APL-130277

Apomorphine Hydrochloride

Clinical Study Protocol CTH-302

PHASE 3

An Open-Label, Randomized, Crossover Trial utilizing a Single-Blinded Rater to evaluate APL-130277 compared to s.c. Apomorphine in Levodopa Responsive Subjects with Parkinson's Disease Complicated by Motor Fluctuations

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SUNOVION PHARMACEUTICALS INC.
84 Waterford Drive
Marlborough, MA 01752, USA
+1 (508) 481-6700

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	Executive Director Clinical Development, Psychiatry Sunovion Pharmaceuticals Inc.	
Medical Monitor	Executive Medical Director Syneos Health France SARL	
SAE/AESI/Pregnancy Reporting	PPD Pharmacovigilance (PVG)	

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product:
APL-130277

Name of Active Ingredient:
apomorphine hydrochloride

Title of Study:
An Open-Label, Randomized, Crossover Trial utilizing a Single-Blinded Rater to evaluate APL-130277 compared to s.c. Apomorphine in Levodopa Responsive Subjects with Parkinson's Disease Complicated by Motor Fluctuations

Proposed Indication:
"OFF" episodes associated with Parkinson's disease (PD).

Study Centers:
This multicenter study will be conducted at approximately 30 sites in Europe.

Planned Study Period:
July 2018 to December 2021

Phase of Development:
Phase 3

Study Objectives:

Primary Objectives:

The primary objective is to demonstrate the efficacy of sublingual (sl) APL-130277 compared to subcutaneous (sc) apomorphine as a treatment of "OFF" episodes in subjects with Parkinson's Disease (PD) as measured by the change from pre-dose to 90 minutes post-dose in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score.

Secondary Objectives:

The secondary objectives are to demonstrate the efficacy of sublingual (sl) APL-130277 compared to subcutaneous (sc) apomorphine as a treatment of "OFF" episodes in subjects with Parkinson's Disease (PD) as measured by:

- Durability of effect, defined as Investigator confirmed full "ON" within 30 minutes post dose and at 90 minutes post-dose;
- Subject preference for APL-130277 after the subject has completed both APL-130277 and s.c. apomorphine treatment regimens;
- Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose;
- Patient Global Impression of Change of "OFF" episodes (PGI-C).

Safety Objectives:

To evaluate the safety and tolerability of sl APL-130277 at doses of 10 to 30 mg compared to s.c. apomorphine at doses of 2 to 6 mg during titration and the maintenance treatment period through the assessment of: adverse events (AE) with attention to nausea, vomiting, hypotension, syncope, dyskinesia and impulse control disorders; physical examinations (PE) including oropharyngeal and injection site reactions; electrocardiogram (ECG) derived morphology and conduction parameters; vital signs including orthostatic hypotension (OH); frequency of domperidone use; clinically significant changes in laboratory tests; incidence of suicidal thoughts and actions as assessed by the

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Columbia Suicide Severity Rating Scale (C-SSRS); and impulsivity as measured by the Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).

Pharmacokinetic Objectives:

To assess the pharmacokinetics (PK) for apomorphine and metabolites (apomorphine sulfate, norapomorphine, and others as deemed necessary) from plasma samples following dosing with sl APL-130277 and s.c. apomorphine.

Study Design:

This is a two part study: PART A and PART B.

PART A

PART A consists of an open label, crossover titration phase where eligible subjects will be randomized to 1 of 2 treatment sequences in a 1:1 ratio to sl APL-130277 followed by s.c. apomorphine or s.c. apomorphine followed by sl APL-130277. Subjects will undergo dose titration with the first assigned study treatment (APL-130277 or s.c. apomorphine) to tolerance and effect, ie, the tolerable dose that turns the subject from the practically defined "OFF" state to the full "ON" state as determined by both the Investigator and subject. The subject will then be crossed over to the other assigned study treatment (APL-130277 or s.c. apomorphine) and similarly titrated to tolerance and effect. The doses of APL-130277 and s.c. apomorphine determined as optimal in PART A will be used during PART B.

