceed with dosing.

- Provide patient with a home dosing diary (TV1 only; see APPENDIX V: Patient Home Dosing Diary). Diary will be provided for training purposes only. If needed, patients will be retrained at MV1 in the use of the home dosing diary.
- Assess suicidal ideation using C-SSRS (see APPENDIX VI: Columbia Suicide Severity Rating Scale (C-SSRS)). "Since Last Visit" version should be used at these visits.
- Record any AEs/SAEs that have occurred since the last patient visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.
- Provide patient with anti-nausea medication.

Patients who respond to an APL-130277 dose with a full "ON" response within 45 minutes of dosing ***at any*** Titration Visit, will be considered complete from a Dose Titration perspective and may proceed to the Maintenance Treatment Phase of the study. This dose will be used in the Maintenance Treatment Phase of the study. Sites should enter all titration MDS-UPDRS Part III data for the patient into the CRF within 48 hours of the last titration visit for review by the Medical Monitor. NOTE: At all titration visits, at the discretion of the patient and/or Investigator, the next highest dose may be evaluated at a subsequent titration visit following a full "ON" response in order to assess the potential for the next highest dose in inducing an improved full "ON" response. If this dose produces an improved "ON" response relative to the lower dose without impacting patient safety and tolerability, the higher dose will be used during the Maintenance Treatment Phase of the study. If the "ON" response is the same or worse, or this higher dose is not well-tolerated, the previous dose will be used during the Maintenance Treatment Phase of the study.

A full "ON" is defined in Section 13.6.3.1.

Patients who do not achieve a complete and full "ON" response within 45 minutes with the APL-130277 dose given will be asked to return to clinic within the next 3 days for their subsequent Titration Visit, to assess the next highest dose in a manner identical to that on Titration Visit 1 (TV1).

At any point in the visit, patients in the "OFF" state who, in the opinion of the Investigator, can no longer tolerate their "OFF" state may receive rescue L-Dopa (+/- other adjunctive PD medication) at their standard dosage, or at a dosage considered appropriate by the Investigator to achieve an "ON" state. If this occurs, patients can return to the clinic on another day to resume the titration with the next highest dose. However, if the patient cannot tolerate the "OFF" state and does not respond efficaciously to a dose of APL-130277, they will be terminated from the study.

13.4 Maintenance Treatment Phase

This phase of the study will consist of 2 parts – an in-clinic assessment phase and an at-home assessment phase. The former will consist of 4 in-clinic visits where formal assessments of efficacy and safety will be performed following administration of randomized treatment. The latter will be an at-home self-administration phase, where all patients will be instructed to self-administer their doses of randomized treatment (APL-130277 or placebo; 1:1 ratio) in order to treat up to 5 "OFF" episodes (i.e., morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF") per day.

Patients who have successfully completed the Dose Titration Phase of the study will be randomized to their treatment and receive their first dose of randomized treatment on Maintenance Visit 1 (MV1). The dose given will be the same as that determined during the Dose Titration Phase of the study.

13.4.1 MV1 to MV4: In-Clinic Assessments

Maintenance Visit 1 (MV1) may only occur ***a minimum*** of 7 days but ***no later*** than 30 days after the last Dose Titration Phase visit.

The evening prior to each of these visits, patients will be asked to take their last dose of L-Dopa and other adjunctive PD medication ***no later than midnight*** and to return to the clinic in the morning having not taken their normal morning PD medication.

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

- Reconfirm consent.
- Review restriction criteria.
- Randomize patient via the IWRS system (MV1 only; the transaction should occur a sufficient number of days before the Maintenance Visit in order to allow for study drug to be shipped and arrive at the clinic).
- Perform a complete physical examination, including oropharyngeal examination prior to 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 weight.
- Record supine vital signs (BP, HR, RR and Temp) prior to dosing and immediately after the 60 minute MDS-UPDRS Part III assessment. Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Perform a standard 12-lead ECG prior to dosing and 50 minutes after dosing.

- Assess patient using MDS-UPDRS Parts I, II and IV (MV4 only; see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)).
- Assess patient motor function using MDS-UPDRS Part III at t = 0 (just prior to dosing), 15, 30, 45, 60 and 90 minutes after dosing (see APPENDIX IV: Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)).
- If patients are in the "OFF" state, dose with randomized treatment.
- Investigator confirmation of "OFF" or "ON". Investigator will assess "OFF"/"ON" state as part of the MDS-UPDRS Part III assessments. The patient must be in an "OFF" state prior to dosing in order to proceed with dosing.
- Patient confirmation of "OFF" or "ON". Patient should report: "OFF"/"ON" state at t = 0, 15, 30, 45, 60 and 90 minutes after dosing, time to when the study medication is starting to have an effect (if applicable), and time to "OFF" following dosing (if it occurs within 90 minutes of dosing). Patients will also be asked if they attained a full "ON" state anytime within 30 minutes of dosing. The patient must be in an "OFF" state prior to dosing in order to proceed with dosing.
- Dispense outpatient supplies (excluding MV4).
- Collect outpatient supplies (excluding MV1).
- Provide patient with a home dosing diary (excluding MV4).
- Collect patient home dosing diary.
- Assess treatment compliance (excluding MV1).
- Assess suicidal ideation using C-SSRS (see APPENDIX VI: Columbia Suicide Severity Rating Scale (C-SSRS)). "Since Last Visit" version should be used at these visits.
- Provide the patient with the PDQ-39 to complete (see APPENDIX VII: PDQ-39).
- Ask patient to complete the PGI (see APPENDIX IX: PGI). –S to be used at the first visit, -I to be used at all subsequent visits.
- Complete the CGI (see APPENDIX VIII: CGI). –S to be used at the first visit, -I to be used at all subsequent visits.
- Assess using the ESS (see APPENDIX X: ESS).
- Assess caregiver burden using the ZBI (see APPENDIX XI: ZBI).
- Complete the QUIP-RS (see APPENDIX XII: QUIP-RS).

- Provide the patient with the EQ-5D (see APPENDIX XIII: EQ-5D).
- Outpatient self-administration training (MV1 only). Patients will be trained by clinic staff on how to remove study medication from its packaging, and how to handle the sublingual thin films using placebo sublingual thin films supplied to the site. Patients **should not** self-administer the placebo sublingual thin films. Patients cannot be discharged from clinic until satisfactorily completing the training.
- Record any AEs/SAEs that have occurred since the last patient visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.
- Provide patient with anti-nausea medication, if applicable (excluding MV4).

13.4.2 At-Home Assessments

During the 12-week Maintenance Treatment Phase, patients will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their randomized treatment (APL-130277 or placebo) if they experience an "OFF" episode (e.g., morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) during the day while on their current treatment regimen. Patients will be instructed to dose up to 5 "OFF" episodes per day.

Prior to each in-clinic visit during the Maintenance Treatment Phase of the study, patients will be requested to complete a home dosing diary that captures:

- Time of randomized treatment self-administration;
- Patient "ON"/"OFF" state at 30 minutes after dosing.

Patients will complete this diary for every self-administration they perform on each of these 2 days. Clinic staff will call each patient approximately 3 days prior to a scheduled in-clinic visit in order to remind patients to complete their home dosing diary. Patients should be reminded to document when they dose themselves and to accurately report their "ON"/"OFF" status at 30 minutes after dosing.

13.4.3 Telephone Contacts (T2 to T4)

Sites will follow-up with patients at the mid-point between each in-clinic visit in order to assess study medication compliance, patient safety and well-being. If needed, an unscheduled Dose Adjustment Visit will be scheduled with the patient in order to further assess safety and well-being.

Staff should enquire and record any AEs/SAEs that have occurred since the last patient visit, and any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.

13.4.4 End of Study Visit

Approximately 1 week following the completion of the study, patients will be asked to return for a final safety assessment visit. The following procedures will take place at this visit:

- Reconfirm consent.
- Perform a complete physical examination, including oropharyngeal examination, prior to 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 weight.
- Record supine vital signs (BP, HR, RR and Temp). Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Perform a standard 12-lead ECG.
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry and urinalysis). Serum pregnancy for females of child-bearing potential only. Blood collected for this evaluation will not exceed 20 mL.
- Collect outpatient supplies (if applicable).
- Assess treatment compliance (if applicable).
- Assess suicidal ideation using C-SSRS (see APPENDIX VI: Columbia Suicide Severity Rating Scale (C-SSRS)).
- Provide the patient with the PDQ-39 to complete (see APPENDIX VII: PDQ-39).
- Ask patient to complete the PGI-I (see APPENDIX IX: PGI).
- Complete the CGI-I (see APPENDIX VIII: CGI).
- Assess using the ESS (see APPENDIX X: ESS).
- Assess caregiver burden using the ZBI (see APPENDIX XI: ZBI).
- Complete the QUIP-RS (see APPENDIX XII: QUIP-RS).
- Provide the patient with the EQ-5D (see APPENDIX XIII: EQ-5D).
- Record any AEs/SAEs that have occurred since the last patient visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.

13.4.5 Early Terminations

Every effort should be made to have patients complete all study visits. All patients who are terminated early in either the Dose Titration Phase or Maintenance Treatment Phase will all undergo the following assessments:

- Reconfirm consent.
- Perform a complete physical examination, including oropharyngeal examination, prior to 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 weight.
- Record supine vital signs (BP, HR, RR and Temp). Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- Perform a standard 12-lead ECG.
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry and urinalysis). Serum pregnancy for females of child-bearing potential only. Blood collected for this evaluation will not exceed 20 mL.
- Assess suicidal ideation using C-SSRS (see APPENDIX VI: Columbia Suicide Severity Rating Scale (C-SSRS)).
- Record any AEs/SAEs that have occurred since the last patient visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.

Patients whose participation is terminated early in the Maintenance Treatment Phase will also undergo the following assessments in addition to those listed above:

- Collect outpatient supplies (if applicable).
- Assess treatment compliance (if applicable).
- Provide the patient with the PDQ-39 to complete (see APPENDIX VII: PDQ-39).
- Ask patient to complete the PGI-I (see APPENDIX IX: PGI).
- Complete the CGI-I (see APPENDIX VIII: CGI).
- Assess using the ESS (see APPENDIX X: ESS).
- Assess caregiver burden using the ZBI (see APPENDIX XI: ZBI).
- Complete the QUIP-RS (see APPENDIX XII: QUIP-RS).

- Provide the patient with the EQ-5D (see APPENDIX XIII: EQ-5D).

13.4.6 Unscheduled Dose Adjustment Visits

If at any time during the Maintenance Treatment Phase of this study, it is determined that a dose adjustment is required, the patient will return for an unscheduled Dose Adjustment Visit. The following will be performed:

- Reconfirm consent.
- Review restriction criteria.
- Record supine vital signs (BP, HR, RR and Temp). Blood pressure to be measured both supine and standing (measured within 3 minutes of standing).
- IWRS system transaction in order to obtain the proper new dose (if required).
- Dispense new study medication for outpatient dosing (if required).
- Collect remaining study medication provided at the last visit (if required).
- Provide patient home dosing diary and instruct patients to complete it 2 days before their subsequent in-clinic visit.
- Collect patient diaries completed since the last visit.
- Assess treatment compliance.
- Record any AEs/SAEs that have occurred since the last patient visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the patient since the last visit.
- Record reason for the dose adjustment.

This visit may occur over multiple days to accommodate receipt of the new dose of study drug (if necessary).

Dosage adjustments, if in the opinion of the Investigator are necessary for patient safety and tolerability, may reduce the scheduled dose of study drug the next lowest dose (e.g., to the 10 mg dose if the patient is receiving 15 mg). Increases in dosage in this study **will not** be allowed. The Investigator should make all attempts to maintain patients on a stable dose.

Any patient whose dose has been reduced at a Dose Adjustment Visit will self-administer study drug using the lower dosage at home however, all in-clinic visits during the Maintenance Treatment Phase of the study will be assessed using the dose identified during the Dose Titration Phase as inducing a full “ON” response. If, in the opinion of the Investigator, use of this dose cannot be tolerated by the patient, they should be discontinued from the study.

