APL-130277

CTH-301

An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

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Incorporates Amendment 4.00

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1. EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician		O
North America Medical Monitor		
European Union Medical Monitor		
SAE Reporting		

2. INVESTIGATOR APPROVAL STATEMENT

I have read the protocol, CTH-301, Version 5.00, "An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

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

Principal Investigator

Printed Name: _____

Signature: _____

Date: _____

PROTOCOL

An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Protocol: 25 February 2019

Version: 5.00

3. PROTOCOL SYNOPSIS

TITLE	An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy 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 long-term safety and tolerability of APL-130277 in Subjects with Parkinson's disease (PD).
NUMBER OF Subjects	The overall number of subjects is not pre-specified as this is an extension study.
Subject POPULATION ***De Novo* Subjects**	*De Novo* Subjects are defined as patients who have not previously participated in a study with APL-130277. **Inclusion Criteria – *De Novo* Subjects** Subjects who meet each of the following criteria will be eligible for participation in the study: 1. Male or female ≥ 18 years of age. 2. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria (excluding the "more than one affected relative" criterion.). 3. Clinically meaningful response to Levodopa (L-Dopa) 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 at least 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. Subjects 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. Subject 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. Mini–Mental State Examination (MMSE) score > 25. 10. If female and of childbearing potential, must agree to be sexually

	abstinent or use one of the following highly effective methods of birth control: • Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants); • Intrauterine contraceptive system; • Surgical sterilization or partner sterile (must have documented proof); AND One of the following effective methods of birth control: • Male/female condom; • Cervical cap with spermicide; • Diaphragm with spermicide; • Contraceptive sponge. 11. Male subjects must be either surgically sterile, agree to be sexually inactive or use a double-barrier method of birth control (eg, condom and diaphragm with spermicide, condom with cervical cap and spermicide) from first study drug administration until 90 days after final drug administration. 12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures. 13. Able to understand the consent form, and to provide written informed consent. **Exclusion Criteria – *De Novo* Subjects** Subjects 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; Duodopa/Duopa; or APL-130277. 3. Treatment with any form of s.c. apomorphine within 7 days prior to the second Screening Visit (SV2). Subjects 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). 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 (ie, unapproved) medication within 30 days prior to the initial Screening Visit (SV1). 8. Currently taking selective $5HT_3$ antagonists (ie, 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. Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Pituitary tumors of any duration are excluded. 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. Presence of canker 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.
Subject POPULATION Rollover Subjects	**Inclusion Criteria – Rollover Subjects** Subjects who meet each of the following criteria will be eligible for participation in the study: 1. Completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302 and, in the opinion of the Investigator, would benefit from continued treatment with APL-130277. 2. No major changes in concomitant PD medications since completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302. Any change in PD medications since the previous study should be discussed with the Medical Monitor to determine subject eligibility in the current study. 3. If female and of childbearing potential, must agree to be sexually abstinent or use one of the following highly effective methods of birth control: • Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants); • Intrauterine contraceptive system;

	• Surgical sterilization or partner sterile (must have documented proof); AND One of the following effective methods of birth control: • Male/female condom; • Cervical cap with spermicide; • Diaphragm with spermicide; • Contraceptive sponge. 4. Male subjects must be either surgically sterile, agree to be sexually inactive or use a double-barrier method of birth control (eg, condom and diaphragm with spermicide, condom with cervical cap and spermicide) from first study drug administration until 90 days after final drug administration. 5. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures. 6. Able to understand the consent form, and to provide written informed consent. **Exclusion Criteria Rollover Subjects** Subjects will be excluded from participation in the study for any of the following reasons: 1. Female who is pregnant or lactating. 2. Presence of any major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis (including clinically significant hallucinations during the past 6 months) or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult. 3. Presence of any clinically significant medical (including but not limited to CNS, cardiovascular, hepatic, pulmonary, metabolic, or renal events), surgical, or laboratory abnormality that would make study participation unsafe or make treatment compliance difficult. Clinical significance to be determined by the Investigator. 4. Receipt of any investigational (ie, unapproved) medication or participation in any clinical trial of an investigational product within 14 days of completing a previous study with APL-130277. 5. Development of canker or mouth sores within 14 days of completing a previous study using APL-130277. For other clinically significant oral pathology, the Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling such a subject into the study. Clinical significance to be determined by the Investigator. The eligibility of subjects who have experienced AEs related to the oral cavity during the previous study using APL-130277, should be reviewed with the medical monitor and approval obtained. 6. Current suicidal ideation within one year of the screening visit, as evidenced by answering "yes" to Question 4 or 5 on the suicidal

	ideation portion of the C-SSRS at Screening or attempted suicide within 5 years.
Subject POPULATION CTH-301 Completer Subjects	CTH-301 Completer Patients are defined as patients who have previously completed the CTH-301 study under protocol version 3.00. **Inclusion Criteria -** CTH-301 Completer Subjects Subjects who meet each of the following criteria will be eligible for participation in the study: 1. Completion of the CTH-301 study under protocol version 3.00, and in the opinion of the Investigator, would benefit from continued treatment with APL-130277. 2. If female and of childbearing potential, must agree to be sexually abstinent or use one of the following highly effective methods of birth control: • Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants); • Intrauterine contraceptive system; • Surgical sterilization or partner sterile (must have documented proof); AND One of the following effective methods of birth control: • Male/female condom; • Cervical cap with spermicide; • Diaphragm with spermicide; • Contraceptive sponge. 3. Male subjects must be either surgically sterile, agree to be sexually inactive or use a double-barrier method of birth control (eg, condom and diaphragm with spermicide, condom with cervical cap and spermicide) from first study drug administration until 90 days after final drug administration. 4. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures. 5. Able to understand the consent form, and to provide written informed consent. **Exclusion Criteria - CTH-301 Completer Subjects** Patients will be excluded from participation in the study for any of the following reasons: 1. Female who is pregnant or lactating. 2. Presence of any major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis (including clinically significant hallucinations during the past 6 months) or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.

	3. Presence of any clinically significant medical (including but not limited to CNS, cardiovascular, hepatic, pulmonary, metabolic, or renal events), surgical, or laboratory abnormality that would make study participation unsafe or make treatment compliance difficult. Clinical significance to be determined by the Investigator. 4. Receipt of any investigational (ie, unapproved) medication or participation in any clinical trial since completing the CTH-301 study. 5. Development of canker or mouth sores since completing the CTH-301 study. For other clinically significant oral pathology, the Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling such a patient into the study. Clinical significance to be determined by the Investigator. 6. Current suicidal ideation as evidenced by answering "yes" to Question 4 or 5 on the suicidal ideation portion of the C-SSRS at the Screening Visit Phase 2 (SVP2).
STUDY DESIGN	This is a multi-center, open-label, Phase 3 study in L-Dopa responsive PD subjects with motor fluctuations, designed to evaluate the long-term safety, tolerability and efficacy of APL-130277. *Screening Procedures for De Novo Subjects* *De Novo* subjects are defined as subjects who have not previously participated in a study with APL-130277. Before any study procedures are performed on any subject, informed consent must be obtained at an initial Screening Visit (SV1). If required by the Investigator, and following receipt of subject consent, the Investigator may review the subject's medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the subject may be eligible for study participation and continuation onto the second Screening Visit (SV2). Subjects recruited to participate in the study, and who have provided full consent to participate, will be asked to attend the second Screening Visit (SV2), and will be instructed to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Their normal morning dose of L-Dopa (*without* adjunctive PD medication) will be administered in the clinic approximately two hours after their normally scheduled second dose of PD medication, following confirmation of an "OFF" episode by the Investigator, to ensure that they experience a full "ON" response. Eligibility criteria will be assessed and subject "ON"/"OFF" training will be performed. Subjects will be asked to return to clinic in the morning of Titration Visit 1 (TV1) for the Dose Titration Phase of the study, and will be instructed to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication.

	Screening Procedures for Rollover Subjects Rollover subjects are defined as subjects who have previously completed any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302. Subjects will be required to attend the Screening Visit and applicable eligibility assessments will be performed. This visit will occur up to 14 days after the final visit of the previous APL-130277 study. Subjects will present to clinic following their normal PD medication regimen and should not withhold any of their normal PD medications. Screening procedures will be performed while subject is in the "ON" state. Subjects will begin treatment at the last APL-130277 dose level they were taking in the previous study. These subjects will not undergo titration. however, if during the screening visit, the Investigator determines a dose adjustment is necessary, the subject will have dose adjustment visits. Subjects who fail the screening process will be allowed to rescreen once if agreed by the Medical Monitor. *Screening Procedures for CTH-301 Completer Subjects* CTH-301 Completer subjects are defined as subjects who have previously completed the CTH-301 study under protocol version 3.00. Subjects who previously completed the CTH-301 study and are re-enrolling into CTH-301 will be required to attend the Screening Visit Phase 2 (SVP2) and applicable eligibility assessments will be performed. Eligibility criteria will be assessed and once a patient is deemed eligible, the site will contact the subject to have them return to the clinic 5 to 28 days later and follow study procedures beginning at LTS Visit 7. These subjects will resume treatment with APL-130277 at the dose he/she was administered prior to completing study CTH-301. If this dose is no longer effective, the subject will return to the clinic for dose adjustment visits. Subjects who fail the screening process will be allowed to rescreen once if agreed by the Medical Monitor. *Dose Titration Phase - De Novo Subjects Only* On Titration Visit 1 (TV1), subjects will be asked to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications and following confirmation by both the Investigator and subject that they are in the "OFF" state, patients will be treated with 10 mg APL-130277. Efficacy (MDS-UPDRS Part III) will be performed prior to dosing, and at 15, 30, 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 approximately 50 minutes after dosing. Subjects who respond to the 10 mg APL-130277 dose with a full "ON" response within 45 minutes at TV1, as assessed by both the patient and

	Investigator, will be considered complete from a Dose Titration Phase perspective, and can proceed to the Long-Term Safety (LTS) Phase of the study. These subjects will be asked to return to the clinic for LTS Visit 1 (LTS V1). A full "ON", as assessed by the subject, is defined as: a period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a subject feels he/she can perform normal daily activities; 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 subject has adequate motor function to allow them to perform their normal daily activities. Subjects who develop symptoms such as nausea and/or vomiting which warrant treatment may receive anti-emetic therapy (US sites – Tigan® [trimethobenzamide hydrochloride; 300 mg t.i.d.]; non-US sites – domperidone [10 mg b.i.d.]). If initiated, anti-emetic therapy should be stopped when clinically indicated. Anti-emetic medication should not be administered prophylactically. Subjects who do not achieve a full "ON" response (as defined above) with their 10 mg APL-130277 dose will restart their normal PD medications and will be asked to return to clinic within the next 3 days for Titration Visit 2 (TV2), to assess the next highest dose (ie, 15 mg) in a manner identical to that on Titration Visit 1 (TV1), with identical evaluations. All subjects will be asked to arrive at the clinic after their usual morning dose of PD medications, but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications before being dosed with 15 mg APL-130277. Subjects who achieve a full "ON" (as defined above) within 45 minutes of receiving the 15 mg dose will be considered complete from a Dose Titration Phase perspective, and can proceed to the LTS Phase. Subjects 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 highest dose of APL-130277 (20 mg [TV3], 25 mg [TV4], 30 mg [TV5] or 35 mg [TV6], as appropriate). For subjects dosed with 35 mg, the first sublingual film (ie, 20 mg) will be placed under the tongue for 3 minutes before placing the second sublingual film (ie, 15 mg) under the tongue immediately after and without delay. For each visit in the Dose Titration Phase, the site will arrange subject transfers, if needed. Alternatively, subjects may be monitored in the clinic overnight if such facilities exist and the subject consents. These occurrences will not be considered a SAE. Safety and efficacy assessments will be performed at each visit exactly as described above. Subjects who achieve a full "ON" response at any titration visit may proceed to the LTS Phase. At all titration visits, at the discretion of the subject 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 subject safety and tolerability, the higher dose will be used during the LTS 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 LTS Phase of the study. During the Dose Titration Phase visits, if in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the Visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. If this occurs, subjects can return to the clinic on another day to resume the titration with the next highest dose. If a dose of APL-130277 cannot be found that provided a full "ON" response, the subject 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 subjects 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 Early Termination Visit performed. Dosing days in the Dose Titration Phase are not required occur consecutively, but the Dose Titration Phase must be completed within 21 days. Following completion of the titration phase, subjects will return to clinic for LTS V1 where they will be given their open-label study medication (APL-130277) and appropriate training for self-administration. Titration in this study may be modified following a review of the Dose Titration Phase data from CTH-300 by a Data Safety Monitoring Board (DSMB). If, after review of the data from CTH-300, the DSMB determines that in-clinic titration is not necessary and that dose titration can be safely accomplished in an outpatient setting, the Dose Titration Phase paradigm may be modified. *LTS Phase Year 1 – In-clinic Visits – De Novo and Rollover Subjects Only* *De novo* subjects who successfully completed the Dose Titration Phase of the study will be asked to return to the clinic on LTS Day 1 (LTS V1) where they will be given their dose of APL-130277. This visit will up to 21 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. Rollover subjects who successfully completed the Screening visit (SV1) will return to the clinic up to 21 days after SV1. These subjects will receive the same dose they received in the previous study, unless the Investigator deems a dose adjustment is necessary. All subjects will be asked to arrive at the clinic after their usual morning dose of PD medications, but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications. Following a confirmed "OFF" state by both the subject and Investigator, subjects will be dosed with their study medication and assessments of efficacy and safety will be

	performed up to 90 minutes after dosing. During this visit, De novo subjects only, will be trained by clinic staff on how to remove study medication from its packaging and how to self-administer their dose using placebo sublingual films supplied to the site. Subjects **should not** self-administer the placebo sublingual films. Subjects cannot be discharged from the clinic until satisfactorily completing the training. **At the in-clinic visits, staff will dose subjects with APL-130277 by placing the sublingual film under the subject's tongue (see Section 14.2 for full dosing details). Subjects will be asked to follow the same process of study drug administration during the at-home portions of the study.** During LTS Phase Year 1 of the study, subjects will return to the clinic at 4 weeks for LTS Visit 2 (LTS V2), 12 weeks for LTS Visit 3 (LTS V3), 24 weeks for LTS Visit 4 (LTS V4), 36 weeks for LTS Visit 5 (LTS V5), and 48 weeks for LTS Visit 6 (LTS V6). At LTS V3, LTS V4, LTS V5, and LTS V6, subjects will be dosed with APL-130277 and the procedures performed at these visits will be similar to those performed at LTS V1. LTS V2 will be a safety visit only. At the LTS in-clinic visits where the subject is dosed with APL-130277, if in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. Where possible, administration of rescue L-Dopa should be delayed until after the 90 minute efficacy assessments are complete. Following LTS V6, subjects will be asked to return to the clinic approximately 4 months (16 weeks ± 1 week) later for LTS Visit 7 (LTS V7). Evaluation of subjects who choose to withdraw from the study at any time will be conducted in accordance with Section 12.8, Early Terminations. All PD medications must remain stable during LTS Phase Year 1, and any changes should be avoided unless absolutely necessary and approved by the Medical Monitor. Changes in medications for the treatment of other medical disorders are allowed with permission from the Medical Monitor. *LTS Phase Year 1 – At Home Assessments – De Novo and Rollover Subjects Only* During the LTS Phase, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their study treatment (APL-130277) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day during the waking period. Subjects will be instructed to wait a minimum of 2 hours between doses taken at home. For 2 days prior to the in-clinic visits, subjects will be requested to complete a dosing diary that captures: • Time of APL-130277 treatment self-administration; • Subject "ON"/"OFF" states at 30 minutes after dosing. • The type of "OFF" experienced (ie, morning akinesia; delayed