For both APL-130277 and sc apomorphine, the subject must achieve a full "ON" within 30 minutes of dosing. Depending on the magnitude and duration of the full "ON" response, the Investigator has the option of uptitrating the subject to the next higher dose of either APL-130277 or s.c. apomorphine (not to exceed 30 mg or 6 mg, respectively) in order to assess whether the subject has an improved "ON" (determined by the onset, magnitude and duration of effect as measured by the MDS-UPDRS part III and ON/OFF response). Further uptitrations to higher doses should be performed if the investigator deems the subject's "ON" responses are inadequate. The subject must be in a full "OFF" state prior to uptitration. The effective dose for both APL-130277 and s.c. apomorphine must be approved by the medical monitor based on review of the titration data including MDS-UPDRS Part III and ON/OFF data prior to randomization.

To the extent possible, the investigator should titrate the subject to comparable dose levels for both APL-130277 and sc apomorphine.

Antiemetic (domperidone) can be used prophylactically or if clinically warranted, at the Investigator's discretion.

<u>APL-130277 Dose Titration</u>

The titration of APL-130277 will start in the clinic at 10 mg, while the subject is in a practically defined "OFF" state after withholding Parkinson's disease medication beginning at midnight the night before. If the subject fails to convert from a practically defined "OFF" to a full "ON" within 30 minutes (per both the Investigator and subject), the subject will be instructed on how to self-administer increasing doses of APL-130277 and will continue the titration process at home.

If the 10 mg dose of APL-130277 results in a full "ON" within 30 minutes (per both the Investigator and subject), but not an optimal full "ON" response, unless there are safety/tolerability concerns, the next higher dose, 15 mg, should be administered at home in order to assess for an optimal "ON"

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response. Uptitration in 5 mg increments should continue at home until the subject achieves the optimal "ON" response.

The site will contact the subject daily to determine the titration response and query for tolerability/safety issues. If the site, ascertains the dose of APL-130277 provides an optimal ON response, the subject will return to the clinic for a Dose Confirmatory Visit (DCV) within 5-7 days of APL Titration Visit (TV) 1, or earlier as determined by the investigator, to confirm the efficacy and tolerability of the selected dose. If the investigator deems the ON response inadequate during the DCV, the subject may continue uptitration in clinic during the subject's next full OFF state or at home. Following further uptitration at home, additional DCVs should take place at the clinic within 5 days of one another.

If the Investigator determines there are tolerability issues with APL-130277 during home titration, the subject will be instructed to withhold further administration of APL-130277 and come to the clinic for an unscheduled clinic visit.

A schematic showing the flow of APL-130277 titration is shown in Figure 1.

Subcutaneous Apomorphine Dose Titration

For de novo subjects, titration with s.c. apomorphine will take place in the clinic only, starting at 2 mg.

Subject taking s.c. apomorphine prior to screening are allowed in the study. Following a washout period of at least 1 day, subjects must enter titration at the dose they were taking prior to screening . Uptitration may take place at the investigator's discretion.

Schematics showing the flow of s.c. apomorphine titration is shown in Figure 2 and Figure 3.

PART B

Following a 3 to 7 day washout period, eligible subjects will enter PART B of the study and be randomized to 1 of 2 treatment sequences in a 1:1 ratio; 4-weeks of open-label treatment with sl APL-130277 followed by 4-weeks of open-label treatment with s.c. apomorphine, or 4-weeks of open label treatment with s.c. apomorphine followed by 4-weeks of open-label treatment with sl APL-130277.

Subjects will be instructed to continue with their regular PD medication regimen(s), and to dose themselves with their randomized open-label study treatment (APL-130277 or s.c. apomorphine) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) during the waking day. Subjects will be instructed to dose up to 5 "OFF" episodes per day and to complete a daily home dosing diary. APL-130277 and sc apomorphine doses must be separated by at least 2 hours in-clinic.

During the 4-week treatment period, subjects will return to the clinic for safety and efficacy assessments at 2-week intervals. Subjects will attend the clinic visits in the morning after withholding antiparkinsonian medications, including APL-130277 and s.c. apomorphine, beginning at midnight the night before the visit. The subject must be in the full "OFF" state prior to performing study assessments at clinic visits. If a subject is not in the full "OFF" state, the clinical site should wait until subject is in the full "OFF" state before performing study assessments at the clinic visits. Alternatively, the subject may return to the clinic the following day for study assessments in the Full "OFF" state.