13.5 Duration of Treatment

The approximate duration of participation in this study from Screening until final study completion is 135 days.

13.6 Assessments

13.6.1 Order of Assessments

The following summarizes the suggested sequence of assessments prior to dosing during the second Screening Visit (SV2), Dose Titration Phase and the in-clinic visits during the Maintenance Treatment Phase of the study:

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

The following summarizes the suggested sequence of assessments after dosing during the second Screening Visit (SV2), Dose Titration Phase and the in-clinic visits during the Maintenance Treatment Phase of the study:

MDS-UPDRS Part III - Patient "OFF"/"ON" status - ECG – 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.

13.6.2 Clinical Safety Assessments

13.6.2.1 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; musculoskeletal system; central and peripheral nervous system; and skin; to be done at the second Screening Visit (SV2), and MV1 to MV4.

Abbreviated physical examinations at all scheduled timepoints must include head-eyes-ears-nose and throat; cardiovascular system; respiratory system; abdomen; and skin; to be done at t = 0 (just prior to dosing) and 120 minutes post dosing at visits at TV1 to TV6.

All 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 patient provides consent to do so.

13.6.2.2 Vital Signs

Vital signs (HR, RR, BP and body temperature) will be measured at various timepoints after the patient has been in a supine position for 5 minutes. Vital signs will be measured at all scheduled study visits. Vital signs (BP only) will also be measured within three minutes of standing at all timepoints.

During the Dose Titration Phase, if the 60 minute MDS-UPDRS Part III assessment is not performed since the patient did not experience a full "ON" response within 45 minutes of dosing, the vital signs assessment will be performed at the approximate time it would have been scheduled if the MDS-UPDRS Part III assessment were performed.

Study personnel will carefully monitor patients 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.

13.6.2.3 12-Lead ECGs

A standard 12-lead ECG will be performed at all timepoints outlined in the protocol. A triplicate 12-lead ECG will be performed at the second Screening Visit (SV2) only. If required by the Investigator to assess patient eligibility, a triplicate ECG may be performed at SV1 instead, but will not be repeated at SV2.

ECGs will be performed in a semi-recumbent position and after 5 minutes of rest.

The following parameters will be reported in the CRF:

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

All ECGs should be assessed by the Investigator and deemed "Normal", "Abnormal, not clinically significant" and "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.

ECG assessments will be centralized and performed by a suitable vendor contractor by the Sponsor.

13.6.2.4 Modified Hoehn and Yahr

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

13.6.2.5 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 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

13.6.2.6 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 patient 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.

13.6.2.7 C-SSRS

Formal assessments of patient suicidal ideation and behavior will be assessed at the second Screening Visit (SV2) and all in-clinic visits during the Dose Titration Phase and Maintenance Treatment Phase of the study. A final assessment will be performed at the time of termination, regardless if it is scheduled (i.e., at EOS visit) or an early termination/withdrawal.

At the Screening Visit (SV2), the C-SSRS ‘Screening’ assessment tool will be used. Patients 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.

The Investigator should closely monitor the responses of patients during the interview and watch for signs that suggest current suicidal ideation or intent.

13.6.2.8 Other Safety and Quality of Life Assessments

The following assessments will be performed in this study at the timepoints indicated in the Schedule of Events:

- PDQ-39
- PGI
- CGI
- ESS

- ZBI – Optional; to be completed if caregiver is present and consent is provided.
- QUIP-RS
- EQ-5D

These assessments will be performed at any point during the scheduled visit in accordance with the guidelines for each (see applicable Appendices).

13.6.2.9 Medical History

At the Screening Visits, the Investigator (or designate) will review the patient's medical history in order to ascertain the patient's eligibility. The medical history should assess the patient'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 patients 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.

13.6.3 Efficacy Assessments

13.6.3.1 Confirmation of "OFF" or "ON" Episodes

"OFF" and "ON" Training of Patients at SV2

At Screening Visit 2 (SV2), patients 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, patients 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 patient that this is an "OFF" period or "OFF" episode. The Investigator should clearly explain to the patient that this "OFF" time is when their medication has worn off, and does not provide benefits in terms of mobility, slowness and stiffness.

Patients will then take their normal morning dose of L-Dopa. Once the Investigator determines that the patient is experiencing an "ON" state, they should educate the patient that this is an "ON" state. The Investigator should clearly explain to the patient 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 patient 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 eCRF.

Any patient 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 patient as "OFF".

** Not applicable for at-home assessments using the patient dosing diary.

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

- A period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a patient 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 patient 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 patient with study medication (or their standard L-Dopa dose at the second Screening Visit (SV2)). The same assessor should be utilized for each patient throughout the study.

Patients 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)).

At each Dose Titration and Maintenance Treatment Visit, the Investigator will assess "OFF/"ON" state as part of the MDS-UPDRS Part III assessments.

At each Dose Titration and Maintenance Treatment Visit, the patient should report: "OFF"/"ON" state at 0, 15, 30, 45, 60 and 90 minutes after dosing (site staff should prompt the patient). Patients will also be asked if they attained a full "ON" state anytime within 30 minutes of dosing. Patients should also report: time to when the study medication is starting to have an effect (if applicable), and time to "OFF" following dosing (if it occurs within 90 minutes of dosing). The timing of this should begin when the study medication sublingual thin film has fully dissolved, and can be recorded using a stopwatch or other suitable timing device. These times should be documented on the appropriate form of the CRF.

During the Dose Titration Phase only, patient and Investigator assessments of "OFF" and "ON" state may cease if the patient does not experience a full "ON" state within 45 minutes of dosing.

13.6.3.2 MDS-UPDRS Parts I, II and IV

Investigators will administer Part I (Non-Motor Aspects of Experiences of Daily Living), Part II (Motor Aspects of Experiences of Daily Living) and Part IV (Motor Complications) at the second Screening Visit (SV2) and at Maintenance Visit 4 (MV4).

13.6.3.3 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) and at 15, 30, 45, 60 and 90 minutes after dose administration (or L-Dopa administration at the second Screening Visit (SV2)). The same assessor should be utilized for each patient throughout the study.

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 SV2.

During the Dose Titration Phase only, Investigator assessments may cease if the patient does not experience a full "ON" state within 45 minutes of dosing.

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 site staff member can perform the assessment if approved by the Sponsor.

13.6.3.4 Patient Home Dosing Diary

Patients will be given a home dosing diary on TV1 of the Dose Titration Phase, and at each visit during the Maintenance Treatment Phase of the study (excluding MV4). The patient diary will collect the following information:

- Date;
- Patient Number;
- Time study treatment is self-administered;
- Patient "ON"/"OFF" status at 30 minutes following dosing;

The diary provided on TV1 will be used for patient training purposes only and the information collected will not be included in the CRF. Patients will be asked to complete the diary using their normal dose of L-Dopa and other adjunctive PD medication as the self-administration timepoint, and return this diary on Maintenance Visit 1 (MV1). Staff should review the completed diary and re-train patients on diary completion, as necessary. Site staff should remind patients at this visit that moving forward, the diary **must be completed only when the patient self-administers their intended study treatment**, not their other standard PD medication.

During the Maintenance Treatment Phase of the study, patients will complete the home dosing diary on the 2 days prior to their next scheduled in-clinic visit. Site staff will call all patients approximately 3 days before the scheduled in-clinic visit in order to confirm the next visit and remind them to complete the home dosing diary as part of their procedures in the study. Patients should bring their completed home dosing diary with them at their scheduled visit.

13.7 Assessment of Treatment Compliance

Treatment compliance will be assessed by counting the number of unused study medication pouches returned by patients at each in-clinic visit during the Maintenance Treatment Phase of this study relative to the amount given at the preceding visit. Discrepancies in the amount taken and that retrieved will be queried by the Investigator and documented in the appropriate CRF.

The responsible monitors will verify the data being reported in the CRF versus the study medication returned by each patient.

14 ADVERSE EVENTS

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

14.1.1 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.

14.1.2 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.

Due to the nature of patients being enrolled in this study, and the given study objectives, patients who are admitted for their titration and maintenance "OFF" exam <u>will not</u> be considered a SAE.

14.1.3 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

14.1.4 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.)

14.1.5 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.

14.1.6 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.

14.1.7 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.).

14.1.8 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 patient's death, the outcome of death should be indicated for the AE attributed as the cause of death in the death certificate or summary.

14.1.9 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).

14.1.10 Follow-up of Patients 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 patient's medical record.

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

If AEs occur in a patient 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 patient. Patient 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.

When a patient has an AE that requires that the Investigator be unblinded, the Investigator can obtain the treatment assignment from the IWRS system. The site is expected to notify the Study Medical Monitor before breaking the study blind, unless it is in the patient's best interest if the blind is broken immediately. Note: in most circumstances it is not necessary to unblind a patient, even if an SAE has occurred. For many drugs there is no specific therapy for AEs. The appropriate course of action is to stop the investigational drug, and treat the signs and symptoms resulting from the AE.

14.1.12 Notification of Serious Adverse Events

The Investigator must report all SAEs and pregnancies promptly to Cynapsus or its designee, by completing an SAE form (which will be provided) and fax within 24 hours of first becoming aware of the event. Fax: 1-877-464-7787.

In the event of an issue with the fax line; the Investigator should forward the SAE form via email to INCDrugSafety@INCresearch.com.

The Investigator will be able to contact Dr. Jordan Dubow, the study Medical Monitor, at +1 (224) 213-2114.

If a SAE is reported via telephone, the Investigator must follow up the initial telephone notification by completing a SAE form and faxing it to 1-877-464-7787.

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

- Patient's study number and initials
- Patient's date of birth
- Patient'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). ("Is there a reasonable possibility that the investigational drug caused the SAE? Yes or No?")
- Whether and when the Investigator was unblinded as to the patient's treatment assignment

Any missing or additional relevant information concerning the serious (or unexpected) AE should be provided in a written follow-up report.

The Investigator is required to comply with applicable regulations regarding the notification of his/her IRB/ REB/IEC.

15 TREATMENTS

15.1 Treatments Administered (APL-130277 and Placebo)

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 patients. 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.

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

Individual sublingual thin films of APL-130277 will be supplied packed into unit dose pouches. 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 (a 20 mg dose first followed immediately by the 15 mg dose). In this study, placebo sublingual thin films will also be prepared which will be identical in appearance, size and colour, but contain no active ingredient (i.e., apomorphine).

15.2 Administration of Study Medication

During the Dose Titration Phase, all patients will be dosed by clinic staff with increasing doses of APL-130277 starting with 10 mg at Titration Visit 1 (TV1). Patients 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 towards the tongue (i.e., the side of the film that does not have an alphanumeric printing), and ask patients to close their mouth naturally. Patients should not swallow the medication and should also try not to swallow their saliva for at least 3 minutes. If, upon inspection at the three minute mark, the film is not completely dissolved, patients 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 patient feels the film has fully dissolved prior to the three minute mark, they should indicate this to site staff by raising their hand, who will then verify. If upon inspection, the film is not completely dissolved, patients 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.

On Maintenance Visit 1 (MV1), all patients will undergo outpatient self-administration training with clinic staff using placebo sublingual thin films. This training is performed in order to familiarize patients with the self-administration process during the Maintenance Treatment Phase of the study. Staff should demonstrate to patients the process of opening the individual dose pouches and handling the individual sublingual thin films. Patients **should not** self-administer the placebo sublingual thin films. Patients will not be dismissed until they have adequately been trained and site staff feel confident they understand the full process.

Prior to each self-administration, patients will be instructed to consume a glass of water immediately prior to dosing, and ensure the sublingual space is free of excess water. Using their hands, patients (or their caregivers) should place the product beneath the tongue, with the drug side facing up towards the tongue (i.e., the side of the film that does not have an alphanumeric printing), and close their mouth naturally. **Patients should not swallow the medication and should also try not to swallow their saliva for at least 3 minutes, or until they feel the film has fully dissolved.**

To administer the 35 mg dose, patients will be instructed to administer the 20 mg dose first, and then immediately after 3 minutes have elapsed, administer the 15 mg dose.