	"ON"; wearing "OFF"; no "ON"; or sudden "OFF"). Between each in-clinic visit, subjects will be contacted at the midpoint between visits by the site to assess subject well-being and safety. If required due to safety concerns or lack of efficacy, subjects will be asked to return to the clinic for additional evaluations at an unscheduled Dose Adjustment Visit. *LTS Phase Years 2, 3, 4, and 5 – In-clinic Visits - All Subjects* During LTS Phase Years 2 to 5, subjects will return to the clinic every 4 months (16 weeks). These visits will be safety visits only. Subjects will return to the clinic to have safety assessed and receive additional study drug (APL-130277). Subjects may continue to participate in the study until the Sponsor terminates the study, or until commercial availability of APL-130277 in the patient's country. If a patient continues in the study beyond LTS Phase Year 5, the protocol will be amended to accommodate additional in clinic visits every 4 months (16 weeks). Evaluation of subjects who choose to withdraw from the study at any time will be conducted in accordance with Section 12.8, Early Terminations. All PD medications should remain stable during LTS Phase Years 2 to 5, and any changes should be avoided unless approved by the Medical Monitor. Changes in medications for the treatment of other medical disorders are allowed with permission from the Medical Monitor. *LTS Phase Years 2, 3, 4, and 5 – At Home Assessments – All Subjects* During LTS Phase Years 2 to 5, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their study treatment (APL-130277) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between doses taken at home. For 2 days prior to the in-clinic visits, subjects will be requested to complete a dosing diary that captures: • Time of APL-130277 treatment self-administration; • Subject "ON"/"OFF" states at 30 minutes after dosing. • The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF"). Between each in-clinic visit, subjects will be contacted at the midpoint between visits by the site to assess subject well-being and safety. If required due to safety concerns or lack of efficacy, subjects will be asked to return to the clinic for additional evaluations at an unscheduled Dose Adjustment Visit.
INVESTIGATIONAL DRUG	APL-130277 Doses of 10 mg, 15 mg, 20 mg, 25 mg, 30 mg and 35 mg (given as 2 films consisting of 20 mg and then 15 mg). For subjects dosed with 35 mg, instructions will be given to place the first

	sublingual film (ie, 20 mg) under the tongue for 3 minutes before placing the second sublingual film (ie, 15 mg) under the tongue immediately and without delay.
REFERENCE PRODUCT	N/A
TREATMENT REGIMENS	Dose titration (*De novo* subjects only) from 10 mg up to 35 mg APL-130277 in 5 mg increments, and long-term outpatient treatment with dose adjustments based on efficacy, safety and tolerability. De novo subjects will receive the dose selected during the titration phase. Rollover Subjects will receive the same dose of APL-130277 that they received in their previous study. Completer subjects will receive the same dose of APL-130277 that they received previously. Dose adjustments are allowed for any subject.
PRIOR AND CONCOMITANT TREATMENTS: **PROHIBITED TREATMENT**	The following prior and/or concomitant treatments will not be allowed during the course of this study: • Treatment with any form of s.c. apomorphine is prohibited as follows: o from 7 days prior to the second Screening Visit (SV2) until study completion for *De Novo* subjects o from the time of the Screening Visit for Rollover subjects, until study completion o from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects until study completion. • Any selective $5HT_3$ antagonist (eg, ondansetron, granisetron, dolasetron, palonosetron, alosetron) are prohibited as follows: o from 30 days prior to the initial Screening Visit (SV1) for *De Novo* subjects until study completion o from 14 days prior to the Screening Visit for Rollover subjects until study completion o from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects 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: o **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; o Cinnarizine; o 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. • Any sublingual medicinal product, including Vitamin B6. • Any other preparation of Vitamin B6. • Medicinal/recreational marijuana.
PRIOR AND CONCOMITANT TREATMENTS: **PERMITTED TREATMENTS**	Anti-emetic medication is optional and can be initiated at the Investigator's discretion if clinically warranted. If initiated, anti-emetic therapy should be stopped when clinically indicated. Anti-emetic medication should not be administered prophylactically. 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. NOTE: Domperidone is not indicated for longer than 7 continuous days of use. Extended use beyond 7 days should be discussed with the Medical Monitor. • Stable doses of an L-Dopa formulation with or without other stable adjunctive PD therapies is permitted with no planned medication changes during the study as follows: ○ from at least 4 weeks prior to the initial Screening Visit (SV1) for *De Novo* subjects ○ within 14 days of completing the previous study for Rollover subjects ○ from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects • MAO-B inhibitors will be allowed but must be stable as follows: ○ for at least 8 weeks prior to the initial Screening Visit (SV1) for *De Novo* subjects ○ for at least 14 days after completion of the previous study for Rollover subjects ○ from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects.

	• Any other medication other than those identified as Prohibited Treatments are allowed, provided they are stable (within 14 days after completing the previous study for Rollover subjects or within 4 weeks for De novo subjects). Other therapies should only be administered as necessary for the treatment of the subject, at the discretion of the Investigator. All concomitant medications must be recorded in the appropriate Case Report Form (CRF) for the subject.
STUDY DURATION	Subjects may participate in the study until the Sponsor terminates the study, or until commercial availability of APL-130277 in the patient's country.
INVESTIGATIVE SITES OR COUNTRIES	This multicenter study will be conducted worldwide.
STUDY ENDPOINTS	Primary Endpoint • Evaluation of safety and tolerability data collected, based on incidence of adverse events in the LTS Phase. Secondary Efficacy Endpoints • Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS-UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase. • Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase. • The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the dosing diary entries. Other Efficacy Endpoints • CGI-I post dosing. • PGI-I post dosing. • Change from baseline in the PDQ-39. • Change from baseline in the MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living. • Percentage of subjects with Investigator-rated full “ON” response within 30 minutes during the titration period. • Change from baseline in the Epworth Sleepiness Scale (ESS). Safety Endpoints • Observed values and Change in 12-lead ECGs, • Incidences of oropharyngeal and dopaminergic AEs, • C-SSRS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS)

STATISTICAL METHODS SUMMARY	*Analysis Sets* All subjects who are enrolled into this study and receive at least one dose of study medication will be included in the full analysis set for each study phase. The safety and efficacy data will be primarily analyzed in the full analysis set in each study phase, but additional summaries will be done separately for *De Novo* Subjects and Rollover Subjects. *Safety Analyses* The analysis of the safety data will focus on data collected during the LTS Phase. In addition, all safety data will be reported separately for the Dose Titration Phase. Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be summarized by body system and preferred term. The AE analysis will focus on the dopaminergic (nausea, vomiting, OH) and oral TEAEs. Descriptive statistics will be used to summarize the overall incidence of TEAEs. *Efficacy Analyses* The efficacy endpoints will be analyzed both for the full analysis set and separately for Rollover Subjects and for *De Novo* Subjects. The changes from baseline in the continuous efficacy endpoints will be summarized descriptively. The categorical endpoints will be analyzed using subject counts and percentages.

4. STUDY DESIGN FLOW CHART

Table 2: Table of Events - Screening (All Subjects) and Dose Titration Phase (De novo Subjects Only)

Procedures	Screening				Dose Titration Phase (*De novo* Subjects Only)[1]					
	Screening (*de novo*)[2]		Screening (Rollover)[2]	Screening (CTH-301 Completer)	Titration Visit 1	Titration Visit 2	Titration Visit 3	Titration Visit 4	Titration Visit 5	Titration Visit 6
Study Visit	SV1	SV2	SV	SVP2	TV1	TV2	TV3	TV4	TV5	TV6
Day (± 2 days)	-28 to -1		Up to 21 days	-28 to -1	Day 1 up to 21					
Outpatient Visit[4]	X	X[4]	X	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Written Informed Consent	X		X	X						
Review Entry Criteria	X	X	X	X						
Review Restriction Criteria	X		X	X	X	X	X	X	X	X
Medical History/Demographics		X[2]	X	X						
Complete Physical Exam, including Oropharyngeal Exam[5]		X[2]	X	X						
Abbreviated Physical Exam, including Oropharyngeal Exam[6]					X	X	X	X	X	X
BMI, weight and height[8]		X[2]	X	X						
Vital Signs [9, 10]		X[2]	X	X	X	X	X	X	X	X
12-Lead ECG[10, 11]		X[2]	X	X	X	X	X	X	X	X
Clinical Laboratory Tests		X	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
Confirmation of L-Dopa Responsiveness		X								
Clinical Confirmation of "OFF" or full "ON"[13]		X			X	X	X	X	X	X
Patient Confirmation of "OFF" or full "ON"[13]					X	X	X	X	X	X
In-Clinic Dosing					X	X	X	X	X	X

Table 2: Table of Events - Screening (All Subjects) and Dose Titration Phase (De novo Subjects Only) (Continued)

Procedures	Screening				Dose Titration Phase (*De novo* Subjects Only)[1]					
	Screening (*de novo*)[2]		Screening (Rollover)[2]	Screening (CTH-301 Completer)	Titration Visit 1	Titration Visit 2	Titration Visit 3	Titration Visit 4	Titration Visit 5	Titration Visit 6
Study Visit	SV1	SV2	SV	SVP2	TV1	TV2	TV3	TV4	TV5	TV6
Day (± 2 days)	-28 to -1		Up to 21 days	-28 to -1	Day 1 up to 21					
Provide Patient Dosing Diary[15]					X[16]					
Patient "OFF" versus "ON" Training		X[17]								
C-SSRS[18]		X	X	X	X	X	X	X	X	X
PDQ-39		X	X							
ESS		X	X							
Caregiver Burden (Zarit Burden Interview [ZBI])[23]		X	X							
QUIP-RS		X	X							
AEs/Serious AEs (SAEs)		X[3]	X[3]	X[3]	X	X	X	X	X	X
Previous/Current Concomitant Medications		X	X	X	X	X	X	X	X	X

Table Footnotes

Table 3: Table of Events - LTS Phase Year 1 (*De Novo* and Rollover Patients Only)

Procedures	**LTS Phase Year 1**											**Dose Adjustment Visit**[25]	**Termination Visit**
	LTS Visit 1	**Telephone Call**	**LTS Visit 2**	**Telephone Call**	**LTS Visit 3**	**Telephone Call**	**LTS Visit 4**	**Telephone Call**	**LTS Visit 5**	**Telephone Call**	**LTS Visit 6**		
Study Visit	**LTS V1**	**T1**	**LTS V2**	**T2**	**LTS V3**	**T3**	**LTS V4**	**T4**	**LTS V5**	**T5**	**LTS V6**	**NA**	**ET**
LTS Study Day (± 3 days)	**1**	**14**	**28**	**56**	**84**	**126**	**168**	**210**	**252**	**294**	**336**	**-**	**-**
LTS Study Week	**-**	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**-**	**-**
LTS Study Month [7]	**-**	**-**	**1**	**-**	**3**	**-**	**6**	**-**	**9**	**-**	**12**	**-**	**-**
Outpatient Visit[4]	**X**		**X**		**X**		**X**		**X**		**X**	**X**	**X**
Review Restriction Criteria	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Complete Physical Exam, including Oropharyngeal Exam[5]	**X**		**X**		**X**		**X**		**X**		**X**		**X**
Weight	**X**		**X**		**X**		**X**		**X**		**X**		**X**
Vital Signs [9, 10]	**X**		**X**		**X**		**X**		**X**		**X**	**X**	**X**
12-Lead ECG[10, 11]	**X**		**X**		**X**		**X**		**X**		**X**		**X**
Clinical Laboratory Tests					**X**		**X**		**X**		**X**		**X**
MDS-UPDRS Parts I, II and IV					**X**		**X**		**X**		**X**		
MDS-UPDRS Part III[10, 12]	**X**				**X**		**X**		**X**		**X**		
Clinical Confirmation of "OFF" or full "ON"[13]	**X**				**X**		**X**		**X**		**X**		
Patient Confirmation of "OFF" or full "ON"[13]	**X**				**X**		**X**		**X**		**X**		
In-Clinic Dosing	**X**[14]				**X**[14]		**X**[14]		**X**[14]		**X**[14]		
Dispense Study Medication assigned by the IWRS for Outpatient Dosing	**X**		**X**		**X**		**X**		**X**		**X**	**X**	
Collect Study Medication			**X**		**X**		**X**		**X**		**X**	**X**	**X**[22]
Provide Patient Dosing Diary[15]	**X**		**X**		**X**		**X**		**X**		**X**	**X**	
Collect Patient Dosing Diary[15]	**X**[15]		**X**		**X**		**X**		**X**		**X**	**X**	**X**[22]

Table 3: Table of Events - LTS Phase Year 1 (*De Novo* and Rollover Patients Only) (Continued)

Procedures	LTS Phase Year 1											Dose Adjustment Visit[25]	Termination Visit
	LTS Visit 1	Telephone Call	LTS Visit 2	Telephone Call	LTS Visit 3	Telephone Call	LTS Visit 4	Telephone Call	LTS Visit 5	Telephone Call	LTS Visit 6		
Study Visit	**LTS V1**	**T1**	**LTS V2**	**T2**	**LTS V3**	**T3**	**LTS V4**	**T4**	**LTS V5**	**T5**	**LTS V6**	**NA**	**ET**
LTS Study Day (± 3 days)	**1**	**14**	**28**	**56**	**84**	**126**	**168**	**210**	**252**	**294**	**336**	**-**	**-**
LTS Study Week	**-**	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**-**	**-**
LTS Study Month [7]	**-**	**-**	**1**	**-**	**3**	**-**	**6**	**-**	**9**	**-**	**12**	**-**	**-**
IP accountability and Treatment Compliance			X		X		X		X		X	X	X[22]
C-SSRS[18]	X		X		X		X		X		X		X
PDQ-39	X						X		X		X		X[22]
PGI[19]	X						X		X		X		X[22]
CGI[19]	X						X		X		X		X[22]
ESS	X						X		X		X		X[22]
Caregiver Burden (Zarit Burden Interview [ZBI])[23]	X						X		X		X		X[22]
QUIP-RS	X						X		X		X		X[22]
Outpatient Self-Administration Training	X[14]												
Blood Sampling for PK Analysis	X[20]				X[20]		X[20]		X[20]		X[20]		
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous/Current Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Reasons(s) for Dose Adjustment												X	

Table Footnotes

Table 4: Table of Events - LTS Phase Year 2 (All Patients)

Procedures	LTS Phase Year 2						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 7	Telephone Call	LTS Visit 8	Telephone Call	LTS Visit 9		
Study Visit	**T6**	**LTS V7**	**T7**	**LTS V8**	**T8**	**LTS V9**	**N/A**	**ET**
LTS Study Week (± 1 week)	**56**	**64**	**72**	**80**	**88**	**96**	**-**	**-**
LTS Study Month [7]	**-**	**16**	**-**	**20**	**-**	**24**	**N/A**	**-**
Outpatient Visit[4]		X		X		X	X	X
Review Restriction Criteria	X	X	X	X	X	X	X	
Complete Physical Exam, including Oropharyngeal Exam[5]		X		X		X		X
Weight		X		X		X		X
Vital Signs [9, 10]		X		X		X	X	X
12-Lead ECG[10, 11]		X [24]		X		X		X
Clinical Laboratory Tests		X [24]		X		X		X
Dispense Study Medication assigned by the IWRS for Outpatient Dosing		X		X		X	X	
Collect Study Medication		X [24]		X		X	X	X
Provide Patient Dosing Diary[15]		X		X		X	X	
Collect Patient Dosing Diary[15]		X [24]		X		X	X	X
IP accountability and Treatment Compliance		X [24]		X		X	X	X
C-SSRS[18]		X		X		X		X
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X
Previous/Current Concomitant Medications	X	X	X	X	X	X	X	X
Record Reason(s) for Dose Adjustment							X	
PDQ-39								X
PGI[19]								X
CGI[19]								X
ESS								X

Table 4: Table of Events - LTS Phase Year 2 (All Patients) (Continued)

Procedures	LTS Phase Year 2						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 7	Telephone Call	LTS Visit 8	Telephone Call	LTS Visit 9		
Study Visit	**T6**	**LTS V7**	**T7**	**LTS V8**	**T8**	**LTS V9**	**N/A**	**ET**
LTS Study Week (± 1 week)	**56**	**64**	**72**	**80**	**88**	**96**	**-**	**-**
LTS Study Month [7]	**-**	**16**	**-**	**20**	**-**	**24**	**N/A**	**-**
Caregiver Burden (Zarit Burden Interview [ZBI])[23]								**X**
QUIP-RS								**X**
Ease of Use Questionnaire								**X**

Table Footnotes

Table 5: Table of Events - LTS Phase Year 3 (All Patients)

Procedures	LTS Phase Year 3						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 10	Telephone Call	LTS Visit 11	Telephone Call	LTS Visit 12		
Study Visit	**T9**	**LTS V10**	**T10**	**LTS V11**	**T11**	**LTS V12**	**N/A**	**ET**
LTS Study Week (± 1 week)	**104**	**112**	**120**	**128**	**136**	**144**		**-**
LTS Study Month [7]	**-**	**28**	**-**	**32**	**-**	**36**	**N/A**	**-**
Outpatient Visit[4]		X		X		X	X	X
Review Restriction Criteria	X	X	X	X	X	X	X	
Complete Physical Exam, including Oropharyngeal Exam[5]		X		X		X		X
Weight		X		X		X		X
Vital Signs [9, 10]		X		X		X	X	X
12-Lead ECG[10, 11]		X		X		X		X
Clinical Laboratory Tests		X		X		X		X
Dispense Study Medication assigned by the IWRS for Outpatient Dosing		X		X		X	X	
Collect Study Medication		X		X		X	X	X
Provide Patient Dosing Diary[15]		X		X		X	X	
Collect Patient Dosing Diary[15]		X		X		X	X	X
IP accountability and Treatment Compliance		X		X		X	X	X
C-SSRS[18]		X		X		X		X
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X
Previous/Current Concomitant Medications	X	X	X	X	X	X	X	X
Record Reason(s) for Dose Adjustment							X	
PDQ-39								X
PGI[19]								X
CGI[19]								X
ESS								X
Caregiver Burden (Zarit Burden Interview [ZBI])[23]								X

Table 5: Table of Events - LTS Phase Year 3 (All Patients) (Continued)

Procedures	LTS Phase Year 3						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 10	Telephone Call	LTS Visit 11	Telephone Call	LTS Visit 12		
Study Visit	**T9**	**LTS V10**	**T10**	**LTS V11**	**T11**	**LTS V12**	**N/A**	**ET**
LTS Study Week (± 1 week)	**104**	**112**	**120**	**128**	**136**	**144**		**-**
LTS Study Month [7]	**-**	**28**	**-**	**32**	**-**	**36**	**N/A**	**-**
QUIP-RS								**X**
Ease of Use Questionnaire								**X**

Table Footnotes

Table 6: Table of Events - LTS Phase Year 4 (All Patients)