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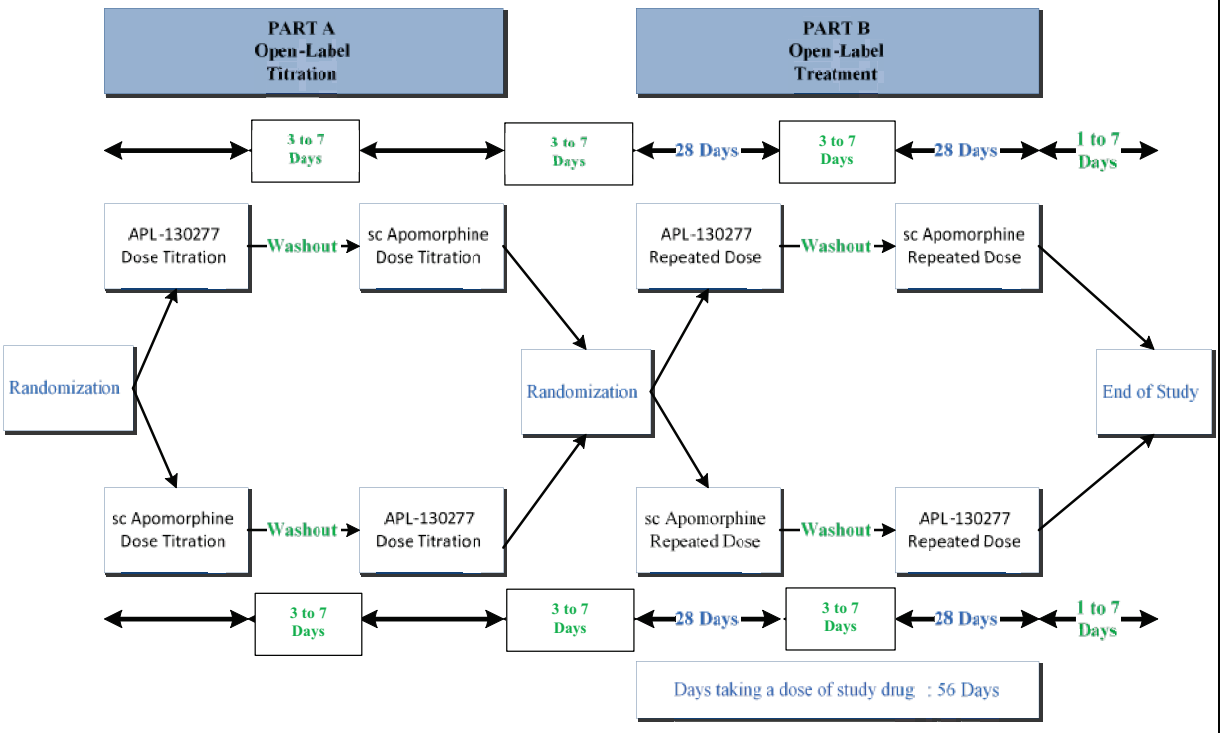
In PART B, the MDS-UPDRS Part III, CGI-S, CGI-I, and ON/OFF assessment will be assessed by a rater blinded to the subject's study treatment. The rater's blind in PART B will be maintained by:

- Ensuring the blinded rater does not witness the in-clinic dosing;
- Ensuring any visible injection sites are covered by the subject's clothing (or other item, eg, hospital gown, robe, etc.);
- Because sublingually dosed APL-130277 can leave blue residue on the subject's tongue, when the subject is dosed in-clinic with s.c. apomorphine, he/she will also be sublingually administered Placebo APL-130277;
- The site will take steps to protect source data and eCRFs to ensure the blinded rater does not become aware of the subject's study treatment at any time during the study.

Selected sites will also collect pre- and post-dose samples for pharmacokinetic (PK) analysis for apomorphine and metabolites.

The subject will then be crossed over to the other study treatment (APL-130277 or s.c. apomorphine) for additional 4-weeks of open-label treatment, with subjects returning to the clinic for safety and efficacy assessments throughout the treatment period.

Study Schematic



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Number of Subjects (planned):
A total of approximately 106 subjects will be randomized into the open-label dose titration phase (PART A).