All patients will be instructed to complete individual home dosing diaries on the 2 days immediately preceding each in-clinic visit during the Maintenance Treatment Phase.

At each outpatient visit, patients will be provided sufficient study medication in order to self-administer for up to 5 “OFF” episodes per day for a month. Study medication that was not used, will be collected by each site and inventoried.

15.3 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. Unit dose pouches of the study medication must be stored at controlled room temperature: 68-77°F (20-25°C), within a properly secured storage room. Temperature logs must be maintained for the storage room.

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 by the patient and that no remaining supplies are in the Investigator's possession. Certificates of delivery and returns must be signed and filed in the Study Site File.

15.4 Packaging and Labeling

Each package of investigational drug product, containing 150 individual dose peelable foil laminate pouches, will be labeled with study-specific information meeting all the applicable regulatory requirements, including specifying the dose of apomorphine. Investigational drug product will be administered in the clinic.

Individual sublingual thin films of APL-130277 will be supplied packed into unit dose pouches. Individual pouches will be labelled with all applicable information.

15.5 Drug Accountability

Drug supplies, which will be provided by Cynapsus or a CRO appointed by Cynapsus, 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 patient, and the return to Cynapsus 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 patients. The Investigator, pharmacist, and/or investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol and reconcile all investigational product(s) received from Cynapsus. At the time of return to Cynapsus, the Investigator or site designate must verify that all unused or partially used drug supplies have been returned by the clinical trial patient 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 Cynapsus and appropriate regulatory agencies as required. The investigational drug will only be administered to patients participating in this study. Only authorized study site personnel may supply or administer the investigational drug.

15.6 Method of Assigning Patients to Treatment Groups

Patients will be randomized to one of the following treatments using an IWRS system:

- APL-130277; or
- Placebo

The strength (i.e., 10 mg, 15 mg, 20 mg, 25 mg, 30 mg or 35 mg) to be given will be determined during the Dose Titration Phase of the study, and as adjusted (i.e., reduced) in the Maintenance Treatment Phase of the study based on safety/tolerability assessed during unscheduled Dose Adjustment Visits.

The IWRS vendor will allocate treatments for each patient.

15.7 Randomization and Blinding

At Screening, the IWRS will assign a unique patient identification number to the patient known as the Screening Number. This number will be associated with the patient throughout the study. Every patient 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.

The patients will be centrally randomized at a study level. No stratification factors will be used.

The treatment assignment will be determined by a randomization list prepared by the biostatistics group of INC Research and utilized in the IWRS. The 5-digit randomization number is used to identify the treatment (active or placebo) of the kits that will be assigned to the patient. All kits assigned to the patient will be of the same treatment the patient was randomized to.

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

When the Dose Titration Phase for a patient is complete, sites should enter all titration MDS-UPDRS Part III data for that patient into the CRF within 48 hours of the last titration visit for review by the Medical Monitor.

16 STATISTICAL ANALYSES

16.1 Statistical Analysis Plan

Full statistical considerations, table mock-ups and final analysis of safety and efficacy data collected in this study will be outlined in a formal Statistical Analysis Plan. This plan will be finalized prior to locking the database and unblinding of the final datasets.

16.2 Analysis Populations

16.2.1 Safety Population

All patients who are randomized and receive one dose of study medication will be included in the safety population. The safety population will be used for the analysis of the safety endpoints and the patients will be grouped according to the treatment that they received.

16.2.2 Modified Intent-to-Treat (mITT) Population

All patients who are randomized, receive at least one dose of study medication and have efficacy data from at least one post-randomization evaluation will comprise the mITT population and will be used in the efficacy analysis. The mITT population will be used for the efficacy analysis, and patients will be grouped according to the randomized treatment group.

16.3 Sample Size Calculation

The study intends to show the superiority in UPDRS motor score of sublingual apomorphine compared with placebo. Assuming a treatment difference of 7 points and standard deviation of 10 points, a sample size of 44 patients per group or 88 patients for two groups will provide ≥ 90% power to detect a statistically significant difference at the 0.05 level, using a two-sample t-test. Assuming a 10% dropout rate during the titration phase and a 15% dropout rate during the maintenance phase, the study plans to enroll approximately 126 patients into the Dose Titration Phase and to randomize approximately 114 patients into the Maintenance Treatment Phase.

16.4 Efficacy Analysis

The primary endpoint of the study is the change from pre-dose in MDS-UPDRS MOTOR score after 30 minutes at 12 weeks (Maintenance Visit 4, MV4). The difference between APL-130277 and placebo at MV4 will be estimated using a MMRM. The model will include the observed change from pre-dose MDS-UPDRS MOTOR score values after 30 minutes at Maintenance Visit 1 (MV1), Maintenance Visit 2 (MV2), Maintenance Visit 3 (MV3) and Maintenance Visit 4 (MV4) as the response values (i.e., no imputation will be done). The treatment difference at 12 weeks will be estimated using contrasts. The MMRM model will include the treatment group (APL-130277 or placebo), visit (MV1, MV2, MV3 and MV4), the stratification variables (if any) and the interaction between the treatment group and visit as fixed factors. The change from pre-

dose in MDS-UPDRS MOTOR score after 30 minutes at the final Titration Visit will be used as a covariate in the model.

The sensitivity analyses of the primary endpoint will be specified in the Statistical Analysis Plan. Sensitivity analysis will include a method to handle missing data (e.g., Analysis of Covariance with last observation carried forward or pattern mixture models using multiple imputation), definition of analysis population (e.g., patients completing the study or patients who have no major protocol deviations) and statistical method (e.g., Analysis of Covariance models separately for each visit).

The primary and secondary endpoints will be tested using a hierarchical approach. The primary endpoint will be tested first and the difference will be declared statistically significant if the nominal two-sided p-value is less than 0.05. In case the primary objective is statistically significant, the secondary endpoint ranked first will be tested using a nominal significance level of 0.05 based on two-sided tests. The testing will continue in a hierarchical manner as long as the previously ranked endpoint was statistically significant.

The continuous secondary endpoints will be analyzed using a MMRM model similar to the one used for the primary endpoint. The categorical endpoints will be analyzed using Cochran-Mantel-Haenszel test stratified by the stratification variables, if any. The time-to-event endpoints will be described using the Kaplan-Meier method along with group comparisons analyzed using the Cox proportional hazards model. For categorical and time-to-event endpoints, each visit will be tested separately. In case of missing data, the last value will be carried forward for the categorical and time-to-event endpoints.

16.5 Safety Analysis

The analysis of the safety data will focus on the comparison of APL-130277 and placebo during the Maintenance Treatment Phase. In addition, all safety data will be reported separately for the Dose Titration Phase.

Adverse events will be tabulated by treatment group according to the 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. For vital signs and ECG parameters, the changes from pre-dose to post-dose assessments of the corresponding day will be calculated and compared between the treatment groups using descriptive statistics. In addition, the changes from baseline in the pre-dose values will be compared between the treatment groups. The changes in laboratory values and C-SSRS from baseline to subsequent visits will be compared as well.

17 STUDY CONDUCT

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

17.1 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 Cynapsus with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by Cynapsus and the relevant governing authorities.

See APPENDIX II: Regulations and Guidelines for additional information.

17.2 Study Initiation

Clinical site staff may not screen or enroll patients into the study until receiving notification from Cynapsus 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 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.

17.3 Study Documentation

17.3.1 Investigator's Regulatory Documents

The regulatory documents listed below must be received from the Investigator and reviewed and approved by Cynapsus or its designee before the clinical site can initiate the study and before

Cynapsus 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)
	PI signed FDA Form 1572 / Qualified Investigator Undertaking

Additional documentation requirements may be communicated by Cynapsus staff (or its designate).

17.3.2 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 patients who sign an ICF.

The vendor selected to perform CRF design will be responsible for drafting CRFs for the study, which Cynapsus 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. Cynapsus 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 patient 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 Cynapsus 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 patients who sign an ICF.

CRFs/EDC modules are considered confidential documents and should be handled and stored accordingly. Cynapsus 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 patient 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 patient'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.

17.3.3 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 patient's eligibility for the study.

Original versions of the laboratory reports and ECG tracings will be retained at the clinical site with the patient's source documents, and anonymized copies provided to Cynapsus with the CRF copies.

17.4 Data Quality Assurance

Cynapsus and its designees will perform quality control and assurance checks on all clinical studies

that it sponsors. Cynapsus, 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.

17.4.1 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 Cynapsus personnel access. The clinical site will be monitored by Cynapsus and/or its designate to ensure compliance with the protocol, GCP, and applicable regulations and guidelines. As representatives of Cynapsus, 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, 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.

17.4.2 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 Cynapsus.

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.

17.4.3 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 Cynapsus.

17.4.4 Data Management

A vendor contracted by Cynapsus 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.

17.4.5 Study Termination

The study may be terminated at Cynapsus' discretion at any time for any reason. If Cynapsus discovers conditions that warrant early termination of the study, the Investigator will be notified by Cynapsus 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 patients enrolled in the study; and
- The decision on the part of Cynapsus to suspend or discontinue testing, evaluation, or development of the investigational product.

17.4.6 Clinical Site Closure

On termination of the study, all screening and ongoing study related procedures conducted at the clinical site will be closed. Cynapsus 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 patient enrollment;
- Administrative reasons.

17.4.7 Data Safety Monitoring Board

A DSMB will be utilized in this study in order to monitor patient safety independently from the Sponsor.

The DSMB will be composed of members who are not participating in the trial, led by a Chair. The DSMB will be responsible for monitoring patient safety, and with the support of an independent statistician, review safety data collected for a planned analysis or other analysis as required by the DSMB. The DSMB, under specific circumstances, may suggest revisions to the current protocol if these improve patient safety and our potential outcomes.

The independent statistician will have access to the randomization code, and will receive regular database transfers. For each safety meeting, the statistician will prepare summary tables, listings and figures, as appropriate, in order to aid the DSMB in making a decision on patient safety. Data used will be as presented in the study database, whether it has undergone quality control and cleaning. Safety data reviewed and analyzed will, at a minimum, include SAEs, AEs that are related to the oropharyngeal examinations, and any other safety data required by the DSMB to make an assessment.

The composition, responsibility and general overview of procedures will be outlined in the DSMB Charter and finalized prior to implementation of any DSMB review.

18 GENERAL CONSIDERATIONS

18.1 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Cynapsus. 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.

18.2 Use of Information and Publication

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

The information developed in this study will be used by Cynapsus 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 Cynapsus. Abstracts, manuscripts, and presentation materials should be provided to Cynapsus for review at least 30 days prior to the relevant submission deadline.

18.3 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 Cynapsus 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 Cynapsus in writing of its intent to destroy all such material. Cynapsus shall have 30 days to respond to the Investigator's notice, and Cynapsus shall have a further opportunity to retain such materials at Cynapsus' expense.

18.4 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 patient.

18.5 Patient Injury

In general, specific to provisions in the clinical trial agreement, if a patient 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, Cynapsus 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, Cynapsus shall comply with such laws or regulations. Where applicable, Cynapsus has taken specific national insurance.

19 REFERENCES

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

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

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20 APPENDICES

20.1 APPENDIX I: APOKYN® Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use APOKYN® safely and effectively. See full prescribing information for APOKYN®.