Procedures	LTS Phase Year 4						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 13	Telephone Call	LTS Visit 14	Telephone Call	LTS Visit 15		
Study Visit	**T12**	**LTS V13**	**T13**	**LTS V14**	**T14**	**LTS V15**	**N/A**	**ET**
LTS Study Week (± 1 week)	**152**	**160**	**168**	**176**	**184**	**192**		**-**
LTS Study Month [7]	**-**	**40**	**-**	**44**	**-**	**48**	**N/A**	**-**
Outpatient Visit[4]		X		X		X	X	X
Review Restriction Criteria	X	X	X	X	X	X	X	
Complete Physical Exam, including Oropharyngeal Exam[5]		X		X		X		X
Weight		X		X		X		X
Vital Signs [9, 10]		X		X		X	X	X
12-Lead ECG[10, 11]		X		X		X		X
Clinical Laboratory Tests		X		X		X		X
Dispense Study Medication assigned by the IWRS for Outpatient Dosing		X		X		X	X	
Collect Study Medication		X		X		X	X	X
Provide Patient Dosing Diary[15]		X		X		X	X	
Collect Patient Dosing Diary[15]		X		X		X	X	X
IP accountability and Treatment Compliance		X		X		X	X	X
C-SSRS[18]		X		X		X		X
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X
Previous/Current Concomitant Medications	X	X	X	X	X	X	X	X
Record Reason(s) for Dose Adjustment							X	
PDQ-39								X
PGI[19]								X
CGI[19]								X
ESS								X
Caregiver Burden (Zarit Burden Interview [ZBI])[23]								X

Table 6: Table of Events - LTS Phase Year 4 (All Patients) (Continued)

Procedures	LTS Phase Year 4						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 13	Telephone Call	LTS Visit 14	Telephone Call	LTS Visit 15		
Study Visit	**T12**	**LTS V13**	**T13**	**LTS V14**	**T14**	**LTS V15**	**N/A**	**ET**
LTS Study Week (± 1 week)	**152**	**160**	**168**	**176**	**184**	**192**		**-**
LTS Study Month [7]	**-**	**40**	**-**	**44**	**-**	**48**	**N/A**	**-**
QUIP-RS								**X**
Ease of Use Questionnaire								**X**

Table Footnotes

Table 7: Table of Events - LTS Phase Year 5 (All Patients)

Procedures	LTS Phase Year 5						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 16	Telephone Call	LTS Visit 17	Telephone Call	LTS Visit 18		
Study Visit	**T15**	**LTS V16**	**T16**	**LTS V17**	**T17**	**LTS V18**	**N/A**	**ET**
LTS Study Week (± 1 week)	**200**	**208**	**216**	**224**	**232**	**240**		**-**
LTS Study Month [7]	**-**	**52**	**-**	**56**	**-**	**60**	**N/A**	**-**
Outpatient Visit[4]		X		X		X	X	X
Review Restriction Criteria	X	X	X	X	X	X	X	
Complete Physical Exam, including Oropharyngeal Exam[5]		X		X		X		X
Weight		X		X		X		X
Vital Signs [9, 10]		X		X		X	X	X
12-Lead ECG[10, 11]		X		X		X		X
Clinical Laboratory Tests		X		X		X		X
Dispense Study Medication assigned by the IWRS for Outpatient Dosing		X		X		X	X	
Collect Study Medication		X		X		X	X	X
Provide Patient Dosing Diary[15]		X		X		X	X	
Collect Patient Dosing Diary[15]		X		X		X	X	X
IP accountability and Treatment Compliance		X		X		X	X	X
C-SSRS[18]		X		X		X		X
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X
Previous/Current Concomitant Medications	X	X	X	X	X	X	X	X
Record Reason(s) for Dose Adjustment							X	
PDQ-39								X
PGI[19]								X
CGI[19]								X
ESS								X
Caregiver Burden (Zarit Burden Interview [ZBI])[23]								X

Table 7: Table of Events - LTS Phase Year 5 (All Patients) (Continued)

Procedures	LTS Phase Year 5						Dose Adjustment Visit[25]	Termination Visit
	Telephone Call	LTS Visit 16	Telephone Call	LTS Visit 17	Telephone Call	LTS Visit 18		
Study Visit	**T15**	**LTS V16**	**T16**	**LTS V17**	**T17**	**LTS V18**	**N/A**	**ET**
LTS Study Week (± 1 week)	**200**	**208**	**216**	**224**	**232**	**240**		**-**
LTS Study Month [7]	**-**	**52**	**-**	**56**	**-**	**60**	**N/A**	**-**
QUIP-RS								**X**
Ease of Use Questionnaire								**X**

Table Footnotes

[1] Only De novo subjects will undergo dose titration. Dosing during the Dose Titration Phase must be completed within 21 days. The initial LTS Visit (LTS V1) must occur up to 21 days after the final Dose Titration Phase visit.

[2] All screening procedures are to be conducted within 28 days prior to Titration Visit 1 for *De Novo* subjects*:* If required by the Investigator, and following receipt of subject consent, the Investigator may review the subject's medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the subject may be eligible for study participation. Procedures performed on SV1 will not be repeated at SV2. Screening procedures are to be conducted up to 14 days after completion of the previous study for Rollover subjects and 5 to 21 days prior to LTS V1.

[3] Adverse event recording and serious adverse event reporting will begin when the subject signs the ICF.

[4] De *novo* Subjects may be monitored in the clinic overnight before Dosing Titration Visits if such facilities exist and the subject 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. Any subject who presents with an adverse event involving the oral cavity must be seen by a qualified dermatologist (or specialist in a related field) within 24 hours. The dermatologist (or specialist in a related field) must examine the subject, and provide a consultation report including photographs of the oral cavity (see Section 13.1.7).

[6] *De novo* subjects will undergo an 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. A window of +/- 10 minutes is given for post-dose abbreviated physical and oropharyngeal examinations during TV1 to TV6.

[7] Months are calculated as 4 weeks.

[8] Both height and weight captured at the Screening Visit (SV2 for *De Novo* subjects*;* SV1 for Rollover subjects; and SVP2 for CTH-301 Completer subjects) to calculate BMI; only weight captured at all other visits.

[9] Vital signs will be assessed once at the Screening Visit (SV2 for *De Novo* subjects*;* SV1 for Rollover subjects; and SVP2 for CTH-301 Completer subjects), all Dose Adjustment Visits, LTS V2, LTS V7 to LTS V17, and ET. At TV1 to TV6 (*De novo* subjects) and at LTS V1, LTS V3, LTS V4, LTS V5, and LTS V6 for all subjects vital signs will be assessed at t = 0 minutes (just prior to dosing) and immediately after the 60 minute MDS-UPDRS Part III assessment. Blood pressure will be measured in both supine and standing positions (to be 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 - Subject "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 for *De Novo* subjects*;* SV1 for Rollover subjects; and SVP2 for CTH-301 Completer subjects); single ECGs at t = 0 (just prior to dosing) and approximately 50 minutes post dosing at TV1 to TV6 (*De novo* subjects) and at LTS V1, LTS V3, LTS V4, LTS V5, and LTS V6 for all subjects; single ECG at LTS V2 and ET.

[12] MDS-UPDRS Part III (Motor Function) to be assessed at t = 0 (just prior to dosing), 15, 30, 60 and 90 minutes post dosing at the Screening Visit (SV2; *De Novo* subjects only). If the patient does not experience an "ON" within 90 minutes, the site should record the time when the subject turns "ON" and perform an additional MDS-UPDRS Part III assessment at this time. MDS-UPDRS Part III (Motor Function) will be assessed at t = 0 (just prior to dosing), 15, 30, and 60 minutes post dosing at TV1 to TV6, and LTS V1, LTS V3, LTS V4, LTS V5, and LTS V6. During the Dose Titration Phase only (*De novo* subjects only), these assessments may cease if the subject does not experience a full "ON" response within 30 minutes of dosing.
All Part III assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.

[13] Investigator/subject confirmation of "OFF" or "ON" at SV2 (*De Novo* subjects only).
At TV1 to TV6 and LTS V1, LTS V3, LTS V4, LTS V5, and LTS V6, the Investigator will assess "OFF/ON" state as part of the MDS-UPDRS Part III assessments, except at 30 minutes, which will be assessed independent of the MDS-UPDRS Part III. During the Dose Titration Phase (*De novo* subjects only), these assessments may cease if the patient does not experience a full "ON" response within 30 minutes of dosing.
At TV1 to TV6 and LTS V1, LTS V3, LTS V4, LTS V5, and LTS V6, the subject should report: "OFF"/"ON" state at 0, 15, 30, 45 and 60 minutes after dosing.
Subjects should also report the time to when the study medication is starting to have an effect (if applicable), and time to "OFF" following dosing (if it occurs within 60 minutes of dosing). Note: The timing of this should begin when the study medication sublingual film has fully dissolved, and can be recorded using a stopwatch or other suitable timing device.
During the Dose Titration Phase only (*De novo* subjects only), these assessments may cease if the subject does not experience a full "ON" response within 30 minutes of dosing.

[14] Dosing in clinic from outpatient supplies. At LTS V1 De novo Subjects (only) will receive outpatient self-administration training.

[15] Sites will call each patient 3 days before an applicable in-clinic LTS visit to remind patients to complete the Subject Dosing Diary. Diary will record: time when patient self-administers a dose; subject "ON"/"OFF" status at 30 minutes following dosing; the type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF"). At LTS V1, the diary will be collected from De novo Subjects only.

[16] Subject Dosing Diary provided on TV1 (De novo subjects only) will be provided for training purposes only. During this phase, subjects should be instructed to use their scheduled PD medication administration as the reference point. At LTS V1, the diary will be collected from De novo Subjects. If needed, subjects will be retrained on LTS V1 in the use of the dosing diary.

[17] Subject "OFF" versus "ON" Training will occur as part of the L-Dopa challenge at SV2 (*De Novo* subjects only).

[18] "Screening" scale to be used at the Screening Visit (SV2 for *De Novo* subjects*;* SV1 for Rollover suubjects; and SVP2 for CTH-301 Completer subjects); "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] Blood collection for APL-130277 PK analyses will occur in up to 24 subjects from up to 6 sites. Samples will be taken at t = 0 (just prior to dosing) and at t = 10, 20, 30, 60, 90, 120, 180, and 240 minutes post dosing.

[21] Intentionally skipped.

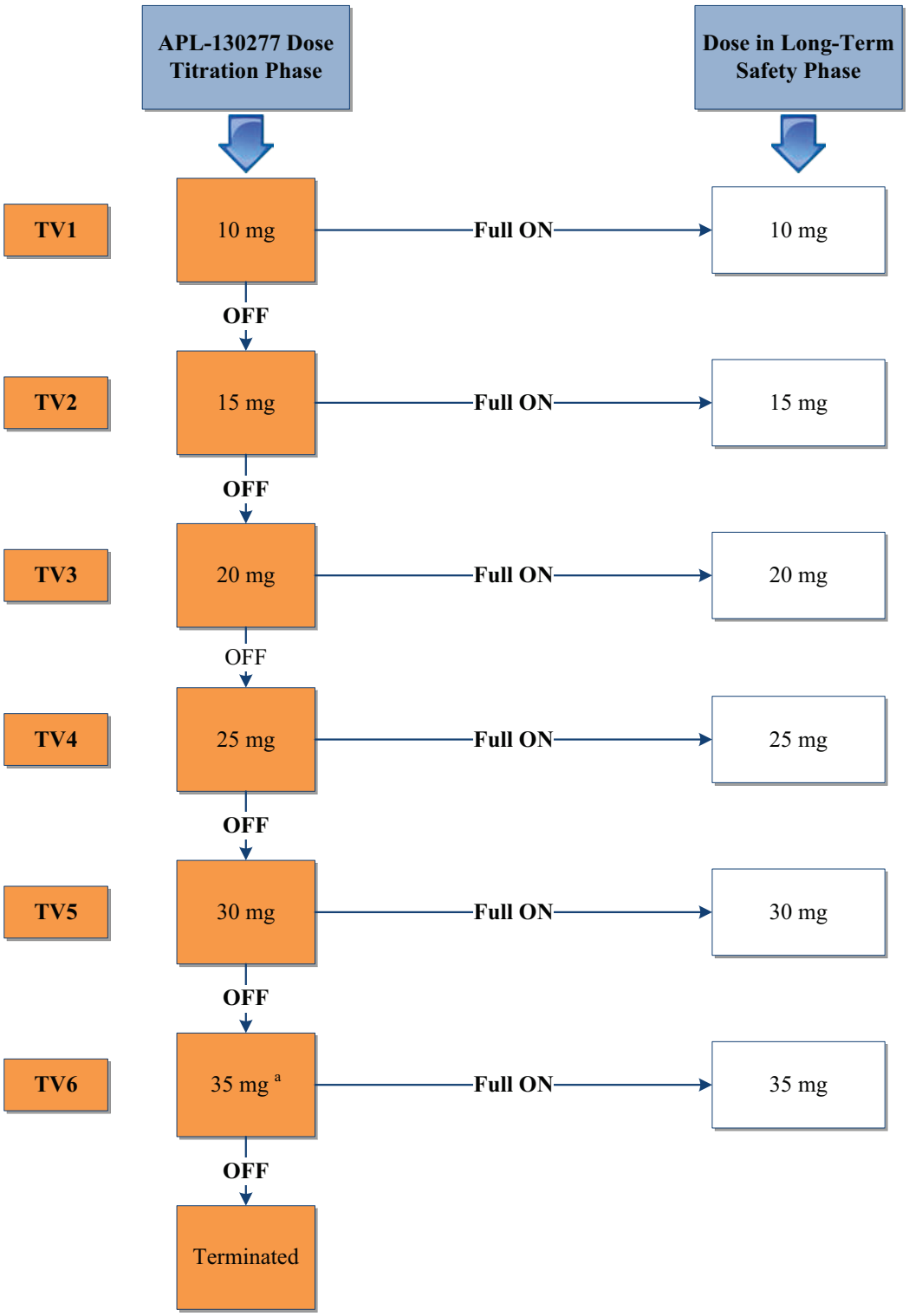
[22] Assessments will not be performed on subjects whose participation is terminated during the Dose Titration Phase of the study.

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

[24] Excluding LTS V7 for CTH-301 Completer subjects.

[25] At the investigator's discretion, the subject may receive the adjusted dose in-clinic and undergo efficacy (MDS-UPDRS part III and ON/OFF assessments up to 90 minutes), and additional safety assessments as deemed appropriate.
Subjects will be contacted by telephone within 3 days after dose adjustment visits for assessment of effect of the dose adjustment and safety.

Figure 1: Dose Titration Phase Dosing Paradigm (*De novo* Subjects Only)



NOTE: Dose titration is for De novo subjects only.

[a] Doses of 35 mg (given as 2 films consisting of 20 mg and then 15 mg).

For *De novo* subjects, at all titration visits, at the discretion of the subject 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 subject safety and tolerability, the higher dose will be used during the LTS 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 LTS Phase of the study.

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6. LIST OF ABBREVIATIONS OR TERMS

Abbreviation or specialist term	Explanation
$5HT_3$	5-hydroxy tryptophan (serotonin)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APO-go®	apomorphine hydrochloride injection
APOKYN®	apomorphine hydrochloride injection
API	active pharmaceutical ingredients
AUC_{last}	area under the concentration-time curve from time zero to the last measurable plasma concentration-time curve using the linear up log down trapezoidal rule.
AUC_{∞}	area under the concentration-time curve from time zero extrapolated to infinity using the linear up log down trapezoidal rule.
AST	aspartate aminotransferase
b.i.d.	twice daily
BLQ	Below the limit of quantification
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
C_{max}	maximum observed plasma concentration
COMT	Catechol O-methyltransferase
CR	chronic release
CRA	Clinical Research Associate
CRF	case report form
CSA	clinical study agreement
C-SSRS	Columbia Suicide Severity Rating Scale
CTH-301 Completer Patients	patients who have previously completed the CTH-301 study
CV%	coefficient of variation
De Novo Patients	patients who have not previously participated in a study with APL-130277
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EDC	electronic data capture

Abbreviation or specialist term	Explanation
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
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LTS	Long-Term Safety
λz	terminal-phase rate constant
MAO-B	monoamine oxidase B
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measurements
M/P ratios	Metabolite to parent ratio of AUC and C_{max}
MRT	mean residence time
MMSE	Mini-mental State Examination
OH	Orthostatic Hypotension
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire
PGI	Patient Global Impression

Abbreviation or specialist term	Explanation
PK	pharmacokinetic
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBC	red blood cell
REB	Research Ethics Board
Rollover Patients	patients who have previously completed any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302
RR	respiratory rate
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SOP	Standard Operating Procedure
$t_{½}$	Terminal-phase half-life
TEAE	treatment emergent adverse events
Temp	temperature
t.i.d.	three times daily
t_{max}	observed time of the maximum concentration
US	United States
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
ZBI	Zarit Burden Interview

7. INTRODUCTION

7.1. Background

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. PD has a prevalence of approximately 0.5% to 1% among persons 65 to 69 years of age, rising to 1% to 3% among persons 80 years of age and older (Tanner, 1996). 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 (Hornykiewicz, 2008).

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 (Mouradian, 1989; Stocchi, 2005). 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 (Ahlskog, 2001).

Predictable motor fluctuations (ie 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 (ie 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 dosed by subcutaneous (s.c.) injection. 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 D_1-like and D_2-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 (APOMORPHINE, 1949; Cotzias, 1970; Corsini, 1979; Millan, MJ; Schwab, 1951).

APOKYN®/APO-go® (apomorphine hydrochloride injection, see Section 19.1) are prescription medicines that reverses "OFF" episodes (end-of-dose wearing-"OFF" and unpredictable "ON"-"OFF" episodes) associated with advancing PD. APOKYN®/APO-go®, which are indicated for the acute, intermittent treatment of hypomobility, "OFF" episodes associated with advanced PD, have 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 to 20 minutes of injection, apomorphine demonstrates a magnitude of effect (ability to convert the patients with PD to the "ON" state) that is comparable to L-Dopa. The effects of a single s.c. injection last for approximately 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 (APOMORPHINE, 1949; Cotzias, 1970; Corsini, 1979; Millan, MJ; Schwab, 1951).

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 of s.c. apomorphine 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.