Diagnosis and Main Criteria for Subject Inclusion:

Principal Inclusion Criteria:

- The subject (and caregiver, if applicable) must be fully informed of and understand the objectives, procedures, and possible benefits and risks of the study, and give written informed consent prior to performing any study-related activities.
- Male or female subject ≥ 18 years of age with a clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria, who have a clinically meaningful response to L-Dopa as determined by the Investigator.
- Subjects at Screening must demonstrate an adequate L-Dopa response on the MDS-UPDRS Part III in the "ON" state compared to the MDS-UPDRS Part III in the "OFF" state and on the Hoehn and Yahr, as determined during the review by Enrollment Adjudication Committee (EAC), Sponsor, and Medical Monitor.
- Receiving stable doses of L-Dopa/carbidopa and/or L-Dopa/benserazide and/or L-Dopa/carbidopa/entacapone (immediate or chronic release) 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 are permitted but must be maintained at a stable dose for at least 4 weeks prior to SV1 with the exception of monoamine oxidase B (MAO-B) inhibitors, which must be maintained at a stable level for at least 8 weeks prior to SV1. Use of Madopar PRN in the 4 weeks prior to screening is permitted. Current use of sc apomorphine by injection at the time of screening is permitted.
- Subjects must experience at least one well defined "OFF" episode per day and have a total daily "OFF" time duration of ≥ 2 hours, based on judgment of physician and subject self-assessment.
- Stage III or less on the modified Hoehn and Yahr scale in the "ON" state.
- Mini–Mental State Examination (MMSE) score > 25.

Principal Exclusion Criteria:

- Atypical or secondary parkinsonism.
- Major focal brain disorders including malignancy or stroke.
- Prior treatment with any of the following: a neurosurgical procedure for PD; continuous subcutaneous (sc) apomorphine infusion; Duodopa/Duopa; or APL-130277.
- Subjects who have permanently stopped use of sc apomorphine injection.

Investigational Product, Dosage and Mode of Administration:
APL-130277 (10 mg, 15 mg, 20 mg, 25 mg, 30 mg), sublingual.

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Duration of Treatment:
The approximate maximum duration of participation in this study from Screening until study completion is 141 days (Up to 59 days in Screening and PART A, Up to 82 days in PART B and End of Study Visit), including up to 7-day washout periods between cross-over periods.

Reference Therapy, Dosage and Mode of Administration:
Subcutaneous apomorphine (2 mg, 3 mg, 4 mg, 5 mg and 6 mg), subcutaneous injection.

Placebo APL-130277 (for blinding and training purposes): will be identical in appearance, size and color to APL-130277, but contain no active ingredient, sublingual.

Selected Concomitant Medications:

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

- Any selective $5HT_3$ antagonist (eg, ondansetron, granisetron, dolasetron, palonosetron, alosetron) from 30 days prior to SV1 until study completion.
- Any dopamine antagonists (excluding domperidone) or dopamine depleting drugs excluding anticholinergics and/or antihistamines with anticholinergic effects.
- As needed use of medications for treating, "OFF" episodes during the trial, including Madopar is prohibited.

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

- Antiemetic therapy with domperidone is optional and can be initiated prophylactically or if clinically warranted at the Investigator's discretion. If initiated, antiemetic therapy should be stopped when judged clinically appropriate. Domperidone is not typically used for longer than 7 days of continuous use. Domperidone use can exceed 7 days continuous use with approval of the Medical Monitor, in line with local regulations.
- Stable doses of an L-Dopa formulation with or without other stable adjunctive PD therapies (from at least 4 weeks prior to SV1 with no planned medication changes during the study).

Benzodiazepines, opiates, and oxycodone, and will be allowed provided the subject has been on a stable dose for 4 weeks prior to SV1, provided the subject has a valid prescription. See Section 10.3 for additional information.

Study Endpoints:

Primary Efficacy Endpoint:

The primary efficacy variable is the change from pre-dose to 90 minutes post-dose in MDS-UPDRS Part III score after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at V3 and V6 of PART B).

Secondary Efficacy Endpoints:

- Durability of effect, defined as an Investigator confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at V3 and V6 of PART B).