APOKYN® (apomorphine hydrochloride injection)
For Subcutaneous Use Only
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------
Warnings and Precautions
Impulse Control/Compulsive Behaviors (5.9) 07/2014

----------INDICATIONS AND USAGE----------
APOKYN is a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease (1)

----------DOSAGE AND ADMINISTRATION----------
- For subcutaneous use only (2.1)
- Always express APOKYN dose in mL to minimize dosing errors (2.1)
- The starting dose of APOKYN is 0.2 mL (2 mg); give the first dose under medical supervision; titrate the dose to effect and tolerance; the maximum recommended dose is 0.6 mL (2.3)
- Treatment with a concomitant antiemetic, e.g., trimethobenzamide, is recommended, starting 3 days prior to the first dose of APOKYN, and for at least the first two months of therapy (2.2, 5.2)
- APOKYN doses must be separated by at least 2 hours (2.6)
- Renal impairment: reduce test dose, and reduce starting dose to 0.1 mL (1 mg) (2.4, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
Multi-dose glass cartridges, 30 mg/3 mL (10 mg/mL) for use with a multiple-dose pen injector (APOKYN Pen) (3, 16)

----------CONTRAINDICATIONS----------
- Concomitant use of APOKYN with $5HT_3$ antagonists, including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron, is contraindicated (4)
- Hypersensitivity to apomorphine, its excipients or sodium metabisulfite (4)

----------WARNINGS AND PRECAUTIONS----------
- For subcutaneous use only; thrombus formation and pulmonary embolism have followed intravenous administration of APOKYN (5.1)
- Falling asleep during activities of daily living, and daytime somnolence may occur (5.3)
- Syncope and hypotension/orthostatic hypotension may occur (5.4, 5.5)
- Falls may occur, or increase (5.6)
- May cause hallucinations and psychotic-like behavior (5.7)
- May cause dyskinesia or exacerbate pre-existing dyskinesia (5.8)
- May cause problems with impulse control and impulsive behaviors (5.9)
- May cause coronary events (5.10)
- May prolong QTc and cause torsades de pointes or sudden death (5.11)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence at least 10% greater on APOKYN than on placebo) were yawning, drowsiness/somnolence, dyskinesias, dizziness/postural hypotension, rhinorrhea, nausea and/or vomiting, hallucination/confusion, and edema/swelling of extremities (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact US WorldMeds at -1-877-727-6596 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Concomitant use of antihypertensive medications and vasodilators: increased risk for hypotension, myocardial infarction, pneumonia, falls, and injuries (7.2)
- Dopamine antagonists such as neuroleptics or metoclopramide, may diminish the effectiveness of APOKYN (7.3)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Geriatric Use: In clinical trials, patients 65 years of age and older were more likely to experience certain adverse events (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APOKYN® (apomorphine hydrochloride injection) is indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease. APOKYN has been studied as an adjunct to other medications *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

APOKYN is indicated for subcutaneous administration only *[see Warnings and Precautions (5.1)]* and only by a multiple-dose APOKYN Pen with supplied cartridges. The initial dose and dose titrations should be performed by a healthcare provider. Blood pressure and pulse should be measured in the supine and standing position before and after dosing.

A caregiver or patient may administer APOKYN if a healthcare provider determines that it is appropriate. Instruct patients to follow the directions provided in the Patients Instructions For Use. Because the APOKYN Pen has markings in milliliters (mL), the prescribed dose of APOKYN should be expressed in mL to avoid confusion.

Visually inspect the APOKYN drug product through the viewing window for particulate matter and discoloration prior to administration. The solution should not be used if discolored (it should be colorless), or cloudy, or if foreign particles are present. Rotate the injection site and use proper aseptic technique *[see How Supplied/Storage and Handling (16) and Patient Counseling Information (17)]*.

2.2 Premedication and Concomitant Medication

APOKYN should be initiated with the use of a concomitant antiemetic *[see Warnings and Precautions (5.2)]*. Oral trimethobenzamide (300 mg three times a day) should be started 3 days prior to the initial dose of APOKYN and continued at least during the first two months of therapy.

Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with drugs of the $5HT_3$ antagonist class including antiemetics (for example, ondansetron, granisetron, dolasetron, palonosetron) and alosetron are contraindicated *[see Contraindications (4)]*.

2.3 Dosing Information

The recommended starting dose of APOKYN is 0.2 mL (2 mg). Titrate on the basis of effectiveness and tolerance, up to a maximum recommended dose of 0.6 mL (6 mg) *[see Clinical Studies (14)]*.

There is no evidence from controlled trials that doses greater than 0.6 mL (6 mg) gave an increased effect and therefore, individual doses above 0.6 mL (6 mg) are not recommended. The average frequency of dosing in the development program was 3 times per day. There is limited experience with single doses greater than 0.6 mL (6 mg), dosing more than 5 times per day and with total daily doses greater than 2 mL (20 mg).

Begin dosing when patients are in an "off" state. The initial dose should be a 0.2 mL (2 mg) test dose in a setting where medical personnel can closely monitor blood pressure and pulse. Both supine and standing blood pressure and pulse should be checked pre-dose and at 20 minutes, 40 minutes, and 60 minutes post-dose (and after 60 minutes, if there is significant hypotension at 60 minutes). Patients who

develop clinically significant orthostatic hypotension in response to this test dose of APOKYN should not be considered candidates for treatment with APOKYN.

If the patient tolerates the 0.2 mL (2 mg) dose, and responds adequately, the starting dose should be 0.2 mL (2 mg), used on an as needed basis to treat recurring "off" episodes. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis.

The general principle guiding subsequent dosing (described in detail below) is to determine that the patient needs and can tolerate a higher test dose, 0.3 mL or 0.4 mL (3 mg or 4 mg, respectively) under close medical supervision. A trial of outpatient dosing may follow (periodically assessing both efficacy and tolerability), using a dose 0.1 mL (1 mg) lower than the tolerated test dose.

If the patient tolerates the 0.2 mL (2 mg) test dose but does not respond adequately, a dose of 0.4 mL (4 mg) may be administered under medical supervision, at least 2-hours after the initial test dose, at the next observed "off" period. If the patient tolerates and responds to a test dose of 0.4 mL (4 mg), the initial maintenance dose should be 0.3 mL (3 mg) used on an as needed basis to treat recurring "off" episodes as an outpatient. If needed, the dose can be increased in 0.1 mL (1 mg) increments every few days on an outpatient basis.

If the patient does not tolerate a test dose of 0.4 mL (4 mg), a test dose of 0.3 mL (3 mg) may be administered during a separate "off" period under medical supervision, at least 2-hours after the previous dose. If the patient tolerates the 0.3 mL (3 mg) test dose, the initial maintenance dose should be 0.2 mL (2 mg) used on an as needed basis to treat existing "off" episodes. If needed, and the 0.2 mL (2 mg) dose is tolerated, the dose can be increased to 0.3 mL (3 mg) after a few days. In such a patient, the dose should ordinarily not be increased to 0.4 mL (4 mg) on an out-patient basis.

2.4 Dosing in Patients with Renal Impairment

For patients with mild and moderate renal impairment, the test dose and starting dose should be reduced to 0.1 mL (1 mg) *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6)]*.

2.5. Dosing in Patients with Hepatic Impairment

Closely monitor patients with mild and moderate hepatic impairment *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.7)]*.

2.6 Re-treatment and Interruption in Therapy

If a single dose of APOKYN is ineffective for a particular "off" period, a second dose should not be given for that "off" episode. The efficacy of the safety of administering a second dose for a single "off" episode has not been studied systematically. Do not administer a repeat dose of APOKYN sooner than 2 hours after the last dose.

Patients who have an interruption in therapy of more than a week should be restarted on a 0.2 mL (2 mg) dose and gradually titrated to effect and tolerability.

3 DOSAGE FORMS AND STRENGTHS

APOKYN 30 mg/3 mL (10 mg/mL) containing apomorphine hydrochloride (as apomorphine hydrochloride hemihydrate), USP is supplied as a clear, colorless, sterile, solution in a 3 mL (30 mg) cartridge. The 3 mL (30 mg) glass cartridge is used with a manual reusable, multiple-dose pen injector (APOKYN Pen). A single cartridge, pen and needle can deliver doses up to 1 mL (10 mg) in 0.02 mL (0.2 mg) increments. The multiple-dose pen injector is provided in a package with six needles.

4 CONTRAINDICATIONS

APOKYN is contraindicated in patients:

- Using concomitant drugs of the $5HT_3$ antagonist class including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron *[see Drug Interactions (7.1)]*. There have been reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron.

- With hypersensitivity/allergic reaction characterized by urticaria, rash, pruritus, and/or various manifestations of angioedema to apomorphine or to any of the excipients including a sulfite (i.e., sodium metabisulfite). Patients with a sulfite sensitivity may experience various allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic attacks. Patients who experience any hypersensitivity/allergic reaction to APOKYN should avoid taking APOKYN again.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Adverse Reactions After Intravenous Administration

Following intravenous administration of APOKYN, serious adverse reactions including thrombus formation and pulmonary embolism due to intravenous crystallization of apomorphine have occurred. Consequently, APOKYN should not be administered intravenously.

5.2 Nausea and Vomiting

APOKYN causes severe nausea and vomiting when it is administered at recommended doses. Because of this, in domestic clinical studies, 98% of all patients were pre-medicated with trimethobenzamide, an antiemetic, for three days prior to study enrollment, and were then encouraged to continue trimethobenzamide for at least 6 weeks. Even with the use of concomitant trimethobenzamide in clinical studies, 31% and 11% of the APOKYN-treated patients had nausea and vomiting, respectively, and 3% and 2% of the patients discontinued APOKYN due to nausea and vomiting, respectively. Among 522 patients treated, 262 (50%) discontinued trimethobenzamide while continuing APOKYN. The average time to discontinuation of trimethobenzamide was about 2 months (range: 1 day to 33 months). For the 262 patients who discontinued trimethobenzamide, 249 patients continued apomorphine without trimethobenzamide for a duration of follow-up that averaged 1 year (range: 0 years to 3 years).

The ability of concomitantly administered antiemetic drugs (other than trimethobenzamide) to reduce the incidence of nausea and/or vomiting in APOKYN-treated patients has not been studied. Antiemetics with anti-dopaminergic actions (e.g., haloperidol, chlorpromazine, promethazine, prochlorperazine, metaclopramide) have the potential to worsen the symptoms in patients with Parkinson's disease and should be avoided.

5.3 Falling Asleep During Activities of Daily Living and Somnolence

There have been reports in the literature of patients treated with APOKYN subcutaneous injections who suddenly fell asleep without prior warning of sleepiness while engaged in activities of daily living. Somnolence is commonly associated with APOKYN, and it is reported that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, even if patients do not give such a history. Somnolence was reported in 35% of patients treated with APOKYN and in none of the patients in the placebo group. Prescribers should reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with APOKYN, advise patients of the risk of drowsiness and ask them about factors that could increase the risk with APOKYN, such as concomitant sedating medications and the presence of sleep disorders. If a patient develops significant daytime sleepiness or falls asleep during activities that require active participation (e.g., conversations, eating, etc.), APOKYN should ordinarily be discontinued. If a decision is made to continue APOKYN, patients should be advised not to drive and to avoid other potentially dangerous activities. There is insufficient information to determine whether dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

5.4 Syncope

In clinical studies, approximately 2% of APOKYN-treated patients experienced syncope.

5.5 Hypotension / Orthostatic Hypotension

Dopamine agonists, including APOKYN, may cause orthostatic hypotension at any time but especially during dose escalation. Patients with Parkinson's disease may also have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk.

Patients undergoing titration of APOKYN showed an increased incidence (from 4% pre-dose to 18% post-dose) of systolic orthostatic hypotension (≥ 20 mmHg decrease) when evaluated at various times after in-office dosing. A small number of patients developed severe systolic orthostatic hypotension (≥ 30 mmHg decrease and systolic BP ≤ 90 mmHg) after subcutaneous apomorphine injection. In clinical trials of APOKYN in patients with advanced Parkinson's disease, 59 of 550 patients (11%) had orthostatic hypotension, hypotension, and/or syncope. These events were considered serious in 4 patients (< 1%) and resulted in withdrawal of APOKYN in 10 patients (2%). These events occurred both with initial dosing and during long-term treatment. Whether or not hypotension contributed to other significant adverse events seen (e.g., falls), is unknown. APOKYN causes dose-related decreases in systolic (SBP) and diastolic blood pressure (DBP) *[see Clinical Pharmacology (12.2)]*.