7.2. Drug Substance

The active ingredient is apomorphine hydrochloride hemihydrate ($C_{17}H_{17}NO_2$•HCl•½H_2O(salt)). Apomorphine is synthesized from morphine, but it is not a narcotic, nor is it a controlled substance. Apomorphine hydrochloride appears as 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-Chemie. 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 in Table 8.

Table 8: Summary of Apomorphine Physico-Chemical Data

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

7.3. Drug Product (APL-130277 Sublingual Film)

The product under development, APL-130277, is a soluble 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. APL-130277 can be administered without regard to food status (ie, either fed or fasted). The product is intended to be an alternative to the injectable form of apomorphine hydrochloride, which is marketed as APOKYN® and as APO-go®.

APL-130277 is manufactured for clinical studies as a bilayer 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 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 film.

Table 9: Physical APL-130277 Characteristics

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

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

The APL-130277 drug product will be manufactured and packaged at ARx, LLC facilities at: 400 Seaks Run Road, Glen Rock, PA 17327, USA and Tapemark Company facilities at: 1685 Marthaler Lane, West St. Paul, MN 55118, 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 films, are compendial (USP, NF or FCC) items and/or are Generally Recognized as Safe (GRAS) and/or have precedent for use in pharmaceutical products approved in the US.

7.4. Summary of Potential Risks and Benefits

Given that APL-130277 uses the same active pharmaceutical ingredient (API) as APOKYN®/APO-go®, and that the pharmacokinetic profile is comparable between the sublingual film and the s.c. injection, the risks associated with the drug will be similar to those seen in the APOKYN®/APO-go® prescribing information (see Section 19.1), except for the significant injection site reactions, which are associated with the mode of administration for APOKYN®/APO-go®. It is assumed that the bioavailability of APL-130277 will be consistent in CTH-301 with that found in previous experience with APL-130277 compared with APOKYN®/APO-go®.

The buffer contained in the inactive layer of APL-130277 is designed to mitigate potential irritation of the oral mucosa seen in other buccal formulations of apomorphine as well as assist in maintaining a stable pH and optimal absorption kinetics. A preclinical hamster study demonstrated no evidence of microscopic or macroscopic irritation but in clinical studies with APL-130277, adverse event reports of irritation of the oral mucosa have been observed. The current study will closely monitor for 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 a sublingually administered formulation may be easier to use, allow more effective and safer 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.

7.5. Rationale

This multi-center, Phase 3 study is designed to evaluate the long-term efficacy, safety and tolerability of APL-130277 in subjects 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 subjects with PD have been previously investigated in both a healthy and PD population, however, a long-term study testing multiple treatments of APL-130277 in both an in-clinic and outpatient setting has not been performed. Such a study will provide long-term information on the effect of APL-130277 on "OFF" episodes based on physician and subject assessment in a controlled clinical setting, and based on subject evaluations in an outpatient setting. This study will provide information on treating "OFF" episodes in a PD subject 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 long-term safety and tolerability of APL-130277 in acutely treating "OFF" episodes (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF").

8. ETHICS

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

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

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

9. OBJECTIVES AND STUDY ENDPOINTS

9.1. Objectives

The primary objective is to evaluate the long-term safety and tolerability of APL-130277 in subjects with Parkinson's disease (PD).

9.2. Study Endpoints

9.2.1. Primary Endpoint

1. Evaluation of safety and tolerability data collected, based on incidence of adverse events in the LTS phase.

9.2.2. Secondary Efficacy Endpoints

1. Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS-UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
2. Percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
3. The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.

9.2.3. Other Efficacy Endpoints

1. CGI-I post dosing.
2. PGI-I post dosing.
3. Change from baseline in the PDQ-39.
4. Change from baseline in the MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living.
5. Percentage of subjects with Investigator-rated full "ON" response within 30 minutes during the titration period.
6. Change from baseline in the Epworth Sleepiness Scale (ESS)

9.2.4. Safety Endpoints

1. Observed Values and Change in 12 lead ECGs,
2. Incidence of oropharyngeal and dopaminergic AEs,
3. C-SSRS, and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP RS)

10. STUDY DESIGN

This is a multi-center, open-label, Phase 3 study in L-Dopa responsive PD subjects with motor fluctuations, designed to evaluate the long-term safety, tolerability, and efficacy of APL-130277.

10.1. General Overview

This study will be an open-label, long-term safety study of APL-130277 for the treatment of up to 5 "OFF" episodes per day. Subjects will return to the clinic at regular intervals for assessments as defined in the schedule of assessments (see Tables 2-7). Subjects may participate in the study until the Sponsor terminates the study, or until commercial availability of APL-130277 in the subject's country.

10.1.1. Screening Visits

10.1.1.1. Screening Procedures for *De Novo* Subjects

De Novo subjects are defined as subjects who have not previously participated in a study with APL-130277.

Before any study procedures are performed on any subject, 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 subject's 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). Subjects recruited to participate in the study, and who have provided full consent to participate, will be asked to attend the second Screening Visit (SV2), and will be instructed to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Their normal morning dose of L-Dopa (*without* adjunctive PD medication) will be administered in the clinic approximately two hours after their normally scheduled second dose of PD medication, following confirmation of an "OFF" episode by the Investigator, to ensure that they experience a full "ON" response. Eligibility criteria will be assessed and subject "ON" /"OFF" training will be performed (see Section 12.11.3.1).

Subjects who fail the screening process will be allowed to rescreen once if agreed by the Medical Monitor.

10.1.1.2. Screening Procedures for Rollover Subjects

Rollover subjects are defined as subjects who have previously completed any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302.

Rollover Subjects will be required to attend the Screening Visit and applicable eligibility assessments will be performed. This visit will occur up to up to 14 days after the final visit of the previous study. Subjects will present to clinic following their normal PD medication regimen and should not withhold any of their normal PD medications. Screening assessments will be performed while subjects are in the "ON" state.

Eligibility criteria will be assessed and eligible subjects will be asked to return to the clinic in the morning of Long-term Safety Visit 1 (LTS V1).

Subjects will begin treatment at the last APL-130277 dose level they were taking in the previous study. These subjects will not undergo titration. If during the screening visit (prior to LTS V1), the Investigator determines a dose adjustment is necessary, the subject will have dose adjustment visits.

Subjects who fail the screening process will be allowed to rescreen once if agreed by the Medical Monitor.

Evaluation of subjects who choose to withdraw from the study at any time will be conducted in accordance with Section 12.8, Early Terminations.

10.1.1.3. Screening Procedures for CTH-301 Completer Subjects

CTH-301 Completer subjects are defined as subjects who have previously completed the CTH-301 study under protocol version 3.00.

Subjects who previously completed the CTH-301 study and are re-enrolling into CTH-301 will be required to attend the Screening Visit Phase 2 (SVP2) and applicable eligibility assessments will be performed. Re-enrolling patients will present to clinic following their normal PD medication regimen and should not withhold any of their normal PD medications.

Eligibility criteria will be assessed and once a subject is deemed eligible, the site will contact the subject to have them return to the clinic 5 to 28 days later and follow study procedures beginning at LTS Visit 7. These subjects will resume treatment with APL-130277 at the dose he/she was administered prior to completing CTH-301. If this dose is no longer considered tolerable or effective, the subject will return to the clinic for dose adjustment visits until a new tolerable or effective dose is established.

Subjects who fail the screening process will be allowed to rescreen once if agreed by the Medical Monitor.

10.1.2. Dose Titration Phase - *De Novo* Subjects Only

On Titration Visit 1 (TV1), subjects will be asked to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled dose of PD medications and following confirmation by both the Investigator and patient that they are in the "OFF" state, subjects will be treated with 10 mg APL-130277. Efficacy (MDS-UPDRS Part III) will be performed prior to dosing, and at 15, 30, 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 approximately 50 minutes after dosing.

Subjects who respond to the APL-130277 10 mg dose with a full "ON" response within 45 minutes at TV1, as assessed by both the patient and Investigator, will be considered complete from a Dose Titration Phase perspective, and can proceed to the LTS Phase of the study. These subjects will be asked to return to the clinic for LTS V1. A full "ON", as assessed by the subject,

is defined as: a period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a subject feels he/she can perform normal daily activities; AND the response is comparable to or better than their normal response to PD medications prior to enrolling in the study (refer to Section 12.11.3.1). 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 subject has adequate motor function to allow them to perform their normal daily activities (refer to Section 12.11.3.1).

Subjects who develop symptoms such as nausea and/or vomiting which warrant treatment may receive anti-emetic therapy (US sites – Tigan® [trimethobenzamide hydrochloride; 300 mg t.i.d.]; non US sites – domperidone [10 mg b.i.d.]). If initiated, anti-emetic therapy should be stopped when clinically indicated. Anti-emetic medication should not be administered prophylactically.

Subjects who do not achieve a full "ON" response (as defined in Section 12.11.3.1) within 45 minutes with their 10 mg APL-130277 dose 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 (ie, 15 mg) in a manner identical to that on Titration Visit 1 (TV1), with identical evaluations.

All subjects will be asked to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications before being dosed with 15 mg APL-130277. Subjects who achieve a full "ON" (as defined in Section 12.11.3.1) within 45 minutes of receiving the 15 mg dose will be considered complete from a Dose Titration Phase perspective, and can proceed to the LTS Phase. Subjects who do not achieve a full "ON" response (as defined in Section 12.11.3.1) 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 (20 mg [TV3], 25 mg [TV4], 30 mg [TV5], or 35 mg [TV6], as appropriate). For subjects dosed with 35 mg, the first sublingual film (ie, 20 mg) will be placed under the tongue for 3 minutes before placing the second sublingual film (ie, 15 mg) under the tongue immediately after and without delay.

For each visit in the Dose Titration Phase, the site will arrange subject transfers, if needed. Alternatively, subjects may be monitored in the clinic overnight if such facilities exist and the subject consents. These occurrences will not be considered a SAE. Safety and efficacy assessments will be performed at each visit exactly as described above. Subjects who achieve a full "ON" response at any titration visit may proceed to the LTS Phase.

At all titration visits, at the discretion of the subject 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 subject safety and tolerability, the higher dose will be used during the LTS 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 LTS Phase of the study.

During the Dose Titration Phase visits, if in the opinion of the Investigator the subject 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 a dosage considered appropriate by the Investigator to achieve a full "ON" state. If this occurs, subjects can return to the clinic on another day to resume the titration with the next highest dose. If a dose of APL-130277 cannot be found that provided a full "ON" response, the subject 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 subjects who reach 35 mg at Titration Visit 6 (TV6) and do not exhibit a full "ON" response (as defined in Section 12.11.3.1) within 45 minutes will be terminated from the study and will have the applicable procedures outlined in the Early Termination Visit performed.

Dosing days in the Dose Titration Phase are not required to occur consecutively, but the Dose Titration Phase must be completed within 21 days. Following completion of the titration phase, subjects will return to clinic for LTS V1 where they will be given their open-label study medication (APL-130277) and appropriate training for self-administration.

Titration in this study may be modified following a review of the Dose Titration Phase data from CTH-300 by a Data Safety Monitoring Board (DSMB). If, after review of the data from CTH-300, the DSMB determines that in-clinic titration is not necessary and that dose titration can be safely accomplished in an outpatient setting, the Dose Titration Phase paradigm may be modified.

Evaluation of subjects who choose to withdraw from the study at any time will be conducted in accordance with Section 12.8, Early Terminations.

10.1.3. Long-Term Safety Phase Year 1 – In-clinic Visits – *De Novo* and Rollover Subjects Only

De novo subjects who successfully completed the Dose Titration Phase of the study will be asked to return to the clinic on LTS V1 where they will be given their dose of APL-130277. This visit will occur between up to 21 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.

Rollover subjects who successfully completed the Screening visit (SV1) will return to the clinic on LTS Day 1 up to 21 days after SV1. These subjects will receive the same dose they received in the previous study.

All subjects will be asked to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications. Following a confirmed "OFF" state by both the subject and the Investigator, subjects will be dosed with their study medication and assessments of efficacy and safety will be performed for up to 90 minutes after dosing. During this visit, subjects will be trained by clinic staff on how to remove study medication from its packaging and how to self-administer their dose using placebo treatment sublingual films supplied to the site. Subjects **should not** self-administer the placebo sublingual films. Subjects cannot be discharged from clinic until satisfactorily completing the training.

At the in-clinic visits, staff will dose subjects with APL-130277 by placing the sublingual film under the subject's tongue (see Section 14.2 for full dosing details). Subjects will be

asked to follow the same process of study drug administration during the at-home portions of the study.

During LTS Phase Year 1 of the study, subjects will return to the clinic at 4 weeks for LTS Visit 2 (LTS V2), 12 weeks for LTS Visit 3 (LTS V3), 24 weeks for LTS Visit 4 (LTS V4), 36 weeks for LTS Visit 5 (LTS V5), and 48 weeks for LTS Visit 6 (LTS V6). At LTS V3, LTS V4, LTS V5, and LTS V6, subjects will be dosed with APL-130277 and the procedures performed at these visits will be similar to those performed on LTS V1. LTS V2 will be a safety visit only.

At the LTS in-clinic visits where the subject is dosed with APL-130277, if in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. Where possible, administration of rescue L-Dopa should be delayed until after the 90 minute efficacy assessments are complete.

Following LTS V6, subject will be asked to return to the clinic approximately 4 months (16 weeks ± 1 week) later for LTS Visit 7 (LTS V7).

Evaluation of subjects who choose to withdraw from the study at any time will be conducted in accordance with Section 12.8, Early Terminations.

All PD medications must remain stable during LTS Phase Year 1, and any changes should be avoided unless absolutely necessary and approved by the Medical Monitor. Changes in medications for the treatment of other medical disorders are allowed with permission from the Medical Monitor.

10.1.4. Long-Term Safety Phase Year 1 – At Home Assessments – *De Novo* and Rollover Subjects Only

During LTS Phase Year 1, subjects will be instructed to continue with their regular PD medication regimen(s), but they should dose themselves with their study treatment (APL-130277) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between doses taken at home.

For 2 days prior the in-clinic visits, subjects will be requested to complete a home dosing diary that captures:

- Time of randomized treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing.
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

Between each in-clinic visit, subjects will be contacted at the midpoint between visits by the site to assess subject well-being and safety. If required due to safety concerns or lack of efficacy, subjects 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.

10.1.5. Long-Term Safety Phase Years 2, 3, 4, and 5 – In-clinic Visits - All Patients

During LTS Phase Years 2 to 5, subjects will return to the clinic every 4 months (16 weeks). These visits will be safety visits only.

Subjects will return to the clinic to have safety assessed and receive additional study drug (APL-130277).

Subjects may continue to participate in the study until the Sponsor terminates the study, or until commercial availability of APL-130277 in the subject's country. If a subject continues in the study beyond LTS Phase Year 5, the protocol will be amended to accommodate additional in clinic visits every 4 months (16 weeks).

Evaluation of subjects who choose to withdraw from the study at any time will be conducted in accordance with Section 12.8, Early Terminations.

All PD medications should remain stable during LTS Phase Years 2 to 5, and any changes should be avoided unless approved by the Medical Monitor. Changes in medications for the treatment of other medical disorders are allowed with permission from the Medical Monitor.

10.1.6. LTS Phase Years 2, 3, 4, and 5 – At Home Assessments – All Subjects

During LTS Phase Years 2 to 5, subjects will be instructed to continue with their regular PD medication regimen(s), but they should dose themselves with their study treatment (APL-130277) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between doses taken at home.

For 2 days prior the in-clinic visits, subjects will be requested to complete a home dosing diary that captures:

- Time of randomized treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing.
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

Between each in-clinic visit, subjects will be contacted at the midpoint between visits by the site to assess subject well-being and safety. If required due to safety concerns or lack of efficacy, subjects 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.

10.2. Blinding

This is an open-label study; there will be no blinding.

10.3. Data Safety Monitoring Board

A formal 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;

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 implementation of any DSMB review.

11. SUBJECT POPULATION

11.1. 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.

The overall number of subjects is not pre-specified as this is an extension study.

11.1.1. Criteria for *De Novo* Subjects

De Novo Subjects are defined as subjects who have not previously participated in a study with APL-130277.

11.1.1.1. Inclusion Criteria – *De Novo* Subjects

A subject 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 (excluding the "more than one affected relative" criterion) (see Section 19.14).
3. Clinically meaningful response to L-Dopa 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 at least 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. Subject 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. Subject 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 be sexually abstinent or use one of the following highly effective methods of birth control:
    - Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants);
    - Intrauterine contraceptive system;

- Surgical sterilization or partner sterile (must have documented proof); AND

One of the following effective methods of birth control:

- Male/female condom;
- Cervical cap with spermicide;
- Diaphragm with spermicide;
- Contraceptive sponge.

11. Male subjects must be either surgically sterile, agree to be sexually inactive or use a double-barrier method of birth control (eg, condom and diaphragm with spermicide, condom with cervical cap and spermicide) from first study drug administration until 90 days after final drug administration.
12. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures.
13. Able to understand the consent form, and to provide written informed consent.

11.1.1.2. Exclusion Criteria – *De Novo* Subjects

A subject 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; Duodopa/Duopa; or APL-130277.
3. Treatment with any form of s.c. apomorphine within 7 days prior to the second Screening Visit (SV2). 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).
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 (ie, unapproved) medication within 30 days prior to the initial Screening Visit (SV1).
8. Currently taking selective $5HT_3$ antagonists (ie, 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. Subject has a history of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Pituitary tumors of any duration are excluded.
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. Presence of canker or mouth sores in the 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.

11.1.2. Criteria for Rollover Subjects

Rollover Subjects are defined as subjects who have previously completed any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302.