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- Subject preference for APL-130277 treatment (either somewhat or definitely prefer APL) as recorded for question 9 of the TPQ. This assessment is scheduled to be performed after the subject has completed both APL-130277 and s.c. apomorphine treatment regimens (assessed in clinic at V6 of PART B).
- Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).
- Patient Global Impression of Change (PGI-C): Subject improvement of "OFF" episodes, defined as very much better, much better or a little better after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).

Other Efficacy Endpoints (PART B):

- Other efficacy variables will include analysis of: Clinical Global Impression of Improvement (CGI-I), MDS-UPDRS – Parts I, II, III, and IV Score, Time to Full and Partial "ON", Expanded Home Dosing Diaries including percent of "ON" episodes without troublesome dyskinesia based on the 3 consecutive days prior to V2, V3, V5, and V6, dyskinesia questionnaire, Parkinson's Disease Questionnaire-39 (PDQ-39) Total Index Score and subscale scores, European Quality of Life – 5 Dimensions (EQ-5D-5L), and Ease of Use questionnaire.

Methodology concerning the analysis of these variables will be provided in the Statistical Analysis Plan (SAP).

Safety Endpoints:

Evaluation of safety and tolerability of APL-130277 compared to s.c. apomorphine as measured by AEs, physical examination including assessment of oropharyngeal AEs and injection-site related AEs, 12-lead ECGs, vital signs including OH, clinical laboratory tests, and C-SSRS and QUIP-RS assessments.

Pharmacokinetic Endpoints:

Pharmacokinetic concentration-time data for apomorphine and metabolites (apomorphine sulfate, norapomorphine, and others as deemed necessary) will be evaluated and PK parameters (including but not limited to C_{max}, t_{max}, AUC_t, parent-to-metabolite ratios of C_{max} and AUC_t) will be estimated by noncompartmental methods from plasma samples using actual elapsed time from dosing. Details and methodology concerning the analysis of these variables will be provided in a separate PK analysis plan. A separate and stand-alone PK report will be provided.

Statistical Methods:

General Statistical Methods
Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Standard error of the mean (SEM) will also be provided for summaries of efficacy data, if relevant. Descriptive statistics for categorical data will include frequency counts and percentages. The total number of subjects in the treatment group overall (N) will be used as the denominator for percent calculations, unless stated otherwise. Statistical testing will be 2-sided using a 5% significance level, unless otherwise specified.

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Efficacy Analyses

The efficacy analyses will be performed using the modified intent to treat (mITT) populations defined in Section 15.2.2. The primary and secondary endpoints will be tested in hierarchical order to maintain an overall type I error rate of 0.05. The primary endpoint will be tested first. If there is a statistically significant treatment difference, the following secondary endpoints will be tested sequentially for statistical significance in the hierarchical order shown below:

1. Durability of effect, defined as an Investigator confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at V3 and V6 of PART B);
2. Subject preference for APL-130277 treatment (either somewhat or definitely prefer APL-130277) after the subject has completed both APL-130277 and s.c. apomorphine treatment regimens (assessed in-clinic at V6 of PART B);
3. Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B);
4. Patient Global Impression of Change (PGI-C): Subject improvement of "OFF" episodes, defined as very much better, much better or a little better after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).

The primary endpoint will be analyzed in the PART B mITT population and compared between the treatment groups using a linear mixed model (SAS Mixed procedure), as described by Tao et al. (2015). The mixed model for the change from pre-dose to 90 minutes in the MDS-UPDRS Part III score as the response outcomes, includes the following variables: treatment group, visit week (0, 2, 4), treatment by visit week interaction, PART B sequence and period as fixed factors. The Week 0 visit pre-dose MDS-UPDRS Part III motor score will be used as a covariate. Subject nested within the PART B sequence will be included as a random effect and an AR(1) covariance structure will be used for the repeated measures over time (visit week). The Kenward-Roger (KR) method will be used to calculate degrees of freedom. The least square (LS) mean, standard error, and LS mean treatment difference, along with the 95% confidence interval (CI) and p-value will be provided.