The hypotensive effects of APOKYN may be increased by the concomitant use of alcohol, antihypertensive medications, and vasodilators (especially nitrates). Patients should avoid alcohol when using APOKYN. Check blood pressure for hypotension and orthostatic hypotension in patients APOKYN with concomitant antihypertensive medications and/or vasodilators *[see Drug Interactions (7.2)]*.

5.6 Falls

Patients with Parkinson's disease (PD) are at risk of falling due to underlying postural instability, possible autonomic instability, and syncope caused by the blood pressure lowering effects of the drugs used to treat PD. Subcutaneous APOKYN might increase the risk of falling by simultaneously lowering blood pressure and altering mobility *[see Clinical Pharmacology (12.2)]*.

In clinical trials, 30% of patients had events that could reasonably be considered falls and about 5% of patients had falls that were considered serious.

5.7 Hallucinations / Psychotic-Like Behavior

In clinical studies, hallucinations were reported by 14% of the APOKYN-treated patients. In one randomized, double-blind, placebo-controlled study, hallucinations or confusion occurred in 10% of patients treated with APOKYN and 0% of patients treated with placebo. Hallucinations resulted in discontinuation of APOKYN in 1% of patients.

Post marketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior after starting or increasing the dose of APOKYN. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations, including paranoid ideation, delusions, hallucinations, confusion, disorientation, aggressive behavior, agitation, and delirium.

Patients with a major psychotic disorder should ordinarily not be treated with APOKYN because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of APOKYN *[see Drug Interactions (7.3)]*.

5.8 Dyskinesias

APOKYN may cause dyskinesia or exacerbate pre-existing dyskinesia. In clinical studies, dyskinesia or worsening of dyskinesia was reported in 24% of patients. Overall, 2% of APOKYN-treated patients withdrew from studies due to dyskinesias.

5.9 Impulse Control/Compulsive Behaviors

Case reports suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges and the inability to control these urges while taking one or more of the medications, including APOKYN, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with APOKYN. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking APOKYN.

5.10 Coronary Events

In clinical studies, 4% of patients treated with APOKYN experienced angina, myocardial infarction, cardiac arrest and/or sudden death; some cases of angina and myocardial infarction occurred in close proximity to APOKYN dosing (within 2 hours), while other cases of cardiac arrest and sudden death were observed at times unrelated to dosing. APOKYN has been shown to reduce resting systolic and diastolic blood pressure and may have the potential to exacerbate coronary (and cerebral) ischemia in patients with known cardiovascular and cerebrovascular disease. If patients develop signs and symptoms of coronary or cerebral ischemia, prescribers should re-evaluate the continued use of APOKYN.

5.11 QTc Prolongation and Potential for Proarrhythymic Effects

There is a small dose related prolongation of QTc interval with doses of APOKYN greater than 6 mg *[See Clinical Pharmacology (12.2)]*. Doses greater than 6 mg do not provide additional clinical benefit and are not recommended.

Drugs that prolong the QTc interval have been associated with torsades de pointes and sudden death. The relationship of QTc prolongation to torsades de pointes is clearest for larger increases (20 msec and greater), but it is possible that smaller QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, bradycardia, concomitant use of other drugs that prolong the QTc interval, or genetic predisposition (e.g., congenital prolongation of the QT interval). Although torsades de pointes has not been observed in association with the use of APOKYN at recommended doses in clinical studies, experience is too limited to rule out an increased risk. Palpitations and syncope may signal the occurrence of an episode of torsades de pointes.

The risks and benefits of APOKYN treatment should be considered prior to initiating treatment with APOKYN in patients with risk factors for prolonged QTc.

5.12 Withdrawal-Emergent Hyperpyrexia and Confusion

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

5.13 Melanoma

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

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

5.14 Fibrotic Complications

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse reactions are believed to be related to the ergoline structure of these dopamine agonists, whether other, nonergot derived dopamine agonists, such as APOKYN, can cause these reactions is unknown.

5.15 Priapism

APOKYN may cause prolonged painful erections in some patients. In clinical studies, painful erections were reported by 3 of 361 APOKYN-treated men, and one patient withdrew from APOKYN therapy because of priapism. Although no patients in the clinical studies required surgical intervention, severe priapism may require surgical intervention.

5.16 Retinal Pathology in Albino Rats

In a 2-year carcinogenicity study of apomorphine in albino rat, retinal atrophy was detected at all subcutaneous doses tested (up to 0.8 mg/kg/day or 2 mg/kg/day in males or females, respectively; less than the maximum recommended human dose of 20 mg/day on a body surface area (mg/m^2) basis). Retinal atrophy/degeneration has been observed in albino rats treated with other dopamine agonists for prolonged periods (generally during 2-year carcinogenicity studies). Retinal findings were not observed in a 39-week subcutaneous toxicity study of apomorphine in monkey at doses up to 1.5 mg/kg/day, a dose similar to the MRHD on a mg/m^2 basis. The clinical significance of the finding in rat has not been established but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in the Warnings and Precautions section of labeling:

- Nausea and Vomiting *[see Warnings and Precautions (5.2)]*

- Syncope *[see Warnings and Precautions (5.4)]*
- Hypotension/Orthostatic Hypotension *[see Warnings and Precautions (5.5)]*
- Falls *[see Warnings and Precautions (5.6)]*
- Hallucinations/Psychotic-Like Behavior *[see Warnings and Precautions (5.7)]*
- Dyskinesias *[see Warnings and Precautions (5.8)]*
- Coronary Events *[see Warnings and Precautions (5.10)]*
- Priapism *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions (number of unique patients experiencing an adverse reaction associated with treatment per total number of patients treated) observed in the clinical trials of a drug cannot be directly compared to the incidence of adverse reactions in the clinical trials of another drug and may not reflect the incidence of adverse reactions observed in practice.

In placebo-controlled trials, most patients received only one subcutaneous dose of APOKYN. All patients received concomitant levodopa and 86% received a concomitant dopamine agonist. All patients had some degree of spontaneously occurring periods of hypomobility ("off episodes") at baseline.

The most common adverse reactions (APOKYN incidence at least 10% greater than placebo incidence) observed in a placebo-controlled trial were yawning, drowsiness/somnolence, dyskinesias, dizziness/postural hypotension, rhinorrhea, nausea and/or vomiting, hallucination/confusion, and edema/swelling of extremities.

Table 1 presents the most common adverse reactions reported by APOKYN-naïve Parkinson's disease patients who were enrolled in a randomized placebo-controlled, parallel group trial and who were treated for up to 4 weeks (Study 1) *[see Clinical Studies (14)]*. Individual APOKYN doses in this trial ranged from 2 mg to 10 mg, and were titrated to achieve tolerability and control of symptoms.

Table 1: Adverse Reactions Occurring in Two or More APOKYN-Treated Patients in Study 1

	APOKYN (n = 20)	**PLACEBO** (n = 9)
	%	%
Yawning	40	0
Dyskinesias	35	11
Drowsiness or Somnolence	35	0
Nausea and/or Vomiting	30	11
Dizziness or Postural Hypotension	20	0
Rhinorrhea	20	0
Chest Pain/Pressure/Angina	15	11
Hallucination or Confusion	10	0
Edema/Swelling of Extremities	10	0

Other Adverse Reactions

Injection Site Reactions

Patients treated with APOKYN subcutaneous injections during clinical studies, 26% of patients had injection site reactions, including bruising (16%), granuloma (4%), and pruritus (2%).

In addition to those in Table 1, the most common adverse reactions in pooled APOKYN trials (occurring in at least 5% of the patients) in descending order were injection site reaction, fall, arthralgia, insomnia, headache, depression, urinary tract infection, anxiety, congestive heart failure, limb pain, back pain,

Parkinson's disease aggravated, pneumonia, confusion, sweating increased, dyspnea, fatigue, ecchymosis, constipation, diarrhea, weakness, and dehydration.

7 DRUG INTERACTIONS

7.1 $5HT_3$ Antagonists

Based on reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron, the concomitant use of APOKYN with $5HT_3$ antagonists,s including antiemetics (for example, ondansetron, granisetron, dolasetron, palonosetron) and alosetron, is contraindicated.

7.2 Antihypertensive Medications and Vasodilators

The following adverse events were experienced more commonly in patients receiving concomitant antihypertensive medications or vasodilators (n = 94) compared to patients not receiving these concomitant drugs (n = 456): hypotension 10% vs 4%, myocardial infarction 3% vs 1%, serious pneumonia 5% vs 3%, serious falls 9% vs 3%, and bone and joint injuries 6% vs 2%. The mechanism underlying many of these events is unknown, but may represent increased hypotension *[see Warnings and Precautions (5.5, 5.6)]*.

7.3 Dopamine Antagonists

Since APOKYN is a dopamine agonist, it is possible that concomitant use of dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of APOKYN. Patients with major psychotic disorders, treated with neuroleptics, should be treated with dopamine agonists only if the potential benefits outweigh the risks.

7.4 Drugs Prolonging the QT/QTc Interval

Caution should be exercised when prescribing APOKYN concomitantly with drugs that prolong the QT/QTc interval *[see Warnings and Precautions (5.11)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. APOKYN has been shown to be teratogenic in rabbits and embryolethal in rats when given at clinically relevant doses. APOKYN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No adverse developmental effects were observed when apomorphine (0.3 mg/kg/day, 1 mg/kg/day, 3 mg/kg/day) was administered by subcutaneous injection to pregnant rat throughout organogenesis; the highest dose tested (3 mg/kg/day) is 1.5 times the MRHD (20 mg/day) on a mg/m^2 basis. Administration of apomorphine (0.3 mg/kg/day, 1 mg/kg/day, 3 mg/kg/day) by subcutaneous injection to pregnant rabbits throughout organogenesis resulted in an increased incidence of malformations of the heart and/or great vessels at the mid and high doses tested; the no-effect dose is less than the MRHD on a mg/m^2 basis.

Apomorphine (0.3 mg/kg/day, 1 mg/kg/day, 3 mg/kg/day), administered by subcutaneous injection to females throughout gestation and lactation, resulted in increased offspring mortality at the highest dose tested. There were no effects on developmental parameters or reproductive performance in surviving offspring. The no-effect dose for developmental toxicity (1 mg/kg/day) is less than the MRHD on a mg/m^2 basis.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from APOKYN, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the APOKYN clinical development program, there were 239 patients less than age 65 treated with APOKYN and 311 patients who were age 65 years of age or older. Confusion and hallucinations were reported more frequently with patients age 65 and older compared to patients with less than age 65. Serious adverse reactions (life-threatening events or events resulting in hospitalization and/or increased disability) were also more common in patients age 65 and older. Patients age 65 and older were more likely to fall (experiencing bone and joint injuries), have cardiovascular events, develop respiratory disorders, and have gastrointestinal events. Patients age 65 and above were also more likely to discontinue APOKYN treatment as a result of one or more adverse reactions.

8.6 Renal Impairment

The starting APOKYN dose should be reduced in patients with mild or moderate renal impairment because the concentration and exposure (C_{max} and AUC) are increased in these patients. Studies in subjects with severe renal impairment have not been conducted *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Caution should be exercised when administrating APOKYN to patients with mild and moderate hepatic impairment due to the increased C_{max} and AUC in these patients. Studies of subjects with severe hepatic impairment have not been conducted *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

In premarketing clinical experience, APOKYN did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, there are rare postmarketing reports of abuse of medications containing APOKYN or levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state.

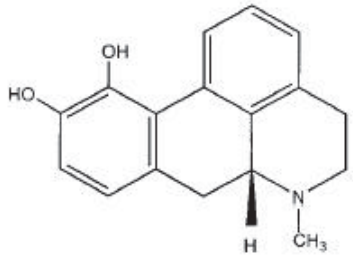
10 OVERDOSAGE

A 62-year-old man accidentally injected 25 mg of APOKYN subcutaneously. After 3 minutes, the patient felt nauseated and lost consciousness for 20 minutes. Afterwards, he was alert with a heart rate 40/minute and a supine blood pressure of 90/50. He recovered completely within an hour.