11.1.2.1. Inclusion Criteria - Rollover Subjects

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

1. Completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302; and, in the opinion of the Investigator, would benefit from continued treatment with APL-130277.
2. No major changes in concomitant PD medications since completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302. Any change in PD medications since the previous study should be discussed with the Medical Monitor to determine subject eligibility in the current study.
3. If female and of childbearing potential, must agree to be sexually abstinent or use one of the following highly effective methods of birth control:
    - Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants);
    - Intrauterine contraceptive system;
    - Surgical sterilization or partner sterile (must have documented proof); AND

    One of the following effective methods of birth control:

    - Male/female condom;
    - Cervical cap with spermicide;

- Diaphragm with spermicide;
- Contraceptive sponge.

4. Male subjects must be either surgically sterile, agree to be sexually inactive or use a double-barrier method of birth control (eg, condom and diaphragm with spermicide, condom with cervical cap and spermicide) from first study drug administration until 90 days after final drug administration.
5. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures.
6. Able to understand the consent form, and to provide written informed consent.

11.1.2.2. Exclusion Criteria – Rollover Subjects

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

1. Female who is pregnant or lactating.
2. Presence of any major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis (including clinically significant hallucinations during the past 6 months) or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.
3. Presence of any clinically significant medical (including but not limited to CNS, cardiovascular, hepatic, pulmonary, metabolic, or renal events), surgical, or laboratory abnormality that would make study participation unsafe or make treatment compliance difficult. Clinical significance to be determined by the Investigator.
4. Receipt of any investigational (ie, unapproved) medication or participation in any clinical trial of an investigational product since completing a previous study using APL-130277.
5. Development of canker or mouth sores within 14 days of completing a previous study using APL-130277. For other clinically significant oral pathology, the Investigator should follow-up with an appropriate specialist on any finding, if indicated, before enrolling such a subject into the study. Clinical significance to be determined by the Investigator. The eligibility of subjects who have experienced AEs related to the oral cavity during the previous study using APL-130277, should be reviewed with the medical monitor and approval obtained.
6. Current suicidal ideation within one year of the screening visit, as evidenced by answering "yes" to Question 4 or 5 on the suicidal ideation portion of the C-SSRS at Screening or attempted suicide within 5 years.

11.1.3. Criteria for CTH-301 Completer Subjects

CTH-301 Completer Patients are defined as patients who have previously completed the CTH-301 study under protocol version 3.00.

11.1.3.1. Inclusion Criteria - CTH-301 Completer Subjects

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

1. Completion of the CTH-301 study under protocol version 3.00, and in the opinion of the Investigator, would benefit from continued treatment with APL-130277.
2. If female and of childbearing potential, must agree to be sexually abstinent or use one of the following highly effective methods of birth control:
   - Hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants);
   - Intrauterine contraceptive system;
   - Surgical sterilization or partner sterile (must have documented proof); AND

   One of the following effective methods of birth control:
   - Male/female condom;
   - Cervical cap with spermicide;
   - Diaphragm with spermicide;
   - Contraceptive sponge.
3. Male subjects must be either surgically sterile, agree to be sexually inactive or use a double-barrier method of birth control (eg, condom and diaphragm with spermicide, condom with cervical cap and spermicide) from first study drug administration until 90 days after final drug administration.
4. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures.
5. Able to understand the consent form, and to provide written informed consent.

11.1.3.2. Exclusion Criteria – CTH-301 Completer Subjects

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

1. Female who is pregnant or lactating.
2. Presence of any major psychiatric disorder including, but not limited to, dementia, bipolar disorder, psychosis (including clinically significant hallucinations during the past 6 months) or any disorder that, in the opinion of the Investigator, requires ongoing treatment that would make study participation unsafe or make treatment compliance difficult.
3. Presence of any clinically significant medical (including but not limited to CNS, cardiovascular, hepatic, pulmonary, metabolic, or renal events), surgical, or laboratory abnormality that would make study participation unsafe or make treatment compliance difficult. Clinical significance to be determined by the Investigator.
4. Receipt of any investigational (ie, unapproved) medication or participation in any clinical trial since completing the CTH-301 study.
5. Development of canker or mouth sores since completing the CTH-301 study. For other clinically significant oral pathology, the Investigator should follow-up with an

appropriate specialist on any finding, if indicated, before enrolling such a patient into the study. Clinical significance to be determined by the Investigator.

6. Current suicidal ideation as evidenced by answering "yes" to Question 4 or 5 on the suicidal ideation portion of the C-SSRS at the Screening Visit Phase 2 (SVP2).

11.2. Prior and Concomitant Treatments

11.2.1. Prohibited Treatments

The following prior and/or concomitant treatments will not be allowed during the course of this study:

- Treatment with any form of s.c. apomorphine is prohibited as follows:
  - from 7 days prior to the second Screening Visit (SV2) until study completion for *De Novo* subjects
  - from the time of the Screening Visit for Rollover subjects, until study completion
  - from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects until study completion.
- Any selective $5HT_3$ antagonist (eg, ondansetron, granisetron, dolasetron, palonosetron, alosetron) are prohibited as follows:
  - from 30 days prior to the initial Screening Visit (SV1) for *De Novo* subjects until study completion
  - from 14 days prior to the Screening Visit for Rollover subjects until study completion
  - from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects 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.
- Any sublingual medicinal product, including Vitamin B6.
- Any other preparation of Vitamin B6.
- Medicinal/recreational marijuana.

11.2.2. Permitted Treatments

Anti-emetic medication is optional and can be initiated at the Investigator's discretion if clinically warranted. If initiated, anti-emetic therapy should be stopped when clinically indicated. Anti-emetic medication should not be administered prophylactically.

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. NOTE: Domperidone is not indicated for longer than 7 continuous days of use. Extended use beyond 7 days should be discussed with the Medical Monitor.
- Stable doses of an L-Dopa formulation with or without other stable adjunctive PD therapies is permitted with no planned medication changes during the study as follows:
  - from at least 4 weeks prior to the initial Screening Visit (SV1) for *De Novo* subjects
  - within 14 days of completing the previous study for Rollover subjects
  - from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects
- MAO-B inhibitors will be allowed but must be stable as follows:
  - for at least 8 weeks prior to the initial Screening Visit (SV1) for *De Novo* subjects
  - for at least 14 days after completion of the previous study for Rollover subjects
  - from the Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects.
- Any other medication other than those identified as Prohibited Treatments are allowed, provided they are stable (within 14 days after completing the previous study for Rollover subjects or within 4 weeks for De novo subjects).

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.

11.3. Subject Withdrawal from the Study

Subjects 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.

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

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

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

If a subject is removed or withdraws from the study, the procedures outlined in the ET Visit will be performed, where possible. Subjects withdrawn/terminated during the Dose Titration Phase will have fewer assessments performed than those withdrawn/terminated during the LTS Phase (refer to Section 4 and Section 12.8 for additional details on the procedures to be performed).

12. STUDY PROCEDURES

This study will consist of the following:

1. Screening Visits (SV1 and SV2; *De Novo* subjects only); OR
   Screening Visit (SV; Rollover subjects only)
   Screening Visit (SVP2; CTH-301 Completer subjects only)
2. Dose Titration Phase (*De Novo* Subjects only)
   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)
3. Long-Term Safety (LTS) Phase Year 1 (*De Novo* and Rollover Subjects only)
   a. Long-Term Safety Visit 1 (LTS V1)
   b. Long-Term Safety Visit 2 (LTS V2)
   c. Long-Term Safety Visit 3 (LTS V3)
   d. Long-Term Safety Visit 4 (LTS V4)
   e. Long-Term Safety Visit 5 (LTS V5)
   f. Long-Term Safety Visit 6 (LTS V6)
   g. Telephone Call (T1 to T5)
   h. Unscheduled Dose Adjustment Visits
4. Long-Term Safety (LTS) Phase Year 2 (All Subjects)
   a. Long-Term Safety Visit 7 (LTS V7)
   b. Long-Term Safety Visit 8 (LTS V8)
   c. Long-Term Safety Visit 9 (LTS V9)
   d. Telephone Call (T6 to T8)
   e. Unscheduled Dose Adjustment Visits
5. Long-Term Safety (LTS) Phase Year 3 (All Subjects)
   a. Long-Term Safety Visit 10 (LTS V10)
   b. Long-Term Safety Visit 11 (LTS V11)
   c. Long-Term Safety Visit 12 (LTS V12)
   d. Telephone Call (T9 to T11)
   e. Unscheduled Dose Adjustment Visits
6. Long-Term Safety (LTS) Phase Year 4 (All Patients)
   a. Long-Term Safety Visit 13 (LTS V13)
   b. Long-Term Safety Visit 14 (LTS V14)
   c. Long-Term Safety Visit 15 (LTS V15)
   d. Telephone Call (T12 to T14)
   e. Unscheduled Dose Adjustment Visits

7. Long-Term Safety (LTS) Phase Year 5 (All Patients)
    a. Long-Term Safety Visit 16 (LTS V16)
    b. Long-Term Safety Visit 17 (LTS V17)
    c. Long-Term Safety Visit 18 (LTS V18)
    d. Telephone Call (T15 to T17)
    e. Unscheduled Dose Adjustment Visits

    Note: If a patient continues in the study beyond LTS Phase Year 5, the protocol will be amended to accommodate additional in clinic visits every 4 months (16 weeks).

8. Early Termination Visit (All subjects)

12.1. Screening Visits

12.1.1. Screening Procedures for *De Novo* Subjects

De Novo Patients are defined as patients who have not previously participated in a study with APL-130277.

Subjects must sign an ICF before any screening-related procedures are performed at an initial Screening Visit (SV1).

Following receipt of subject consent, the subject will be asked to return to the clinic for the second Screening Visit (SV2). All screening assessments must be performed within 28 days before Titration Visit 1 (TV1).

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

- Register the visit in the IWRS to obtain the subject screening number.
- Review inclusion/exclusion criteria.
- Review restriction criteria.
- Record demographics and detailed medical history, including review of medications taken within 6 months prior to the initial Screening Visit (SV1), current treatment regimens, drug, alcohol and smoking history.
- Perform a complete physical examination, including an oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure height and weight; calculate BMI.

- Record vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- 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 subject using the Modified Hoehn and Yahr scale (for a sample, see Section 19.3).
- Assess subject using MDS-UPDRS Parts I, II and IV (for a sample, see Section 19.4).
- Assess subject motor function using MDS-UPDRS Part III at t = 0 (just prior to L-Dopa administration), 15, 30, 60 and 90 minutes after L-Dopa administration (for a sample, see Section 19.4). If the subject does not experience an "ON" within 90 minutes of dosing, the site should record the time when the subject turns "ON" and perform an additional MDS-UPDRS Part III assessment at this time.
- Confirm L-Dopa responsiveness. Subjects will take their normal dose of L-Dopa ***without*** their normal adjunctive PD medication.
- Investigator confirmation of "OFF" or "ON".
- Perform subject training in order to distinguish "OFF" versus "ON" episodes (see Section 12.11.3.1).
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). The "Screening" scale should be used at this visit.
- Provide the subject with the PDQ-39 to complete (for a sample, see Section 19.7).
- Provide the subject with the EQ-5D (for a sample, see Section 19.13).
- Assess using the ESS (for a sample, see Section 19.10).
- Assess caregiver burden using the ZBI (for a sample, see Section 19.11).
- Complete the QUIP-RS (for a sample, see Section 19.12).
- Begin adverse event recording and serious adverse event reporting when the subject signs the ICF.
- Begin recording of any new concomitant medications and/or changes to current concomitant medications being used by the subject.

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

12.1.2. Screening Procedures for Rollover Subjects

Rollover Subjects are defined as subjects who have previously completed any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302.

Rollover Subjects must sign an ICF before any screening-related procedures are performed at the Screening Visit. Following receipt of subject consent, applicable assessments will be performed to ensure eligibility before continuing to the LTS Phase. Screening assessments will be performed while subjects are in the "ON" state. Subjects will be trained to assess their "OFF" and "ON" states during Screening visits.

All screening assessments must be performed up to 21 days before Long-term Safety Visit 1 (LTS V1).

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

- Register the visit in the IWRS to obtain the subject screening number.
- Review inclusion/exclusion criteria.
- Review restriction criteria.
- Record demographics and detailed medical history, including review of medications taken within 6 months prior to the initial Screening Visit, current treatment regimens, drug, alcohol and smoking history.
- Perform a complete physical examination, including an oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure height and weight; calculate BMI.
- Record vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- 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.
- Assess subject using MDS-UPDRS Parts I, II and IV (for a sample, see Section 19.4).

- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). The "Screening" scale should be used at this visit.
- Provide the subject with the PDQ-39 to complete (for a sample, see Section 19.7).
- Assess using the ESS (for a sample, see Section 19.10).
- Assess caregiver burden using the ZBI (for a sample, see Section 19.11).
- Complete the QUIP-RS (for a sample, see Section 19.12).
- Begin recording concomitant medications.
- Begin adverse event recording and serious adverse event reporting when the subject signs the ICF.
- Begin recording of any new concomitant medications and/or changes to current concomitant medications being used by the subject.

The Investigator will review all information obtained from the screening procedures. If the subject is not eligible, the subject will be a screening failure and will not attend any other visits. Subjects who fulfill all entry criteria will be found eligible to participate in the study and an appointment for LTS V1 will be made.

12.1.3. Screening Procedures for CTH-301 Completer Subjects

CTH-301 Completer Subjects are defined as subjects who have previously completed the CTH-301 study under protocol version 3.00.

Subjects who have previously completed the CTH-301 study under protocol version 3.00 and are re-enrolling into CTH-301 must sign an ICF before any screening-related procedures are performed at the Screening Visit Phase 2 (SVP2). Following receipt of subject consent, applicable assessments will be performed. All screening assessments must be performed within 28 days.

The following procedures will be performed by study staff at SVP2:

- Register the visit in the IWRS to obtain the subject screening number.
- Review inclusion/exclusion criteria.
- Review restriction criteria.
- Record any new medical history and medications taken since completion of the CTH-301 study.
- Perform a complete physical examination, including an oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure height and weight; calculate BMI.
- Record vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to

4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.

- 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.
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). The "Screening" scale should be used at this visit.
- Begin adverse event recording and serious adverse event reporting when the patient signs the ICF.
- Begin recording of any new concomitant medications and/or changes to current concomitant medications being used by the patient.

The Investigator will review all information obtained from the screening procedures. If the subject is not eligible, the subject will be a screening failure from SVP2 and will not attend any other visits. Subjects who fulfill all entry criteria and found eligible to participate in the study will be asked to return to clinic 5 to 28 days later and follow study procedures beginning at LTS Visit 7. These subjects will resume treatment with APL-130277 at the dose he/she was administered prior to completing CTH-301. If this dose is no longer considered tolerable or effective, the subject will return to the clinic for dose adjustment visits until a new tolerable or effective dose is established.

12.2. Dose Titration Phase (TV1 to TV6) - *De Novo* Subjects Only

12.2.1. TV1 to TV6

On the day of these visits, subjects will be asked to come to the clinic having taken their usual morning PD medication; but before taking their next dose of PD medications. The subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications. If needed, the site will arrange subject transfers.

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 film and 15 mg sublingual film, sequentially).

Subjects who develop symptoms such as nausea and/or vomiting which warrant treatment may receive anti-emetic therapy (US sites – Tigan® [trimethobenzamide hydrochloride; 300 mg t.i.d.]; non-US sites – domperidone [10 mg b.i.d.]). If initiated, anti-emetic therapy should be stopped when clinically indicated. Anti-emetic medication should not be administered prophylactically.

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

- Register the visit in IWRS to enroll the subject in the Titration Phase and obtain the Titration kit number (TV1 only).
- 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. A window of +/- 10 minutes is given for post-dose abbreviated physical and oropharyngeal examinations during TV1 to TV6.
- Record vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- Perform a standard 12-lead ECG prior to dosing and approximately 50 minutes after dosing.
- Assess subject motor function using MDS-UPDRS Part III at t = 0 (just prior to dosing), 15, 30, 60, and 90 minutes after dosing (for a sample, see Section 19.4). 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 subjects 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, except at 45 minutes, which will be assessed independent of the MDS-UPDRS Part III. The subject 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 subject does not experience a full "ON" response within 45 minutes of dosing.
- Subject confirmation of "OFF" or "ON". Subject should report: "OFF"/"ON" state at t = 0, 15, 30, 45, 60, and 90 minutes after dosing.
- Subject 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). Note: The timing of this should begin when the study

medication sublingual film has fully dissolved, and can be recorded using a stopwatch or other suitable timing device.

- Provide subject with a home dosing diary (TV1 only; see Section 19.5). Diary will be provided for training purposes only. If needed, subject will be retrained at LTS V1 in the use of the home dosing diary.
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at these visits.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

Subjects 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 Phase perspective and may proceed to the LTS Phase. This dose will be used in the LTS 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 subject 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 the lower dose without impacting subject safety and tolerability, the higher dose will be used during the LTS 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 LTS Phase of the study.

A full "ON" is defined in Section 12.11.3.1.

Subjects 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, subjects 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 a dosage considered appropriate by the Investigator to achieve an "ON" state. If this occurs, subjects can return to the clinic on another day to resume the titration with the next highest dose. If a dose of APL-130277 cannot be found that provides a full "ON" response, the subject will be terminated from the study.

12.3. Long-Term Safety (LTS) Treatment Phase Year 1 – *De Novo* and Rollover Subjects Only

The long-term safety phase year 1 of the study will consist of 2 parts –in-clinic assessments and at-home assessments. The former will consist of 6 in-clinic visits where formal assessments of efficacy and/or safety will be performed. The latter will be an at-home self-administration, where all subjects will be instructed to self-administer their doses of APL-130277 in order to treat up to 5 "OFF" episodes (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden

"OFF") per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

De novo Subjects who have successfully completed the Dose Titration Phase of the study will receive their dose of open-label study treatment on LTS V1. The dose given will be the same as that determined during the Dose Titration Phase of the study.