Safety Analyses

Safety data will be summarized descriptively in the safety populations defined in Section 15.2.1 according to treatment received. Safety data will generally be summarized separately for study PART A and PART B.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events (AEs) that start after the subject receives the first dose of study treatment will be summarized. PART A AEs are defined as all AEs that start on or after the date of the first dose of study drug (APL-130277 or s.c. apomorphine) in PART A, but before the date of the first dose of study drug in PART B. PART B AEs are defined as all AEs that start on or after the date of the first dose of study drug in PART B. Within each part of the study, the AE will be assigned to the study treatment (APL-130277 or s.c. apomorphine) that was given during the day of the AE onset (or the last study treatment that was given before the onset of the AE). AEs will be summarized by SOC and PT and by treatment group. AEs with onset after the last dose of the study treatment are attributed to the treatment received during the last treatment period. Both event and subject counts, where applicable,

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will be summarized. The counts will be complemented by percentages calculated for the subject counts unless otherwise specified.

Orthostatic hypotension will be defined as a reduction in systolic BP of 20 mmHg or more, and/or a reduction in diastolic BP of 10 mmHg or more, for the standing measurement compared to the supine measurement. The proportion of subjects with orthostatic hypotension will be tabulated by visit and time point, by treatment group. In addition, other continuous safety parameters (clinical laboratory values, vital signs, ECGs) will be summarized descriptively including the change from study baseline and/or pre-dose at each visit.

Sample Size:

The initial sample size calculation is based on the primary endpoint of the study, the mean change from pre-dose in MDS-UPDRS Part III Motor Examination score at 90 minutes post-dose, evaluated at V3 and V6 in PART B. Assuming that the discontinuation rate is 25% in PART A, a total of 106 subjects will be randomized into PART A, so that at least 80 subjects are randomized into PART B. Assuming a 30% discontinuation rate in PART B, approximately 55 subjects are expected to complete PART B. With 55 subjects, the study has 90% power to detect a mean treatment difference between APL-130277 and s.c. apomorphine of 5.5 points for the change in MDS-UPDRS Part III score, assuming a standard deviation of 12 points for the period differences in PART B. The expected mean treatment difference of at least 5.5 points for the change in MDS-UPDRS Part III Score was based on the results of the CTH-300 study comparing APL-130277 to placebo. Per the literature, the change in MDS-UPDRS Part III Score following administration with s.c. apomorphine is similar to placebo at 90 minutes post-dose. A blinded sample size re-assessment (b-SSR) will be performed to assess assumptions regarding nuisance parameters in the above calculation (see Section 15.1).

Table 2: Schedule of Assessments – PART A

Procedure	Screening[a]		Randomization Procedures	APL-130277 Dose Titration[b]					3 to 7 days Washout	s.c. apomorphine Dose Titration[b]		3 to 7 days Washout
	Screening Visit 1	Screening Visit 2		Titration Visit 1	Telephone Calls	Dose Confirmation Visit 1	Additional (if necessary)– Telephone calls[dd]	Additional (if necessary) Dose Confirmation Visit 2 to 4		Titration Visit 1[c]	Titration Visit 2[c] (if needed)	
Study Visit	**SV1**	**SV2**		**APL TV1**	**T1-T3**	**APL DCV1**	**T4-T6**	**APL DCV2-DCV4**		**SC TV1**	**SC TV2**	
Study Day	**-21 to -6**			**1**	**2-5**	**varies[c]**	**varies[c]**	**varies[c]**		**1**	**2**	
In-Clinic Visit	X	X		X		X		X		X	X	
Written Informed Consent	X											
Review Entry Criteria	X	X										
Randomization			X									
Medical History/Demographics	X											
Complete Physical Exam, including Oropharyngeal Site Exam[d]	X											
Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam[e]				X		X		X		X	X	
Body Mass Index (BMI), weight and height[f]	X											
Vital Signs[g,h]	X			X		X		X		X	X	
12-Lead Electrocardiogram (ECG)[h,i]	X			X		X		X		X	X	
Clinical Laboratory Tests[j]	X											
Mini-mental State Examination (MMSE)[h]	X											

Table 2: Schedule of Assessments – PART A (Continued)