11 DESCRIPTION

APOKYN (apomorphine hydrochloride injection) contains apomorphine hydrochloride, a non-ergoline dopamine agonist. Apomorphine hydrochloride is chemically designated as 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate with a molecular formula of $C_{17}H_{17}NO_2 \bullet HCL \bullet ½ H_2O$. Its structural formula and molecular weight are:

Figure 1: Structural Formula and Molecular Weight of Apomorphine



• HCl • 1/2 H_2O

M.W. 312.79

Apomorphine hydrochloride appears as minute, white or grayish-white glistening crystals or as white powder that is soluble in water at 80°C.

APOKYN is a clear, colorless, sterile solution for subcutaneous injection and is available in 3 mL (30 mg) multi-dose cartridges. Each mL of solution contains 10 mg of apomorphine hydrochloride, USP as apomorphine hydrochloride hemihydrate, 1 mg of sodium metabisulfite, NF and 5 mg of benzyl alcohol, NF (preservative) in water for injection, USP. In addition, each mL of solution may contain sodium hydroxide, NF and/or hydrochloric acid, NF to adjust the pH of the solution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

APOKYN is a non-ergoline dopamine agonist with high *in vitro* binding affinity for the dopamine D_4 receptor, and moderate affinity for the dopamine D_2, D_3, and D_5, and adrenergic α_1D, α_2B, α_2C receptors. The precise mechanism of action of APOKYN as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D_2-type receptors within the caudate-putamen in the brain.

12.2 Pharmacodynamics

Prolongation of the QTc Interval: In a placebo-controlled study in which patients received increasing single doses of APOKYN from 2 mg to up to 10 mg, the mean difference in QTc (measured by Holter monitor) between APOKYN and placebo was 0 msec at 4 mg, 1 msec at 6 mg, and 7 msec at 8 mg. Too few patients received a 10 mg dose to be able to adequately characterize the change in QTc interval at that dose.

In a controlled trial in which patients were administered placebo or a single dose of APOKYN (mean dose of 5.2 mg; range of 2 mg to 10 mg), the mean difference between APOKYN and placebo in the change in QTc was about 3 msec at 20 minutes and 90 minutes. In the entire database, 2 patients (one at 2 mg and 6 mg, one at 6 mg) exhibited large QTc increments (> 60 msecs from pre-dose) and had QTc intervals greater than 500 msecs acutely after dosing. Doses of 6 mg or less thus are associated with minimal increases in QTc.

Decreases in blood pressure

Dose-dependent mean decrements in systolic blood pressure ranged from 5 mmHg after 2 mg to 16 mmHg after 10 mg. Dose-dependent mean decrements in diastolic blood pressure ranged from 3 mmHg after 2 mg to 8 mmHg after 10 mg. These changes were observed at 20 minutes, and were maximal between 20 and 40 minutes after dosing. Lesser, but still noteworthy blood pressure decrements persisted up to at least 90 minutes after dosing.

12.3 Pharmacokinetics

Absorption
Apomorphine hydrochloride is a lipophilic compound that is rapidly absorbed (time to peak concentration ranges from 10 minutes to 60 minutes) following subcutaneous administration into the abdominal wall. After subcutaneous administration, apomorphine appears to have bioavailability equal to that of an intravenous administration. Apomorphine exhibits linear pharmacokinetics over a dose range of 2 mg to 8 mg following a single subcutaneous injection of APOKYN into the abdominal wall in patients with idiopathic Parkinson's disease.

Distribution
The plasma-to-whole blood apomorphine concentration ratio is equal to one. Mean (range) apparent volume of distribution was 218 L (123 L to 404 L). Maximum concentrations in cerebrospinal fluid (CSF) are less than 10% of maximum plasma concentrations and occur 10 minutes to 20 minutes later.

Metabolism and Elimination
The mean apparent clearance (range) is 223 L/hr (125 L/hr to 401 L/hr) and the mean terminal elimination half-life is about 40 minutes (range about 30 minutes to 60 minutes).

The route of metabolism in humans is not known. Potential routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation. In vitro, apomorphine undergoes rapid autooxidation.

Special Populations
The clearance of apomorphine does not appear to be influenced by age, gender, weight, duration of Parkinson's disease, levodopa dose or duration of therapy.

Renal Impairment
In a study comparing renally-impaired subjects (moderately impaired as determined by estimated creatinine clearance) to healthy matched volunteers, the AUC_0-∞ and Cmax values were increased by approximately 16% and 50%, respectively, following a single subcutaneous administration of APOKYN into the abdominal wall. The mean time to peak concentrations and the mean terminal half-life of apomorphine were unaffected by the renal status of the individual. Studies in subjects with severe renal impairment have not been conducted. The starting dose for patients with mild or moderate renal impairment should be reduced *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Hepatic Impairment
In a study comparing subjects with hepatic impairment (moderately impaired as determined by the Child-Pugh classification method) to healthy matched volunteers, the AUC_0-∞ and C_{max} values were increased by approximately 10% and 25%, respectively, following a single subcutaneous administration of APOKYN into the abdominal wall. Studies in subjects with severe hepatic impairment have not been conducted *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

Drug-Drug Interactions
Carbidopa/levodopa: Levodopa pharmacokinetics were unchanged when subcutaneous APOKYN and levodopa were co-administrated in patients. However, motor response differences were significant. The threshold levodopa concentration necessary for an improved motor response was reduced significantly, leading to an increased duration of effect without a change in the maximal response to levodopa therapy.

Other Drugs Eliminated Via Hepatic Metabolism
Based upon an *in vitro* study, cytochrome P450 enzymes play a minor role in the metabolism of apomorphine. *In vitro* studies have also demonstrated that drug interactions are unlikely due to apomorphine acting as a substrate, an inhibitor, or an inducer of cytochrome P450 enzymes.

COMT Interactions
A pharmacokinetic interaction of APOKYN with catechol-O-methyl transferase (COMT) inhibitors or drugs metabolized by this route is unlikely since apomorphine appears not to be metabolized by COMT.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Lifetime carcinogenicity studies of apomorphine were conducted in male (0.1 mg/kg/day, 0.3 mg/kg/day, 0.8 mg/kg/day) and female (0.3 mg/kg/day, 0.8 mg/kg/day, 2 mg/kg/day) rats. Apomorphine was administered by subcutaneous injection for 22 months or 23 months, respectively. In males, there was an increase in Leydig cell tumors at the highest dose tested, which is less than the MRHD (20 mg) on a mg/m^2 basis. This finding is of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell tumors in rats are not relevant to humans. No drug-related tumors were observed in females; the highest dose tested is similar to the MRHD on a mg/m^2 basis.
In a 26-week carcinogenicity study in P53-knockout transgenic mice, there was no evidence of carcinogenic potential when apomorphine was administered by subcutaneous injection at doses up to 20 mg/kg/day (male) or 40 mg/kg/day (female).

Mutagenesis
Apomorphine was mutagenic in the *in vitro* bacterial reverse mutation (Ames) and the *in vitro* mouse lymphoma *tk* assays. Apomorphine was clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes and in the *in vitro* mouse lymphoma *tk* assay. Apomorphine was negative in the *in vivo* micronucleus assay in mice.

Impairment of Fertility
Apomorphine was administered subcutaneously at doses up to 3 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) to male and female rats prior to and throughout the mating period and continuing in females through gestation day 6. There was no evidence of adverse effects on fertility or on early fetal viability. A significant decrease in testis weight was observed in a 39-week study in cynomolgus monkey at all subcutaneous dose tested (0.3 mg/kg/day, 1 mg/kg/day, 1.5 mg/kg/day); the lowest dose tested is less than the MRHD on a mg/m^2 basis.

In a published fertility study, apomorphine was administered to male rats at subcutaneous doses of 0.2 mg/kg, 0.8 mg/kg, and 2 mg/kg prior to and throughout the mating period. Fertility was reduced at the highest dose tested.

14 CLINICAL STUDIES

The effectiveness of APOKYN in the acute symptomatic treatment of the recurring episodes of hypomobility, “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes), in patients with advanced Parkinson’s disease was established in three randomized, controlled trials of APOKYN given subcutaneously (Studies 1, 2, and 3). At baseline in these trials, the mean duration of Parkinson’s disease was approximately 11 years. Whereas all patients were using concomitant L-dopa at

baseline, 86% of patients were using a concomitant oral dopaminergic agonist, 31% were using a concomitant catechol-ortho-methyl transferase COMT) inhibitor, and 10% were using a concomitant monoamine B oxidase inhibitor. Study 1 was conducted in patients who did not have prior exposure to APOKYN (i.e., APOKYN naïve) and Studies 2 and 3 were conducted in patients with at least 3 months of APOKYN use immediately prior to study enrollment. Almost all patients without prior exposure to APOKYN began taking an antiemetic (trimethobenzamide) three days prior to starting APOKYN and 50% of patients were able to discontinue the concomitant antiemetic, on average 2 months after initiating APOKYN.

The change from baseline in Part III (Motor Examination) of the Unified Parkinson's Disease Rating Scale (UPDRS) served as the primary outcome assessment measure in each study. Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, postural instability, etc.) in patients with Parkinson's disease.

Study 1

Study 1 was a randomized, double-blind, placebo-controlled, parallel-group trial in 29 patients with advanced Parkinson's disease who had at least 2 hours of "off" time per day despite an optimized oral regimen for Parkinson's disease including levodopa and an oral dopaminergic agonist. Patients with atypical Parkinson's disease, psychosis, dementia, hypotension, or those taking dopamine antagonists were excluded from participation. In an office setting, hypomobility was allowed to occur by withholding the patients' Parkinson's disease medications overnight. The following morning, patients (in a hypomobile state) were started on study treatment in a 2:1 ratio (2 mg of APOKYN or placebo given subcutaneously). At least 2 hours after the first dose, patients were given additional doses of study medication until they achieved a "therapeutic response" (defined as a response similar to the patient's response to their usual dose of levodopa) or until 10 mg of APOKYN or placebo equivalent was given. At each injection re-dosing, the study drug dose was increased in 2 mg increments up to 4 mg, 6 mg, 8 mg, 10 mg of APOKYN) or placebo equivalent.

Of the 20 patients randomized to APOKYN, 18 achieved a "therapeutic response" at about 20 minutes. The mean APOKYN dose was 5.4 mg (3 patients on 2 mg, 7 patients on 4 mg, 5 patients on 6 mg, 3 patients on 8 mg, and 2 patients on 10 mg). In contrast, of the 9 placebo-treated patients, none reached a "therapeutic response." The mean change-from-baseline for UPDRS Part III score for APOKYN group (highest dose) was statistically significant compared to that for the placebo group (Table 2).

Table 2: Mean Change from Baseline in UPDRS Motor Score for Intent-to-Treat Population in Study 1

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from placebo
Placebo	36.3	- 0.1	NA
APOKYN	39.7	- 23.9	- 23.8

Study 2

Study 2 used a randomized, placebo-controlled crossover design of 17 patients with Parkinson's disease who had been using APOKYN for at least 3 months. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received either a single dose of subcutaneous APOKYN (at their usual dose) and placebo on different days in random order. UPDRS Part III scores were evaluated over time. The mean dose of APOKYN was 4 mg (2 patients on 2 mg, 9 patients on 3 mg, 2 patients on 4 mg, and 1 patient each on 4.5 mg, 5 mg, 8 mg, and 10 mg). The mean change-from-baseline UPDRS Part III score for the APOKYN group was statistically significant compared to that for the placebo group (Table 3).