Rollover subjects will receive treatment with the same dose they were on in the previous study.

12.3.1. LTS V1, LTS V3, LTS V4, LTS V5, and LTS V6: In-Clinic Assessments

Long-Term Safety Visit 1 (LTS V1) may occur no later than 21 days after the last Dose Titration Phase visit for De novo subjects, or no later than 21 days after Screening for Rollover subjects.

Subjects will be asked to arrive at the clinic after their usual morning dose of PD medications; but before taking their next dose of medication. Subjects will be required to wait approximately two hours after their normally scheduled second dose of PD medications.

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

- Review restriction criteria.
- 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 vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- Perform a standard 12-lead ECG prior to dosing and approximately 50 minutes after dosing.
- 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 (LTS V3, LTS V4, LTS V5, and LTS V6 only).
- Assess subject using MDS-UPDRS Parts I, II and IV (LTS V3, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.4).
- Assess subject motor function using MDS-UPDRS Part III at t = 0 (just prior to dosing), 15, 30, 60, and 90 minutes after dosing (for a sample, see Section 19.4).
- If subjects are in the "OFF" state, dose with study treatment assigned by the IWRS.

- Investigator confirmation of "OFF" or "ON". Investigator will assess "OFF"/"ON" state as part of the MDS-UPDRS Part III assessments, except at 45 minutes, which will be assessed independent of the MDS-UPDRS Part III. The subject must be in an "OFF" state prior to dosing in order to proceed with dosing.
- Subject confirmation of "OFF" or "ON". Subject should report: "OFF"/"ON" state at t = 0, 15, 30, 45, 60, and 90 minutes after dosing.
- Subject 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). Note: The timing of this should begin when the study medication sublingual film has fully dissolved, and can be recorded using a stopwatch or other suitable timing device.
- Dispense Study Medication assigned by the IWRS for Outpatient Dosing.
- Collect Study Medication (excluding LTS V1).
- Collect Subject Dosing Diary (De novo Subjects only).
- Provide Subject Dosing Diary (see Section 19.5) and provide subject training on proper completion of the diary (at LTS V1). At all other visits, collect subject diary and ensure it was properly completed, and provide retraining on diary completion as necessary.
- Perform IP accountability and assess treatment compliance (excluding LTS V1).
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at these visits.
- Provide the subject with the PDQ-39 to complete (LTS V1, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.7).
- Ask subject to complete the PGI (LTS V1, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.9). PGI–S to be used at the first visit, PGI-I to be used at all subsequent visits.
- Complete the CGI (LTS V1, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.8). CGI–S to be used at the first visit, CGI-I to be used at all subsequent visits.
- Assess using the ESS (LTS V1, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.10).
- Assess caregiver burden using the ZBI (LTS V1, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.11).
- Complete the QUIP-RS (LTS V1, LTS V4, LTS V5, and LTS V6 only; for a sample, see Section 19.12).
- Outpatient self-administration training (LTS V1 for De novo Subjects only). Subjects will be trained by clinic staff on how to remove study medication from its packaging, and how to handle the sublingual films using placebo sublingual films supplied to the

site. Subjects **should not** self-administer the placebo sublingual films. Subjects cannot be discharged from clinic until satisfactorily completing the training.

- Blood sampling for PK analysis (for applicable sites participating in the PK sub-study). Samples will be taken at t = 0 (just prior to dosing) and at t = 10, 20, 30, 60, 90, 120, 180 and 240 minutes post dosing.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- If in the opinion of the Investigator the subject can no longer tolerate the "OFF" state at any point during the visit, the subject may receive rescue L-Dopa (± other adjunctive PD medication) at a dosage considered appropriate by the Investigator to achieve a full "ON" state. Where possible, administration of rescue L-Dopa should be delayed until after the 90 minute efficacy assessments are complete.

12.3.2. LTS V2: In-Clinic Assessment

Subjects will be asked to return to the clinic having taken their usual morning PD medications. The following safety assessments will be conducted:

- Review restriction criteria.
- 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 vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- Perform a standard 12-lead ECG.
- Register the visit in the IWRS to obtain the study medication kit numbers.
- Dispense Study Medication assigned by the IWRS for Outpatient Dosing.
- Collect Study Medication.
- Collect subject's previous home dosing diary. Verify that the diary has been appropriately completed and retrain subject on diary completion as necessary.
- Provide subject with a dosing diary.
- Perform IP accountability and assess treatment compliance.

- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at this visit.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.3.3. LTS Phase Year 1 – At Home Assessments

During the LTS Phase, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their APL-130277 treatment if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

For 2 days prior to in-clinic visits, subjects will be requested to complete a dosing diary (for a sample, see Section 19.5) that captures:

- Time of APL-130277 treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing.
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

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

12.3.4. LTS Phase Year 1 – Telephone Contacts

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

The following safety assessments will be conducted:

- Review restriction criteria.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.4. Long-Term Safety (LTS) Treatment Phase Year 2 - All Subjects

The long-term safety phase year 2 of the study will consist of 2 parts –in-clinic assessments and at-home assessments. The former will consist of 3 in-clinic visits where formal assessments of safety will be performed. The latter will be an at-home self-administration, where all subjects will be instructed to self-administer their doses of APL-130277 in order to treat up to 5 "OFF"

episodes (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF") per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

12.4.1. LTS V7, LTS V8, and LTS V9: In-Clinic Assessment

Subjects will be asked to return to the clinic having taken their usual morning PD medications. The following safety assessments will be conducted:

- Review restriction criteria.
- Perform a complete physical examination, including oropharyngeal examination. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.
- Measure weight.
- Record vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- Perform a standard 12-lead ECG (excluding LTS V7 for CTH-301 Completer Subjects).
- 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 (excluding LTS V7 for CTH-301 Completer Subjects).
- Register the visit in the IWRS to obtain the study medication kit numbers.
- Dispense Study Medication assigned by the IWRS for Outpatient Dosing.
- Collect Study Medication (excluding LTS V7 for CTH-301 Completer Subjects).
- Dispense Study Medication for Outpatient Dosing.
- Provide subject with a dosing diary (see Section 19.5).
- Collect subject's previous dosing diary, excluding TLS V7 for CTH-301 Completer Subjects (see Section 19.5). Verify that the diary has been appropriately completed and retrain subject on diary completion as necessary.
- Perform IP accountability and assess treatment compliance (excluding LTS V7 for CTH-301 Completer Subjects).
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at this visit.
- Record any AEs/SAEs that have occurred since the last subject visit.

- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.4.2. LTS Phase Year 2 – At Home Assessments

During the LTS Phase, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their APL-130277 treatment if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

For 2 days prior to in-clinic visits, subjects will be requested to complete a dosing diary (for a sample, see Section 19.5) that captures:

- Time of APL-130277 treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing;
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

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

12.4.3. LTS Phase Year 2 – Telephone Contacts

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

The following safety assessments will be conducted:

- Review restriction criteria.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.5. Long-Term Safety (LTS) Treatment Phase Year 3 - All Subjects

The long-term safety phase year 3 of the study will consist of 2 parts –in-clinic assessments and at-home assessments. The former will consist of 3 in-clinic visits where formal assessments of safety will be performed. The latter will be an at-home self-administration, where all subjects will be instructed to self-administer their doses of APL-130277 in order to treat up to 5 "OFF" episodes (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF") per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

12.5.1. LTS V10, LTS V11, and LTS V12: In-Clinic Assessment

Subjects will be asked to return to the clinic having taken their usual morning PD medications. The following safety assessments will be conducted:

- Review restriction criteria.
- 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 vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- 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.
- Register the visit in the IWRS to obtain the study medication kit numbers.
- Dispense Study Medication assigned by the IWRS for Outpatient Dosing.
- Collect Study Medication.
- Provide subject with a home dosing diary (see Section 19.5).
- Collect subject's previous home dosing diary (see Section 19.5). Verify that the diary has been appropriately completed and retrain subject on diary completion as necessary.
- Perform IP accountability and assess treatment compliance.
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at this visit.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- Provide the subject with the PDQ-39 to complete (LTS V12 only; for a sample, see Section 19.7).
- Ask subject to complete the PGI-I (LTS V12 only; for a sample, see Section 19.9).
- Complete the CGI-I (LTS V12 only; for a sample, see Section 19.8).

- Assess using the ESS (LTS V12 only; for a sample, see Section 19.10).
- Assess caregiver burden using the ZBI (LTS V12 only; for a sample, see Section 19.11).
- Complete the QUIP-RS (LTS V12 only; for a sample, see Section 19.12).

12.5.2. LTS Phase Year 3 – At Home Assessments

During the LTS Phase, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their APL-130277 treatment if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

For 2 days prior to in-clinic visits, subjects will be requested to complete a dosing diary (for a sample, see Section 19.5) that captures:

- Time of APL-130277 treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing.
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

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

12.5.3. LTS Phase Year 3 – Telephone Contacts

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

The following safety assessments will be conducted:

- Review restriction criteria.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.6. Long-Term Safety (LTS) Treatment Phase Year 4 - All Subjects

The long-term safety phase year 4 of the study will consist of 2 parts –in-clinic assessments and at-home assessments. The former will consist of 3 in-clinic visits where formal assessments of safety will be performed. The latter will be an at-home self-administration, where all subjects will be instructed to self-administer their doses of APL-130277 in order to treat up to 5 "OFF"

episodes (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF") per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

12.6.1. LTS V13, LTS V14, and LTS V15: In-Clinic Assessment

Subjects will be asked to return to the clinic having taken their usual morning PD medications. The following safety assessments will be conducted:

- Review restriction criteria.
- 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 vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- 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.
- Register the visit in the IWRS to obtain the study medication kit numbers.
- Dispense Study Medication assigned by the IWRS for Outpatient Dosing.
- Collect Study Medication.
- Provide subject with a home dosing diary (see Section 19.5).
- Collect subject's previous home dosing diary (see Section 19.5). Verify that the diary has been appropriately completed and retrain subject on diary completion as necessary.
- Perform IP accountability and assess treatment compliance.
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at this visit.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.6.2. LTS Phase Year 4 – At Home Assessments

During the LTS Phase, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their APL-130277 treatment if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

For 2 days prior to in-clinic visits, subjects will be requested to complete a dosing diary (for a sample, see Section 19.5) that captures:

- Time of APL-130277 treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing;
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

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

12.6.3. LTS Phase Year 4 – Telephone Contacts

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

The following safety assessments will be conducted:

- Review restriction criteria.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.7. Long-Term Safety (LTS) Treatment Phase Year 5 - All Subjects

The long-term safety phase year 4 of the study will consist of 2 parts –in-clinic assessments and at-home assessments. The former will consist of 3 in-clinic visits where formal assessments of safety will be performed. The latter will be an at-home self-administration, where all subjects will be instructed to self-administer their doses of APL-130277 in order to treat up to 5 "OFF" episodes (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF") per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

12.7.1. LTS V16, LTS V17, and LTS V18: In-Clinic Assessment

Subjects will be asked to return to the clinic having taken their usual morning PD medications. The following safety assessments will be conducted:

- Review restriction criteria.
- 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 vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- 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.
- Register the visit in the IWRS to obtain the study medication kit numbers.
- Dispense Study Medication assigned by the IWRS for Outpatient Dosing.
- Collect Study Medication.
- Provide subject with a home dosing diary (see Section 19.5).
- Collect subject's previous home dosing diary (see Section 19.5). Verify that the diary has been appropriately completed and retrain subject on diary completion as necessary.
- Perform IP accountability and assess treatment compliance.
- Assess suicidal ideation using C-SSRS (for a sample, see Section 19.6). "Since Last Visit" version should be used at this visit.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

12.7.2. LTS Phase Year 5 – At Home Assessments

During the LTS Phase, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their APL-130277 treatment if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day. Subjects will be instructed to wait a minimum of 2 hours between each dose taken at home.

For 2 days prior to in-clinic visits, subjects will be requested to complete a dosing diary (for a sample, see Section 19.5) that captures:

- Time of APL-130277 treatment self-administration;
- Subject "ON"/"OFF" state at 30 minutes after dosing;
- The type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

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

12.7.3. LTS Phase Year 5 – Telephone Contacts

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

The following safety assessments will be conducted:

- Reconfirm consent.
- Review restriction criteria.
- 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.

12.8. Early Termination Visit

Every effort should be made to have subjects complete all study visits. The following assessments will be conducted when an individual subject discontinues:

- 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 vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness,

dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.

- 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 (for a sample, see Section 19.6).
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.

Subjects who discontinue the study during the LTS Phase will also have the following assessments performed:

- Collect outpatient supplies (if applicable).
- Collect Subject Dosing Diary (if applicable).
- Assess treatment compliance (if applicable).
- Provide the subject with the PDQ-39 to complete (for a sample, see Section 19.7).
- Ask subject to complete the PGI-I (for a sample, see Section 19.9).
- Complete the CGI-I (for a sample, see Section 19.8).
- Assess using the ESS (for a sample, see Section 19.10).
- Assess caregiver burden using the ZBI (for a sample, see Section 19.11).
- Complete the QUIP-RS (for a sample, see Section 19.12).
- Complete Ease of Use Questionnaire (for a sample, see Section 19.15).
- Register the visit in the IWRS.

12.9. Unscheduled Dose Adjustment Visits

If at any time during the LTS Phase of this study it is determined that a dose adjustment is required, where possible the medical monitor should be contacted to discuss the dose adjustment. Once agreed, “Unscheduled Dose Adjustment” should be registered in IWRS, indicating whether the dose adjustment should happen at the next LTS visit or at an unscheduled visit, to obtain the new dose of APL-130277 for the subject. Once IP is at site, subject will return for an unscheduled Dose Adjustment Visit (or this could be combined with the next scheduled LTS visit).

At the investigator’s discretion, the subject may receive the adjusted dose in-clinic and undergo efficacy (MDS-UPDRS part III and ON/OFF assessments up to 90 minutes), and additional safety assessments as deemed appropriate.

Subjects will be contacted by telephone within 3 days after dose adjustment visits for assessment of effect of the dose adjustment and safety.

The following will be performed:

- Review restriction criteria.
- Record vital signs (BP, HR, RR and body temperature). Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.
- Collect remaining study medication provided at the last visit (if required).
- Provide subject home dosing diary (see Section 19.5) and instruct subjects to complete it 2 days before their subsequent in-clinic visit (if applicable).
- Collect subject diaries completed since the last visit (if applicable; see Section 19.5). Verify that the diary has been appropriately completed and retrain subject on diary completion as necessary.
- Assess treatment compliance.
- Record any AEs/SAEs that have occurred since the last subject visit.
- Record any new concomitant medications and/or changes to current concomitant medications being used by the subject since the last visit.
- Record reason for the dose adjustment.
- Dispense new study medication for outpatient dosing (Only after all safety assessments have been completed and deemed safe by the investigator to dispense the new dose to the subject).

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

If, in the opinion of the Investigator, dose adjustments are necessary for subject safety, tolerability or lack of efficacy, the Investigator may adjust the scheduled dose of study drug to the next dose (eg, to the 10 mg dose if the subject is receiving 15 mg, or up to 20 mg dose if subject is receiving 15 mg). The Investigator should make all attempts to maintain subjects on a stable dose.

Any subject whose dose has been reduced or increased at a Dose Adjustment Visit will self-administer study drug using the new dosage at home and at all in-clinic visits for the remainder of the LTS Phase of the study. If, in the opinion of the Investigator, the dose is no longer optimal for the subject, after discussions/approval from the medical monitor, additional dose adjustments could be performed.

12.10. Duration of Treatment

Subjects may participate in the study until the Sponsor terminates the study, or until commercial availability of APL-130277 in the subject's country.

12.11. Assessments

12.11.1. Order of Assessments

The following summarizes the suggested sequence of assessments prior to dosing during SV2 (*de novo patients only*), Dose Titration Phase and the in-clinic visits during the LTS Phase:

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

The following summarizes the suggested sequence of assessments after dosing during SV2 (*de novo subjects only*), Dose Titration Phase and the in-clinic visits during the LTS Phase:

MDS-UPDRS Part III - Subject "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.

12.11.2. Clinical Safety Assessments

12.11.2.1. 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.

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 (*De novo* subjects only). A window of +/- 10 minutes is given for post-dose abbreviated physical examinations during TV1 to TV6.

All examinations performed in this study 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).

Any subject who presents with an adverse event involving the oral cavity must be seen by a qualified dermatologist (or specialist in a related field) within 24 hours. The dermatologist (or specialist in a related field) must examine the subject, and provide a consultation report including photographs of the oral cavity (see Section 13.1.7).

12.11.2.2. Vital Signs

Vital signs (HR, RR, BP and body temperature) will be measured at various timepoints during the study. Vital signs should be measured after the subject has been resting in the supine position for at least 3 minutes. Blood pressure and heart rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of BP and HR. If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.

During the Dose Titration Phase (*De novo* subjects only), if the 60 minute MDS-UPDRS Part III assessment is not performed since the subject 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 (ie 70 minutes).

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.

12.11.2.3. 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) for *De Novo* subjects, at Screening Visit (SV1) for Rollover subjects, and at Screening Visit Period 2 (SVP2) for

CTH-301 Completer subjects. If required by the Investigator to assess *De Novo* Patient eligibility, a triplicate ECG may be performed at SV1, 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 collected:

- 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 contracted by the Sponsor and/or designate.