Table 3: Mean Change from Baseline in UPDRS Motor Score for Intent-to-Treat Population in Study 2

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from placebo
Placebo	40.1	- 3.0	NA
APOKYN	41.3	- 20.0	- 17.0

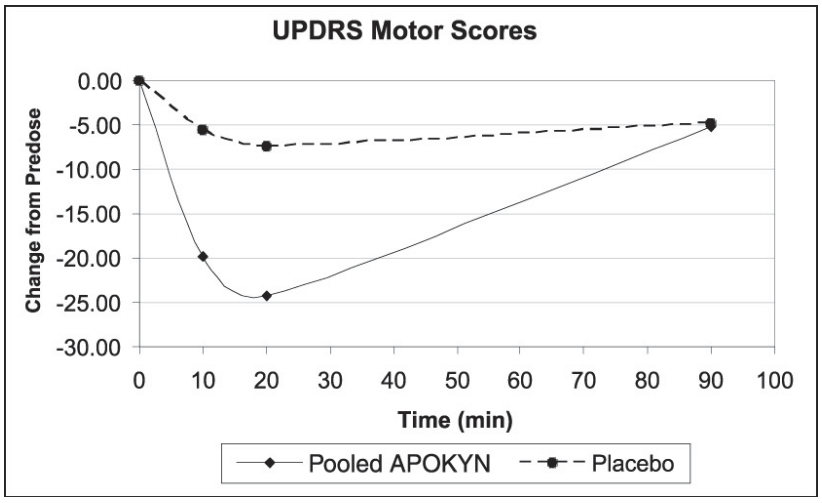
Study 3

Study 3 used a randomized withdrawal design in 4 parallel groups from 62 patients (APOKYN-35; Placebo-27) with Parkinson's disease who had been using APOKYN for at least 3 months. Patients were randomized to one of the following 4 treatments dosed once by subcutaneous administration: APOKYN at the usual dose (mean dose 4.6 mg), placebo at a volume matching the usual APOKYN dose, APOKYN at the usual dose + 2 mg (0.2 mL) (mean dose 5.8 mg), or placebo at a volume matching the usual APOKYN dose + 0.2 mL. Patients received their usual morning doses of Parkinson's disease medications and were followed until hypomobility occurred, at which time they received the randomized treatment. APOKYN doses ranged between 2 mg – 10 mg. The mean change-from-baseline for the APOKYN group for UPDRS Part III scores at 20 minutes post dosing was statistically significant compared to that for the placebo group (Table 4). Figure 2 describes the mean change from baseline in UPDRS Motor Scores over time for pooled APOKYN and placebo administration.

Table 4: Mean Change from Baseline in UPDRS Motor Score for Intent-to-Treat Population in Study 4

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from placebo
Placebo (Pooled)	40.6	- 7.4	NA
APOKYN (Pooled)	42.0	- 24.2	- 16.8

Figure 2: Mean Change from Baseline in UPDRS Motor Scores of Pooled APOKYN Groups and Placebo Group in Study 3



In Study 3, the mean changes-from-baseline for UPDRS Part III scores at 20 minutes post dosing for the APOKYN and higher dose APOKYN groups were 24 and 25, respectively. This result suggests that patients chronically treated at a dose of 4 mg might derive little additional benefit from a dose increment of 2 mg. There was also an increased incidence of adverse reactions in patients randomized to higher APOKYN dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

APOKYN is supplied as a 10 mg/mL clear, colorless, sterile, solution in 3 mL (30 mg) glass cartridges.

NDC 27505-004-05
Cartons of five 3 mL cartridges

APOKYN Pen
The pen injector is provided in a package with six needles and a carrying case.

Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Administration with the APOKYN Pen

Instruct patients and caregivers to read the "Patient Information and Instructions for Use for APOKYN and the dosing pen. Instruct patients to use APOKYN only as prescribed *[See Dosage and Administration (2)]*.

Instruct patients and caregivers that the APOKYN Pen is dosed in milliliters, not milligrams.

Inform patients and caregivers that it is possible to dial in their usual dose of APOKYN even though the cartridge may contain less than that amount of drug. In this case, they will receive only a partial dose with the injection, and the amount left to inject will appear in the dosing window. To complete the correct dose, patients/caregivers will need to "re-arm" the device and dial in the correct amount of the remaining dose. Patients and caregivers should be alerted to the fact that there may be insufficient drug left in the cartridge to deliver a complete dose (for example, patients and caregivers should be urged to keep records of how many doses they have delivered for each cartridge, so that they can replace any cartridge that has an inadequate amount of drug remaining).

Instruct patients to rotate the injection site and to observe proper aseptic technique.

Advise patients that APOKYN is intended only for subcutaneous injection and must not be given intravenously because of the risk of serious complications such as thrombus formation and pulmonary embolism due to crystallization *[see Warnings and Precautions (5.1)]*.

Avoidance of Concomitant Antiemetic Drugs of $5HT_3$ Antagonist Class

Advise patients that they should not use concomitant drugs of the $5HT_3$ antagonist class including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron with APOKYN. Use of APOKYN with concomitant antiemetic drugs of the $5HT_3$ antagonist class is contraindicated because there have been reports of profound hypotension and loss of consciousness when APOKYN was administered with ondansetron *[see Contraindications (4)]*.

Hypersensitivity / Allergic Reactions

Advise patients that hypersensitivity/allergic reaction characterized by urticaria, rash, pruritus, and/or various manifestations of angioedema may occur because of APOKYN or any of its excipients including

a sulfite (i.e., sodium metabisulfite). Inform patients with a sulfite sensitivity that they may experience various allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic attacks. Advise patients who experience any hypersensitivity/allergic reaction to APOKYN that they should avoid taking APOKYN again *[see Contraindications (4)]*.

Nausea and Vomiting

Advise patients that they may experience severe nausea and/or vomiting and that they should begin taking trimethobenzamide 300 mg tablets orally 3 times per day for three days prior to starting APOKYN injections and continue taking it until told by a healthcare provider that trimethobenzamide can be discontinued *[see Warnings and Precautions (5.2)]*.

Falling Asleep Suddenly and Sedation / Sleepiness

Alert patients to the potential sedating effects of APOKYN, including somnolence and falling asleep while engaged in activities of daily living. Instruct patients not to drive a car or engage in other potentially dangerous activities until they have gained sufficient experience with APOKYN to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) occur, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects of alcohol use, advise patients to limit their alcohol intake *[see Warnings and Precautions (5.3)]*.

Syncope

Advise patients that APOKYN may cause syncope *[see Warnings and Precautions (5.4)]*.

Hypotension / Orthostatic Hypotension

Advise patients that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope, and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose at any time (cases have been seen after months of treatment). Instruct patients to rise slowly after sitting or lying down after taking APOKYN. Instruct patients to limit their alcohol intake because it may potentiate the hypotensive effect of APOKYN *[see Warnings and Precautions (5.5)]*.

Falls

Alert patients that they may have increased risk for falling when using APOKYN *[see Warnings and Precautions (5.6)]*.

Hallucinations and/or Psychotic-Like Behavior

Inform patients that hallucinations or other manifestations of psychotic-like behavior can occur. Tell patients if they have a major psychotic disorder, ordinarily they should not use APOKYN because of the risk of exacerbating the psychosis. Patients with a major psychotic disorder should also be aware that many treatments for psychosis may decrease the effectiveness of APOKYN *[see Warnings and Precautions (5.7)]*.

Dyskinesia

Inform patients that APOKYN may cause and/or exacerbate pre-existing dyskinesias *[see Warnings and Precautions (5.8)]*.

Impulse Control / Compulsive Behaviors

Patients and their caregivers should be alerted to the possibility that they may experience intense urges to spend money uncontrollably, intense urges to gamble, increased sexual urges, binge eating and/or other intense urges and the inability to control these urges while taking APOKYN *[see Warnings and Precautions (5.9)]*.

Coronary Events

Inform patients that APOKYN may cause coronary events including angina and myocardial infarction and these outcomes could possibly be related to significant hypotension/orthostatic hypotension *[see Warnings and Precautions (5.10)]*.

QTc Prolongation and Potential for Proarrhythymic Effects

Alert patients that APOKYN may cause QTc prolongation and might produce proarrhythmic effects that could cause torsades de pointes and sudden death. Palpitations and syncope may signal the occurrence of an episode of torsades de pointes *[see Warnings and Precautions (5.11)]*.

Withdrawal-Emergent Hyperpyrexia and Confusion

Advise patients to contact their healthcare provider if they wish to discontinue APOKYN or decrease the dose of APOKYN *[see Warnings and Precautions (5.12)]*.

Melanoma

Advise patients with Parkinson's disease that they have a higher risk of developing melanoma. Advise patients to have a qualified healthcare provider examine that patient's skin periodically for melanomas on a regular basis when using APOKYN *[see Warnings and Precautions (5.13)]*.

Priapism

Advise patients that APOKYN may cause prolonged painful erections and that if this occurs that they should seek medical attention immediately *[see Warnings and Precautions (5.15)]*.

Injection Site Reactions

Inform patients that injections of APOKYN may result in injection site reactions including bruising, granuloma, and pruritus *[see Adverse Reactions (6.1)]*.

Distributed by:

US WorldMeds, LLC
4010 Dupont Circle, Suite L-07
Louisville, KY 40207

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20.2 APPENDIX II: Regulations and Guidelines

20.2.1 Declaration of Helsinki

The Policy of the World Medical Association is available at URL: http://www.wma.net/en/30publications/10policies/b3/

20.2.2 Approval by an IRB/REB/IEC

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

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 Cynapsus 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 patient 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 Cynapsus, before implementation. This written approval will consist of a completed approval form, or written documentation from the IRB/REB/IEC containing the same information.

FDA Regulations

Refer to the following United States Code of Federal Regulations (CFR):

FDA Regulations 21 CFR Parts 50.20 - 50.27

Subpart B - Informed Consent of Human Subjects

FDA Regulations 21 CFR Parts 56.107 - 56.115

Part 56-Institutional Review Boards

Subpart B - Organization and Personnel

Subpart C – IRB Functions and Operations

Subpart D – Records

FDA Regulations 21 CFR Parts 312.50 - 312.70

Subpart D - Responsibilities of Sponsors and Investigators

20.3 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.

20.4 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:

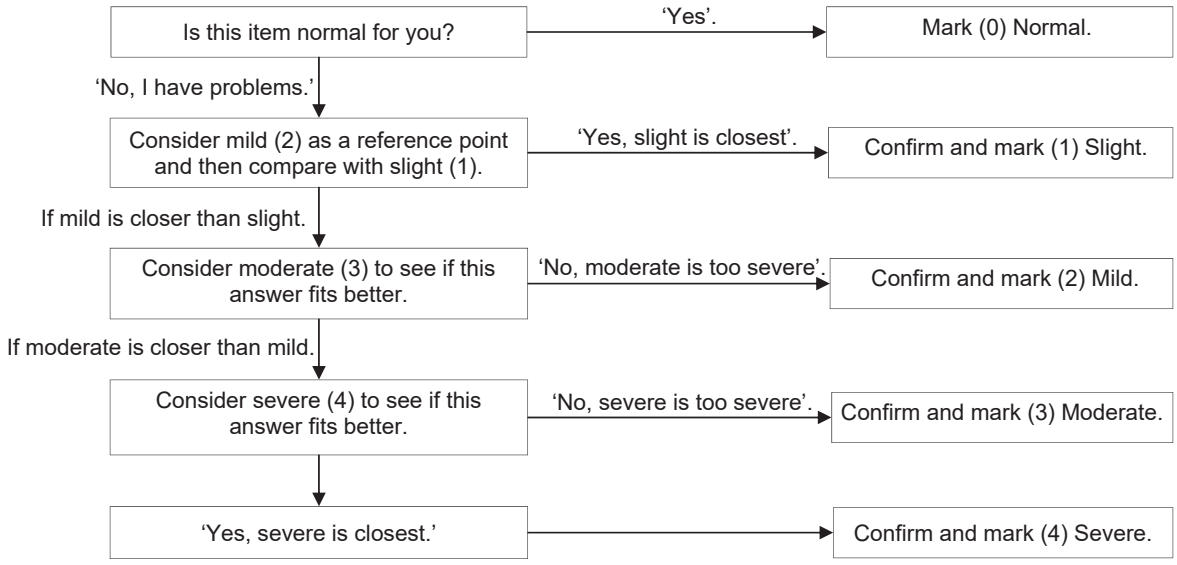
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (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)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

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

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

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

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

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

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

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

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

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

Part III: Motor Examination

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.	R
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.	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.	RUE
1: Slight.:	< 1 cm in maximal amplitude.	
2: Mild:	> 1 cm but < 3 cm in maximal amplitude.	LUE
3: Moderate:	3 - 10 cm in maximal amplitude.	
4: Severe:	> 10 cm in maximal amplitude.	RLE

Lip/Jaw ratings

0: Normal:	No tremor.	LLE
1: Slight:	< 1 cm in maximal amplitude.	
2: Mild:	> 1 cm but < 2 cm in maximal amplitude.	Lip/Jaw
3: Moderate:	> 2 cm but < 3 cm in maximal amplitude.	
4: Severe:	> 3 cm in maximal amplitude.	