12.11.2.4. Modified Hoehn and Yahr

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

No Modified Hoehn and Yahr scale will be performed on Rollover subjects during Screening Visit (SV1) or on CTH-301 Completer subjects at Screening Visit Period 2 (SVP2).

12.11.2.5. 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.

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

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

12.11.2.7. C-SSRS

At the Screening Visit (SV2 for *De Novo* subjects, SV1 for Rollover subjects, or SVP2 for CTH-301 Completer Patients), the C-SSRS 'Screening' assessment tool will be used. Subjects who answer 'Yes' to Questions 4 and 5 at this Visit should be excluded from participation in the study. All subsequent evaluations will utilize the C-SSRS 'Since Last Visit' assessment.

Formal assessments of subject suicidal ideation and behavior will be assessed all in-clinic visits during the Dose Titration Phase and LTS Phase of the study. A final assessment will be performed at the time of early termination.

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

12.11.2.8. 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).

12.11.2.9. Medical History

At the Screening Visits, the Investigator (or designate) will review the subject's medical history in order to ascertain the subject's eligibility. The medical history should assess the 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 subject's 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 (eg, morning akinesia, wearing "OFF, delayed "ON", dose failure, sudden "OFF");
- Number of "OFF" episodes per day;
- Typical length of "OFF" episodes.
- PD medications previously or currently taken, including:
  - dopamine agonists;
  - MAO-B inhibitors;
  - COMT inhibitors;
  - Amantadine;
  - Anti-cholinergics.

12.11.3. Efficacy Assessments

12.11.3.1. Confirmation of "OFF" or "ON" Episodes "OFF" and "ON" Training of Subjects at SV2

"OFF" and "ON" Training

Training will only be performed with *De Novo* subjects only. Rollover subjects and CTH-301 Completer subjects will not be required to undergo "OFF"/"ON" training during the Screening Visit.

At Screening Visit 2 (SV2), *De Novo* subjects will present to the clinic having taken their usual morning dose of L-Dopa and any other adjunctive PD medication; but before taking their next dose of medication. Their normal dose of L-Dopa (**without** adjunctive PD medication) will be administered in the clinic approximately two hours after their normally scheduled second dose of PD medication. Prior to administration of their L-Dopa dose, subjects will be examined by the Investigator in order to verify that they are in the "OFF" state. If they are in the "OFF" state, the

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

Subjects will then take their normal dose of L-Dopa. Once the Investigator determines that the subject is experiencing an "ON" state, they should educate the subject that this is an "ON" state. The Investigator should clearly explain to the subject that an "ON" episode is the period of time where their medication is providing benefit with regard to mobility, slowness and stiffness, and they feel they can perform normal daily activities. Once the 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 subject who cannot differentiate between an "ON" and "OFF" state will be deemed a screen failure.

A window of ± 5 minutes is allowed for both the subject and the Investigator assessments at each post-dose timepoint.

Definitions of Full "ON" and "OFF"

The following definitions will be used in this study:

"OFF" – defined as:

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

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

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

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

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

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

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

Subjects must confirm they are in an "OFF" state prior to dosing with study medication (or their standard L-Dopa dose at the second Screening Visit [SV2; *De Novo* subjects only]).

At each Dose Titration and LTS Phase Year 1 Visit (except LTS V2), the Investigator will assess "OFF"/"ON" state as part of the MDS-UPDRS Part III assessments except at 45 minutes, which will be assessed independent of the MDS-UPDRS Part III.

At each Dose Titration and LTS Phase Year 1 Visit (except LTS V2), the subject should report: "OFF"/"ON" state at 0, 15, 30, 45, 60, and 90 minutes after dosing (site staff should prompt the patient). Subjects 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 60 minutes of dosing). The timing of this should begin when the study medication sublingual 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 (*De novo* subjects only), subject 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.

12.11.3.2. 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 Screening Visit (SV2 for *De Novo* subjects and SV1 for Rollover subjects; CTH-301 Completer subjects will not be required to undergo this assessment at Screening) and at LTS V3, LTS V4, LTS 5, and LTS 6).

12.11.3.3. MDS-UPDRS Part III

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

At SV2 (*De Novo* subjects only), administration will be performed at t = 0 (just prior to dosing) and at 15, 30, 60 and 90 minutes after L-Dopa administration. If the subject does not experience an "ON" within 90 minutes, the site should record the time when the subject turns "ON" and perform an additional MDS-UPDRS Part III assessment at this time.

At all other visits, administration will be performed at t = 0 (just prior to dosing) and at 15, 30, 60, and 90 minutes after dose administration. The same assessor should be utilized for each subject throughout the study.

A window of ± 5 minutes is allowed for post-dose assessments at each timepoint.

These assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging. The modified Hoehn and Yahr will be used during the Screening Visit (SV2 – *De Novo* Patients only).

During the Dose Titration Phase only, Investigator assessments may cease if the subject 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.

12.11.3.4. Subject Dosing Diary

De novo Subjects (only) will be given a home dosing diary on TV1 of the Dose Titration Phase.

All subjects will be given a dosing diary at all LTS Visits. The diary will collect the following information:

- Date;
- Subject Number;
- Time study treatment is self-administered;
- Subject "ON"/"OFF" status at 30 minutes following dosing;
- Type of "OFF" experienced (ie, morning akinesia; delayed "ON"; wearing "OFF"; no "ON"; or sudden "OFF").

The diary provided on TV1 (De novo Subjects only) will be used for training purposes only and the information collected will not be included in the CRF. Subjects 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 LTS V1. Subjects will also be instructed on the different types of "OFF" episodes experienced and how to differentiate between each.

Staff should review the completed diary returned at LTS V1 and re train subjects on diary completion, as necessary. Site staff should remind subjects at this visit that moving forward, the diary must be completed only when the subject self-administers their intended study treatment, not their other standard PD medication.

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

12.11.3.5. Optional Pharmacokinetic (PK) Evaluation

Blood draws for APL-130277 PK analyses will occur during LTS Phase Year 1, where indicated, at t = 0 (just prior to dosing) and at t = 10, 20, 30, 60, 90, 120, 180 and 240 minutes. A window of ± 5 minutes is allowed for post-dose assessments at each timepoint. PK assessments will be performed at select participating sites, and subjects must consent in order to participate in optional PK sub-study. Approximately 6 sites will be chosen, and 4 subjects from each of these are estimated to take part in the sub-study. Dosing date and time as well as PK sampling date and time must be recorded in the CRF. Actual elapse time from dosing will be used in all PK parameter estimations.

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

12.12. Assessment of Treatment Compliance

Treatment compliance will be assessed by counting the number of used and unused study medication pouches returned by subjects at each in-clinic visit during the LTS Phase of this study relative to the amount given at the preceding visit. Discrepancies in the amount previously

dispensed and returned by the subject will be queried by the Investigator and documented in the appropriate CRF. Significant non-compliance, as assessed by the Investigator, may lead to subject dismissal from the study.

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

13. ADVERSE EVENTS

Adverse event recording and serious adverse event reporting will begin when the subject signs the ICF. AEs will be recorded in the CRFs until 7 to 10 days after the last dose of study drug, and SAEs will be reported through 14 days after the last dose of study drug.

13.1.1. Definition of Adverse Events

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

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

13.1.2. Definition of Serious Adverse Events

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

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

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as **important medical events** that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject (or subject) 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 subjects being enrolled in this study, and the given study objectives, subjects who are admitted for their titration and/or LTS Phase "OFF" episodes <u>will not</u> be considered a SAE.

13.1.3. Definition of Severity

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

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

13.1.4. Definition of Start Date, Stop Date, and Duration

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

13.1.5. Action(s) Taken

Actions taken may consist of:

None:	No actions taken.
Discontinued Investigational Drug:	Investigational drug was permanently discontinued because of the AE.
Change Investigational Drug:	Investigational drug was given at a lower dose, at a longer interval between doses, or was temporarily withheld because of the AE.
Treatment:	Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure.
Others:	Other actions, such as an operative procedure, were required because of the AE.

13.1.6. Definition of Expectedness

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

An unexpected AE is an AE for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only

listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

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

13.1.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) for APL-130277 pertaining to the oral cavity requires reporting to the Sponsor or designate. These AESIs include, but are not limited to:

- Stomatitis;
- Oral irritation/oral inflammation/oral pain, including redness
- Oral swelling; edema
- Oral ulcers, including blisters
- Oral infections, including candidiasis
- Oral paresthesia, hypoesthesia,
- Oral sensation alterations such as dysgeusia, ageusia
- Salivary complaints

All AESIs should be reported to the Sponsor or designate, as appropriate, for processing. Instructions for reporting AESIs and their processing will be outlined in a separate study document.

Any subject who presents with an adverse event involving the oral cavity must be seen by a qualified dermatologist (or specialist in a related field) within 24 hours (if it is not possible to report within 24 hours, the Medical Monitor should be consulted immediately to discuss the evaluation plan including timeline). The dermatologist (or specialist in a related field) must examine the subject, and provide a consultation report including photographs of the oral cavity.

Subjects should be instructed to notify the clinical site within 24 hours if they develop any one or more of the oral events noted above.

For all AESIs, if the event meets seriousness criteria, the Investigator will report the event to the Sponsor or designate within 24 hours of the site being made aware of the event, as outlined in Section 13.1.14. All AESIs which do not meet the seriousness criteria will be reported by the Investigator to the Sponsor or designate within 7 days of site awareness (Section 13.1.14).

13.1.8. Definition of Relationship to Investigational Drug(s)

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

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

13.1.9. Definition of Outcome at the Time of Last Observation

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

- Resolved;
- Resolved with sequelae;
- Ongoing;
- Death;
- Unknown.

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

13.1.10. Documentation of Adverse Events

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

- AE name or term;
- When the AE first occurred (start date);
- When the AE stopped (stop date), or an indication of "ongoing";

- How long the AE persisted (optional);
- Severity of the AE;
- Seriousness;
- Actions taken;
- Outcome;
- Investigator opinion regarding the relationship of AE to the investigational drug(s).

13.1.11. Follow-up of Subjects With an Adverse Event

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

13.1.12. Special Procedures for Managing AEs/SAEs

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

Unblinding procedures are not applicable for this study as it is being conducted as an open-label study.

13.1.13. Notification of Serious Adverse Events

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject from signing informed consent through 14 days following the last dose of the study medication, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

An initial / follow-up SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD-PVG within 1 business day of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor will provide the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB), Research Ethics Board (REB), or Independent Ethics Committee (IEC) by the Investigator or the appropriate person at the study center if required per IRB/REB/IEC guidelines.

13.1.14. Notification of Oral Adverse Events of Special Interest

Oral AESIs (Section 13.1.7) that do not meet seriousness criteria (Section 13.1.2) must be reported by the Investigator to the Sponsor within 7 business days of the Investigator or study center staff awareness of the event.

14. TREATMENTS

14.1. Treatments Administered (APL-130277 and Matching Placebo)

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

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 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 or numeric printing.

APL-130277 sublingual films will be provided in 5 strengths: 10 mg, 15 mg, 20 mg, 25 mg and 30 mg. Two sublingual 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 films will also be prepared for training purposes only, which will be identical in appearance, size and color, but contain no active ingredient (ie, apomorphine).

14.2. Administration of Study Medication (APL-130277 and Placebo APL--130277)

During Dose Titration (De novo Subjects only) and applicable visits in the LTS Phase, dosing will occur in the clinic administered by clinic staff. Time of dosing will be the time when the sublingual film is placed underneath the tongue. Subjects will be instructed to consume a glass of water immediately prior to dosing, and staff will ensure the sublingual space is free of excess water.

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

If the subject 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, subjects should be instructed to close their mouth again and hold the study medication under their tongue. Staff may verify at regular intervals, as appropriate, for a duration maximum of 4 minutes in total.

At LTS V1, De novo subjects (only) will undergo outpatient self-administration training with clinic staff using placebo sublingual films. This training is performed in order to familiarize subjects with the self-administration process during the LTS Phase. Staff should demonstrate to subjects the process of opening the individual dose pouches and handling the individual sublingual films. Subjects **should not** self-administer the placebo sublingual films. Subjects 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, subjects 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, subjects (or their caregivers) should place the product beneath the tongue, with the drug side facing up towards the tongue (ie, the side of the film that does not have an alphanumeric printing), and close their mouth naturally. **Subjects 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.**

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

During the in-clinic visits of the Dose Titration Phase (*De novo* subjects only), subjects will be dosed by clinic staff. The time of dosing (t = 0) will be the time when the sublingual film is placed underneath the tongue.

At each outpatient visit, subjects will be provided sufficient study medication in order to self-administer for up to 5 "OFF" episodes per day until their next scheduled visit. Subjects will be instructed to wait a minimum of 2 hours between doses taken at home. Unused study medication will be collected by each site and inventoried.

14.3. Storage

The Investigator is responsible for ensuring the proper storage of study medication according to procedures agreed in advance. Unit dose pouches should be stored at a controlled room temperature: 68-77°F (20-25°C). The study drug should be stored in a limited-access location with appropriate environmental controls (e.g., for temperature) and a mechanism for documenting that required conditions were maintained during the entire storage timeframe.

Temperature excursions between 15°C (59°F) and 30°C (86°F) do not need to be reported to the sponsor, unless the duration exceeds 7 consecutive days.

If the storage conditions fall below 15°C (59°F), reach above 30°C (86°F), or if there is an event where temperatures reach above 25 °C (77°F) up to 30°C (86°F) for at least 7 consecutive days, the excursions should be reported to the sponsor. Please refer to the Pharmacy Manual for additional details and reporting instructions.

Subjects will be instructed to store the study medication at room temperature.

The Investigator must maintain accurate and adequate records including expiry dates, lot number, 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. 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 subject 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.

Refer to Study Pharmacy Manual for additional information.

14.4. Packaging and Labeling

During the Dose Titration Phase, open-label titration kits containining 12 dose level pouches will be supplied to sites. The kits and the individual pouches will be labeled with all applicable information.

Kits of sublingual films of Placebo APL-130277, containing 3 individual dose peelable foil laminate pouches will be supplied for training purposes. The kits and Individual pouches will be labelled with all applicable information.

During the LTS Phase, treatment kits of APL-130277, 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 both in clinic and at home during the LTS Phase.

Refer to the pharmacy manual (or equivalent) for more details.

14.5. Drug Accountability

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

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

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

Refer to Study Pharmacy Manual for additional information.

14.6. Method of Assigning Subjects to Treatment Groups

Subjects will be assigned open-label APL-130277 treatment using an IWRS system.

The strength (ie, 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 for *De novo* subjects.

The strength to be given for Rollover subjects will be the dose they were on in the previous study.

The strength to be given for Completer subjects will be the dose they previously received in study CTH-301 (under protocol version 3.00).

Doses may be adjusted in the LTS Phase of the study based on safety/tolerability and efficacy assessed during unscheduled Dose Adjustment Visits.

14.7. Randomization and Blinding

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

There will be no blinding of treatment and no randomization performed.

When the Dose Titration Phase for a subject is complete (*De novo* subjects only), sites should enter all titration MDS-UPDRS Part III date for that patient into the appropriate CRF within 48 hours of the last titration visit for review by the Medical Monitor.

15. STATISTICAL ANALYSES

15.1. 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.

15.2. Analysis Sets

15.2.1. Titration Full Analysis Set

All subjects who are enrolled in this study and receive one dose of study medication during the dose titration phase will be included in the titration full analysis set. This analysis set will be used for safety and efficacy analysis of titration phase data.

15.2.2. LTS Full Analysis Set

All subjects who are enrolled and receive at least one dose of study medication during the LTS phase will comprise the LTS full analysis set. This set will be used for safety and efficacy analysis of LTS phase data.

15.3. Sample Size Calculation.

The sample size of this safety study is not based on any power calculations.

15.4. Efficacy Analysis

The efficacy endpoints will be analyzed by time point for the LTS Full Analysis set and separately for *De Novo* Subjects and Rollover Subjects.

The changes from baseline in the continuous efficacy endpoints will be summarized descriptively. The categorical endpoints will be analyzed using subject counts and percentages.

15.5. Safety Analysis

The analysis of the safety data will focus on data collected during the LTS Phase. In addition, all safety data will be reported separately for the Dose Titration Phase. The safety data will be primarily analyzed for the full analysis set, but additional summaries will be done separately for *De Novo* Subjects and Rollover Subjects (based on initial enrollment status). Adverse events will be tabulated according to the MedDRA. Treatment-emergent adverse events will be summarized by body system and preferred term. The AE analysis will focus on the dopaminergic TEAEs. Descriptive statistics will be used to summarize the overall incidence of TEAEs.

15.6. Pharmacokinetic Analysis

For plasma PK samples, apomorphine levels and metabolites (norapomorphine and apomorphine sulphate) will be measured in plasma using a validated liquid chromatography-tandem mass

spectrometry (LC-MS/MS) method developed by Info Kinetics. Apomorphine-glucuronide and norapomorphine-glucuronide levels will be measured using a qualified LC-MS/MS method.

Pharmacokinetic parameters will be derived using noncompartmental methods employing WinNonlin® Phoenix version 6.3 or higher (Pharsight, St Louis, MO). Pharmacokinetic analysis will be conducted using concentration-time data for apomorphine and metabolites.

For pharmacokinetic analysis concentrations that are below the limit of quantification (BLQ) will be assigned a value of zero when they precede quantifiable samples in the initial portion of the profile. Following C_{max}, BLQ values embedded between two quantifiable data points will be treated as missing when calculating area under the curve. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) will be treated as missing data. When consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile.