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

Part IV: Motor Complications

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

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

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

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

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

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

A . DYSKINESIAS [exclusive of OFF-state dystonia]

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.	1. Total Hours Awake: _____
3: Moderate:	51 - 75% of waking day.	2. Total Hours with Dyskinesia: _____
4: Severe:	> 75% of waking day.	3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS — **SCORE**

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

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

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

☐

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

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

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

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

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

☐

4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS — **SCORE**

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

20.5 APPENDIX V: Patient Home Dosing Diary

Screening # _____ Site #_____ Investigator: _____
Randomization # _____

CTH-300 Dosing Diary

Date: _____

Instructions: Complete this diary on the 2 days prior to your next study visit. During these two days you will need to write down some information every time you treat an "OFF" episode with study medication (up to 5 times a day).

- Write down the time you take the study medication.
- Place a checkmark in the appropriate box if you are in a full "ON" state or are still in an "OFF" state exactly 30 minutes after taking the study medication.
- If you did not use your study medication on one of the diary days, please mark the date and check off N/A below.

Full "ON" means a period of time where your medication is providing benefit with regard to mobility, stiffness and slowness and where you feel you can perform normal daily activities. This "ON" should feel the same or better than what you felt like when taking your normal Parkinson's disease medications before starting the study.

"OFF" means a period of time when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness.

☐ N/A – did not use study medication.

Dosing Time	"ON"/"OFF" Status 30 minutes after Dosing
Time: _____ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"
Time: _____ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"
Time: _____ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"
Time: _____ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"
Time: _____ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"

Page ___ of ___

20.6 APPENDIX VI: 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* _____

 C-SSRS—Screening (Version 1/14/09) Page 2 of 2

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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

20.7 APPENDIX VII: PDQ-39

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for completing the questionnaire.

20.8 APPENDIX VIII: CGI

Screening # _____ Site #_____ Investigator: _____

Rand. # _____

CGI - Severity (baseline assessment)

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

1 = normal/not at all ill

2 = borderline ill

3 = mildly ill

4 = moderately ill

5 = markedly ill

6 = severely ill

7 = among the most extremely ill of patients

Screening # _____ Site #_____ Investigator: _____

Rand. # _____

CGI - Improvement (subsequent assessments)

Compared to his/her condition on baseline, how much has he/she changed?

1 = very much improved

2 = much improved

3 = minimally improved

4 = no change

5 = minimally worse

6 = much worse

7 = very much worse

20.9 APPENDIX IX: PGI

Screening # _____ Site #_____ Investigator: _____

Rand. # _____

PGI – Severity (baseline assessment)

Ask the patient: “How would you rate your illness at this time”.

1 = normal/not at all ill

2 = borderline ill

3 = mildly ill

4 = moderately ill

5 = markedly ill

6 = severely ill

7 = among the most extremely ill of patients

Screening # _____ Site #_____ Investigator: _____

Rand. # _____

PGI – Change/Improvement (subsequent assessments)

Ask the patient: "Since starting study medication, how has your illness changed?"

1 = very much improved

2 = much improved

3 = minimally improved

4 = No change

5 = minimally worse

6 = much worse

7 = very much worse

20.10 APPENDIX X: ESS

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public place (e.g., a theater or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car or bus, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

ESS - United States/English - Version of 16 Jan 15 - Mapi.
ID037309 / ESS_AU1.0_eng-US1.doc

20.11 APPENDIX XI: ZBI

BURDEN INTERVIEW

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

1. Do you feel that your relative asks for more help than he/she needs?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

2. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

4. Do you feel embarrassed over your relative's behavior?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

5. Do you feel angry when you are around your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

6. Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

7. Are you afraid what the future holds for your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

8. Do you feel your relative is dependent upon you?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

9. Do you feel strained when you are around your relative?

   0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

ZBI – USA/English – Original version
ZBI-22_AU1.0_eng-USori.doc

10. Do you feel your health has suffered because of your involvement with your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

11. Do you feel that you don't have as much privacy as you would like, because of your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

12. Do you feel that your social life has suffered because you are caring for your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

13. Do you feel uncomfortable about having friends over, because of your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

14. Do you feel that your relative seems to expect you to take care of him/her, as if you were the only one he/she could depend on?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

15. Do you feel that you don't have enough money to care for your relative, in addition to the rest of your expenses?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

16. Do you feel that you will be unable to take care of your relative much longer?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

17. Do you feel you have lost control of your life since your relative's illness?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

18. Do you wish you could just leave the care of your relative to someone else?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

19. Do you feel uncertain about what to do about your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

20. Do you feel you should be doing more for your relative?

    0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

ZBI – USA/English – Original version
ZBI-22_AU1.0_eng-USori.doc

21. Do you feel you could do a better job in caring for your relative?

0. Never 1. Rarely 2. Sometimes 3. Quite Frequently 4. Nearly Always

22. Overall, how burdened do you feel in caring for your relative?

0. Not at all 1. A little 2. Moderately 3. Quite a bit 4. Extremely

20.12 APPENDIX XII: QUIP-RS

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Reported by: _____ Patient _____ Informant _____ Patient and Informant

Patient / Subject: _____

Date: _____

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Sex?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Buying?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Eating?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Performing tasks or hobbies?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Repeating simple activities?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)
Taking your PD medications?	___Never(0)	___Rarely(1)	___Sometimes(2)	___Often(3)	___Very often(4)

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Subject: _____

Date: _____

SCORING SHEET

A. Gambling	_____	**(0-16)**
B. Sex	_____	**(0-16)**
C. Buying	_____	**(0-16)**
D. Eating	_____	**(0-16)**
E. Hobbyism-Punding	_____	**(0-32)**
F. PD Medication Use	_____	**(0-16)**
Total ICD Score (A-D)	_____	**(0-64)**
Total QUIP-RS Score (A-F)	_____	**(0-112)**

20.13 APPENDIX XIII: EQ-5D

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

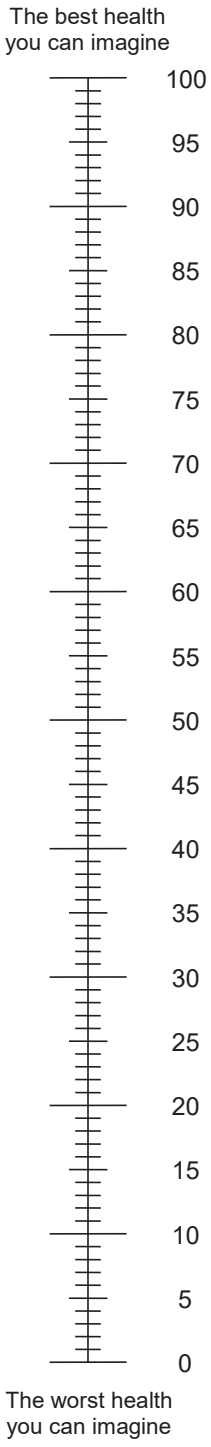
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



20.14 APPENDIX XIV: 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. JNNP 1992;55:181-184.

20.15 APPENDIX XV: Enrollment Adjudication Committee Form

Enrollment Adjudication Committee Form
Cynapsus Protocol Number: CTH-300

ENROLLMENT ADJUDICATION COMMITTEE FORM

Site Investigator and Subject Information	
Site Number: Click here to enter text.	Patient Screening Number: Click here to enter text.
Date of Form Completion: Click here to enter a date.	Gender: ☐M ☐F
Site Contact Phone Number: Click here to enter text.	Age: Click here to enter text.
Site Investigator Name: Click here to enter text.	Screening Date: Click here to enter a date.
Name of Person Completing the Form: Click here to enter text.	Contact Phone Number of Person Completing the form: Click here to enter text.

Parkinson's Disease History	
1. Duration of PD from Time of Diagnosis:	Click here to enter text. months
2. Hoehn & Yahr Stage in the "ON" state:	Click here to enter text. (0-5 in half point increments)
3. Hoehn & Yahr Stage in the "OFF" state:	Click here to enter text. (0-5 in half point increments)
4. MDS-UPDRS Part III Score in the "ON" state:	Click here to enter text.(0-56)
5. MDS-UPDRS Part III Score in the "OFF" state:	Click here to enter text.(0-56)
6. Does patient have a good response to levodopa (> 25% in MDS-UPDRS score)?	☐Yes ☐No
7. Does patient have ≥ 2 hours of off time per day?	☐Yes ☐No
8. Does patient have predictable early morning off periods?	☐Yes ☐No
9. Does patient have severe dyskinesias?	☐Yes ☐No
10. Can patient come back to clinic in off state at regularly scheduled time points – describe how patient will get to clinic with early AM off periods	☐Yes ☐No If yes, describe: Click here to enter text.
11. Does patient have prominent gait disturbance - describe	☐Yes ☐No If yes, describe: Click here to enter text.
12. Does patient have prominent non-motor features - describe	☐Yes ☐No If yes, describe: Click here to enter text.
13. Does patient have prominent cognitive impairment - describe	☐Yes ☐No If yes, describe: Click here to enter text.
14. Has patient had MRI in past 12 months?	☐Yes ☐No If yes, describe: Click here to enter text.

Enrollment Adjudication Committee Form
Cynapsus Protocol Number: CTH-300

15. Has patient had previous imaging of dopamine system?	☐Yes ☐No If yes, what were the results? Click here to enter text.
16. Is there any history of significant psychiatric problems?	☐Yes ☐No If yes, describe: Click here to enter text.
17. Are there any factors that raise a question as to the diagnosis of PD?	☐Yes ☐No If yes, describe: Click here to enter text.
18. Any factors that would preclude patient returning for follow up visits?	☐Yes ☐No If yes, describe: Click here to enter text.
19. Has nausea or vomiting been a problem with the introduction of dopaminergic agents in the past/present?	☐Yes ☐No If yes, describe: Click here to enter text.
20. Does patient suffer from objective or symptomatic orthostatic hypotension?	☐Yes ☐No If yes, describe and provide values: Click here to enter text.
21. Does the patient have cankers or mouth sores?	☐Yes ☐No
22. Has the subject had prior exposure to apomorphine?	☐Yes ☐No
23. Current Concomitant Medications (attach supplemental pages if needed):	

Name of Medicine	Dose	# tabs/ caps	Frequency
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

I have reviewed the above information and approve the subject for further evaluation

_____ Click here to enter a date.
Investigator Signature **Date**

Enrollment Adjudication Committee Form
Cynapsus Protocol Number: CTH-300

please forward to the recipient below	
[redacted]	
Clintrex/Cynapsus Medical Review	
[redacted] ☐ [redacted] ☐ [redacted] Date: Click here to enter a date. Signature: _____	☐ Approved for Enrollment ☐ Not Approved for Enrollment Include reason:Click here to enter text. ☐ Additional information required (specify): Click here to enter text.
Note: Site personnel must print review response and accompanying email correspondence for the patient file.	