The following PK parameters if appropriate for the particular analyte will be estimated by noncompartmental methods from plasma samples (Table 10). Additional parameters may be calculated as necessary. Actual elapsed time from dosing will be used to determine all individual PK parameters. A detailed PK analysis plan will be developed prior to conducting analysis.

Table 10: Pharmacokinetic Parameters to be Estimated

Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	The observed time of the maximum concentration
AUC_{last}	Area under the concentration-time curve from time zero to the last measurable plasma concentration-time curve using the linear up log down trapezoidal rule.
AUC_{∞}	Area under the concentration-time curve from time zero extrapolated to infinity using the linear up log down trapezoidal rule.
λz	Terminal-phase rate constant
$t_{½}$	Terminal-phase half-life
MRT	Mean residence time
M/P ratios	Metabolite to parent ratio of AUC and C_{max}

The individual subject concentration-time data will be listed and displayed graphically on linear and semi-log scales. The concentration-time data will be summarized descriptively in tabular and graphical formats (linear and semi-log scales) overlaid by dose level. Individual PK parameters from the noncompartmental PK analysis will be tabulated, where calculable, and summarized descriptively. The following summary statistics will be presented for PK parameters: N, arithmetic mean, CV%, SD of the arithmetic mean, median, minimum, maximum, geometric mean and CV% of the geometric mean. T_{max} will be presented as N, median, minimum and maximum.

Figures illustrating the time course of mean drug concentration vs. time for each regimen will be overlaid and presented for relevant comparisons on linear and semi-logarithmic scales, as appropriate. Other analyses such as exploring the relationship between PK parameters and dose will be conducted, as appropriate. A standalone PK report will be produced.

16. 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.

16.1. Regulations and Guidelines

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

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

See Section 19.2 for additional information.

16.2. Study Initiation

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

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

16.3. Study Documentation

16.3.1. Investigator's Regulatory Documents

The regulatory documents listed below must be received from the Investigator and reviewed and approved by Sunovion or its designee before the clinical site can initiate the study and before Sunovion will authorize shipment of investigational drug to the clinical site. Copies of the

Investigator's regulatory documents must be retained at the clinical site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the APL-130277 IB, copies of regulatory references, copies of IRB/REB/IEC correspondence, and investigational drug accountability records must be retained as part of the Investigator's regulatory documents. It is the Investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

Table 11: 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/REB/IEC Approvals
Signed Financial Disclosure	IRB/REB/IEC 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 Sunovion staff (or designate).

16.3.2. Case Report Forms

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

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

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

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

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

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

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

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. 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, EDC data will be considered complete.

16.3.3. Source Documents

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

16.4. Data Quality Assurance

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

16.4.1. Monitoring the Study

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

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

16.4.2. Routine Data Collection

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

16.4.3. Expedited Data Collection

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

16.4.4. Data Management

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

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

16.4.5. Study Termination

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

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

16.4.6. Clinical Site Closure

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

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

16.4.7. Data Safety Monitoring Board

A DSMB will be utilized in this study in order to monitor subject 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 subject 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 potential outcomes.

The independent statistician will have access to 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.

17. GENERAL CONSIDERATIONS

17.1. Changes to the Protocol

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

17.2. Use of Information and Publication

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

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

Publication or other public presentation of APL-130277 data resulting from this study requires prior review and written approval of Sunovion. Abstracts, manuscripts, and presentation materials should be provided to Sunovion for review at least 30 days prior to the relevant submission deadline.

17.3. Records Retention

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

17.4. Sample Retention

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

17.5. Subject Injury

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

18. REFERENCES

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

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19. APPENDICES

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

For the most current APOKYN® PI, see
https://www.apokyn.com/sites/all/themes/apokyn/content/resources/Apokyn_PI.pdf

For the most current APO-go® SmPC, see https://www.medicines.org.uk/emc/medicine/12941

19.2. APPENDIX II: Regulations and Guidelines

19.2.1. Declaration of Helsinki

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

19.2.2. 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 Sunovion monitor prior to shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval will consist of a completed Institutional Review Board Approval form or Research Ethics Board Approval form, or written documentation from the IRB or REB containing the same information.

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

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

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

19.3. APPENDIX III: Modified Hoehn and Yahr Scale

Modified Hoehn & Yahr

0:	Asymptomatic.
1:	Unilateral involvement only.
1.5:	Unilateral and axial involvement
2:	Bilateral involvement without impairment of balance.
2.5:	Mild bilateral disease with recovery on pull test.
3:	Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.
4:	Severe disability; still able to walk or stand unassisted.
5:	Wheelchair bound or bedridden unless aided.

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

MDS-UPDRS Permissions

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

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July 1, 2008

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

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

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

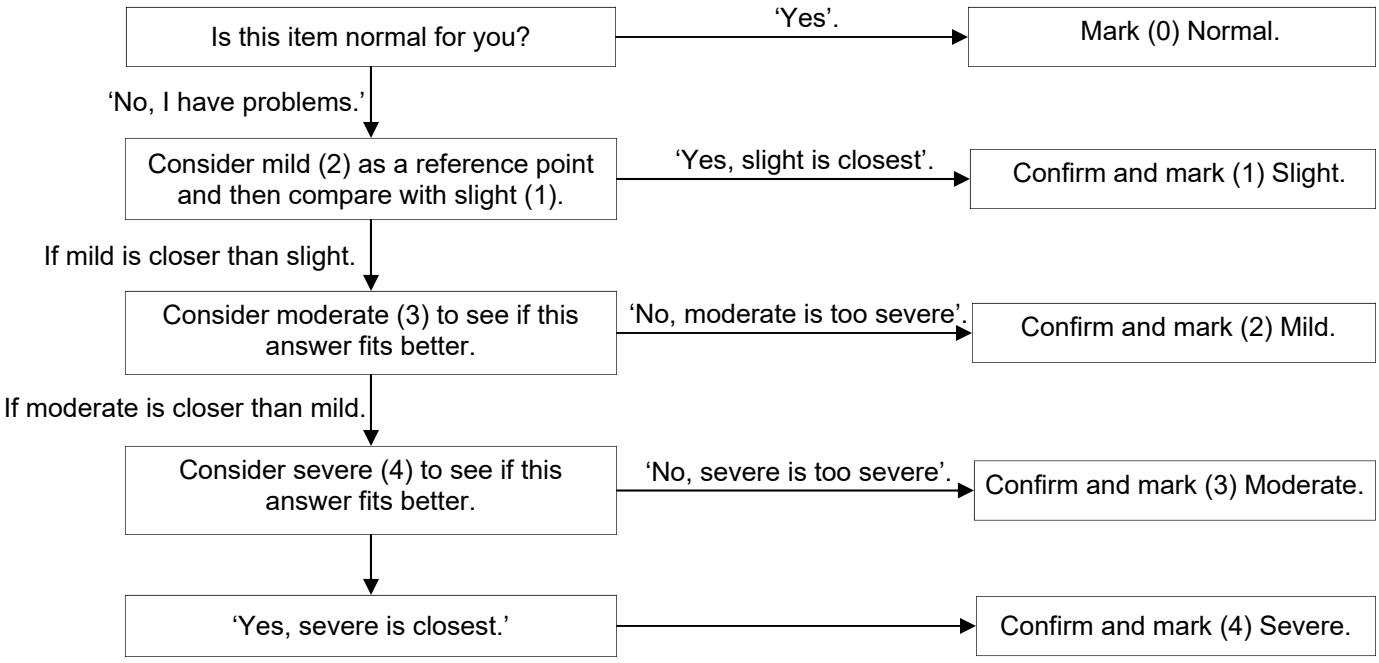
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating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

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

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

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

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



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

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

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

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

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

1.1 COGNITIVE IMPAIRMENT — **SCORE**

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

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

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

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

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

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

SCORE

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

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

0: Normal: No problems present.

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

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

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

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

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

Patient Questionnaire:

Instructions:

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

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

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

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

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

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

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

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

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

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

SCORE

1.7 SLEEP PROBLEMS

Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.

0: Normal: No problems.

1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep.

2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep.

3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night.

4: Severe: I usually do not sleep for most of the night.

☐

1.8 DAYTIME SLEEPINESS

Over the past week, have you had trouble staying awake during the daytime?

0: Normal: No daytime sleepiness.

1: Slight: Daytime sleepiness occurs but I can resist and I stay awake.

2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.

3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people.

4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.

☐

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

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

SCORE

1.13 FATIGUE

Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad

0: Normal: No fatigue.

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

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

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

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

☐

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

2.1 SPEECH

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

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

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

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

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

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

☐

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

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

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

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

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

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

Part III: Motor Examination

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

SCORE

3.3 RIGIDITY

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

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

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

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.

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

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

☐ R

☐ L

SCORE

3.5 HAND MOVEMENTS

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

0: Normal: No problem.

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

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

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

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

☐ R

☐ L

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

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

0: Normal: No problems.

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

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

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

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

☐ R

☐ L

SCORE

3.7 TOE TAPPING

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

0: Normal: No problem.

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

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

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

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

☐ R

☐ L

3.8 LEG AGILITY

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

0: Normal: No problems.

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

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

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

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

☐ R

☐ L

SCORE

3.9 ARISING FROM CHAIR

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

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

☐

3.10 GAIT

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

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

☐

SCORE

3.11 FREEZING OF GAIT

Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment.

0: Normal: No freezing.

1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.

2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.

3: Moderate: Freezes once during straight walking.

4: Severe: Freezes multiple times during straight walking.

☐

3.12 POSTURAL STABILITY

Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13

0: Normal: No problems: Recovers with one or two steps.

1: Slight: 3-5 steps, but subject recovers unaided.

2: Mild: More than 5 steps, but subject recovers unaided.

3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner.

4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.

☐

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

SCORE

3.16 KINETIC TREMOR OF THE HANDS

Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal: No tremor.

1: Slight: Tremor is present but less than 1 cm in amplitude.

2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.

3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.

4: Severe: Tremor is at least 10 cm in amplitude.

☐ R

☐ L

3.17 REST TREMOR AMPLITUDE

Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.
As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

Extremity ratings

0: Normal: No tremor.

1: Slight.: < 1 cm in maximal amplitude.

2: Mild: > 1 cm but < 3 cm in maximal amplitude.

3: Moderate: 3 - 10 cm in maximal amplitude.

4: Severe: > 10 cm in maximal amplitude.

☐ RUE

☐ LUE

☐ RLE

☐ LLE

Lip/Jaw ratings

0: Normal: No tremor.

1: Slight: < 1 cm in maximal amplitude.

2: Mild: > 1 cm but < 2 cm in maximal amplitude.

3: Moderate: > 2 cm but < 3 cm in maximal amplitude.

4: Severe: > 3 cm in maximal amplitude.

☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR

SCORE

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

0: Normal: No tremor.

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

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

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

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

☐

DYSKINESIA IMPACT ON PART III RATINGS

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

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

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

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

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

5: Wheelchair bound or bedridden unless aided.

☐

Part IV: Motor Complications

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

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

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

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

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

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

A . DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

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

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

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

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

SCORE

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

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

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

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

B . MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

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

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

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

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

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

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

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

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

0: Normal: No dystonia OR NO OFF TIME.

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

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

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

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

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

Summary statement to patient: READ TO PATIENT

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

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

MDS UPDRS Score Sheet

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

July 1, 2008

19.5. APPENDIX V: Home Dosing Diary (Sample)

CTH-301 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

- 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.
- Place a checkmark in the appropriate box describing the type of "OFF" you experienced prior to 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	Type of "OFF" Experienced Prior to Dosing
Date: __________ Time: __________ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"	☐ You woke up feeling "OFF" ☐ Your normal PD medication took too long to work ☐ Your normal PD medication stopped working too early ☐ Your normal PD medication didn't work at all ☐ Your normal PD medication suddenly stopped working
Date: __________ Time: __________ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"	☐ You woke up feeling "OFF" ☐ Your normal PD medication took too long to work ☐ Your normal PD medication stopped working too early ☐ Your normal PD medication didn't work at all ☐ Your normal PD medication suddenly stopped working
Date: __________ Time: __________ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"	☐ You woke up feeling "OFF" ☐ Your normal PD medication took too long to work ☐ Your normal PD medication stopped working too early ☐ Your normal PD medication didn't work at all ☐ Your normal PD medication suddenly stopped working
Date: __________ Time: __________ ☐ AM ☐ PM	☐ "ON" ☐ "OFF"	☐ You woke up feeling "OFF" ☐ Your normal PD medication took too long to work ☐ Your normal PD medication stopped working too early ☐ Your normal PD medication didn't work at all ☐ Your normal PD medication suddenly stopped working

19.6. 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 12 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)

Lifetime

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

- ***What did you do?***
- ***Did you_____ as a way to end your life?***
- ***Did you want to die (even a little) when you_____?***
- ***Were you trying to end your life when you _____?***
- ***Or did you think it was possible you could have died from_____?***

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ **No** ☐

Total # of Attempts _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes ☐ **No** ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of interrupted _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of aborted _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ **No** ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ **No** ☐

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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SUICIDAL IDEATION

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

Since Last Visit

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

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

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

Most Severe Ideation: _____ _____

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

Most Severe

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

____

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

____

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

____

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

____

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

____

SUICIDAL BEHAVIOR

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

Since Last Visit

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you_____ as a way to end your life?

Did you want to die (even a little) when you_____?

Were you trying to end your life when you _____?

Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ **No** ☐

Total # of Attempts: _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes ☐ **No** ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of interrupted: _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of aborted: _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ **No** ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ **No** ☐

Suicide:

Yes ☐ **No** ☐

Answer for Actual Attempts Only

Most Lethal Attempt Date: _____

Actual Lethality/Medical Damage:

Enter Code: _____

0. No physical damage or very minor physical damage (e.g., surface scratches).
1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).
2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).
3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).
4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).
5. Death

Potential Lethality: Only Answer if Actual Lethality=0

Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).

Enter Code: _____

0 = Behavior not likely to result in injury
1 = Behavior likely to result in injury but not likely to cause death
2 = Behavior likely to result in death despite available medical care

19.7. APPENDIX VII: Parkinson's Disease Questionnaire (PDQ-39)

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

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

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1.	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2.	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3.	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4.	Had problems walking half a mile?	☐	☐	☐	☐	☐
5.	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6.	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7.	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8.	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question*** before going onto the next page.

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

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always or cannot do at all
9.	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10.	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11.	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12.	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13.	Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
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 check that you have ***ticked one box for each question***
before going onto the next page.

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

*Please **tick 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 conceal 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 by other people's reaction to you?	☐	☐	☐	☐	☐
27.	Had problems with your close personal relationships?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

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

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
28.	Lacked support in the ways you need from your spouse or partner? *If you do not have a spouse or partner, please tick here* ☐	☐	☐	☐	☐	☐
29.	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐
30.	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31.	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32.	Felt your memory was bad?	☐	☐	☐	☐	☐
33.	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34.	Had difficulty with your speech?	☐	☐	☐	☐	☐
35.	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***
before going onto the next page.

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

*Please **tick one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
36.	Felt ignored by people?	☐	☐	☐	☐	☐
37.	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38.	Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39.	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Please check that you have ***ticked one box for each question***.

Thank you for completing the questionnaire.

19.8. APPENDIX VIII: Clinical Global Impression (CGI)

Screening # _____ Site #_____ Investigator: _____

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: _____

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

19.9. APPENDIX IX: Patient Global Impression (PGI)

Screening # _____ Site #_____ Investigator: _____

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: _____

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

19.10. APPENDIX X: Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

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

This refers to your usual way of life in recent times.

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

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

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

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

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre 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, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

19.11. APPENDIX XI: Zarit Burden Interview (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

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

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

19.12. APPENDIX XII: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (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)**

19.13. APPENDIX XIII: European Quality of Life – 5 Dimensions (EQ-5D)

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

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

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

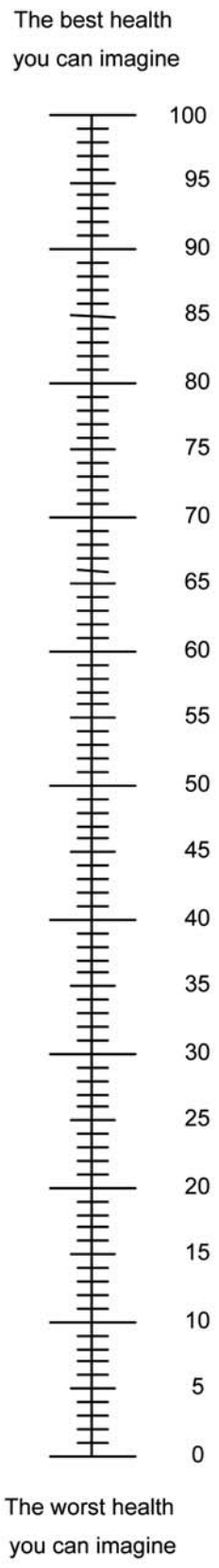
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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= ☐



19.14. 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. *J Neurol Neurosurg Psychiatry.* 1992;55(3):181-4.

19.15. APPENDIX XV: Ease of Use Questionnaire

CTH-301 Ease of Use Questionnaire

Date: _____

Instructions:

Please base your response on your experience over your entire time in the study.

Under each heading, please tick the ONE box that best describes your assessment of the medication and its use.

OPENING THE PACKAGE	
Very easy to open	❑
Easy to open	❑
Neither easy nor difficult to open	❑
Difficult to open	❑
Very difficult to open	❑

HANDLING	
Very easy to handle	❑
Easy to handle	❑
Neither easy nor difficult to handle	❑
Difficult to handle	❑
Very difficult to handle	❑

DOSING	
Very easy to dose myself	❑
Easy to dose myself	❑
Neither easy nor difficult to dose myself	❑
Difficult to dose myself	❑
Very difficult to dose myself	❑