Procedure	Screening[a]		Randomization Procedures	APL-130277 Dose Titration[b]					3 to 7 days Washout	s.c. apomorphine Dose Titration[b]		3 to 7 days Washout
	Screening Visit 1	Screening Visit 2		Titration Visit 1	Telephone Calls	Dose Confirmation Visit 1	Additional (if necessary)– Telephone calls[dd]	Additional (if necessary) Dose Confirmation Visit 2 to 4		Titration Visit 1[c]	Titration Visit 2[c] (if needed)	
Study Visit	**SV1**	**SV2**		**APL TV1**	**T1-T3**	**APL DCV1**	**T4-T6**	**APL DCV2-DCV4**		**SC TV1**	**SC TV2**	
Study Day	**-21 to -6**			**1**	**2-5**	**varies[c]**	**varies[c]**	**varies[c]**		**1**	**2**	
Modified Hoehn and Yahr (in the "OFF" state)		**X**										
Subject "OFF" versus "ON" Training		**X**										
MDS-UPDRS Parts I and II	X											
MDS-UPDRS Part IV	**X**											
MDS-UPDRS Part III[h,k]		**X**		**X**		**X**		**X**		**X**	**X**	
Levodopa (L-Dopa) Challenge[bb]		**X**										
Modified Hoehn and Yahr (in the "ON" state)	**X**	**X**										
In-Clinic Dosing of Study Drug[l]				**X**		**X**		**X**		**X**	**X**	
Investigator rating of "OFF" or "ON"[m]		**X**		**X**		**X**		**X**		**X**	**X**	
Subject rating of "OFF" or "ON"[n]		**X**		**X**		**X**		**X**		**X**	**X**	
Post-dose Assessment of Dyskinesia[o]		**X**		**X**		**X**		**X**		**X**	**X**	
Dispense Study Drug for Outpatient Dosing				**X[p]**		**X[u]**		**X[u]**				

Table 2: Schedule of Assessments – PART A (Continued)

Procedure	Screening[a]		Randomization Procedures	APL-130277 Dose Titration[b]					3 to 7 days Washout	s.c. apomorphine Dose Titration[b]		3 to 7 days Washout
	Screening Visit 1	Screening Visit 2		Titration Visit 1	Telephone Calls	Dose Confirmation Visit 1	Additional (if necessary)– Telephone calls[dd]	Additional (if necessary) Dose Confirmation Visit 2 to 4		Titration Visit 1[c]	Titration Visit 2[c] (if needed)	
Study Visit	**SV1**	**SV2**		**APL TV1**	**T1-T3**	**APL DCV1**	**T4-T6**	**APL DCV2-DCV4**		**SC TV1**	**SC TV2**	
Study Day	**-21 to -6**			**1**	**2-5**	**varies[c]**	**varies[c]**	**varies[c]**		**1**	**2**	
Collect Study Drug and Perform Drug Accountability						X		X				
APL-130277 self-administration Training				X[p]		X[u]		X[u]				
Home Dosing Diary Training[q]				X[p]		X[u]		X[u]				
Provide Home Dosing Diary[r]				X[p]		X[u]		X[u]				
Collect and Review Home Dosing Diary						X		X				
Columbia Suicide Severity Rating Scale (C-SSRS)[s,h]	X			X		X		X		X	X	
Adverse event monitoring	X	X		X	X	X	X	X		X	X	
Prior/concomitant medication review	X	X		X	X	X	X	X		X	X	

Abbreviations: DCV = dose confirmation visit; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; SC = subcutaneous; SV = screening visit; T = telephone call; TV = titration visit.

Table Footnotes

Table 3: Schedule of Assessments – PART B

Procedure	Open-Label Crossover Period 1					*3 to 7 Days Washout*	Open-Label Crossover Period 2					End of Study Visit	Early Termination[x]	Dose Reduction Visit[y]
	Clinic Visit 1	Telephone call	Clinic Visit 2	Telephone call	Clinic Visit 3		Clinic Visit 4	Telephone call	Clinic Visit 5	Telephone call	Clinic Visit 6			
Study Visit	**V1**	**T1**	**V2**	**T2**	**V3**		**V4**	**T3**	**V5**	**T4**	**V6**	**EOS**	**ET**	
Day (± 3)	**1**	**10**	**14**	**24**	**28**		**35**	**45**	**49**	**59**	**63**	**71**	**NA**	**NA**
In-Clinic Visit	X		X		X		X		X		X	X	X	X
Randomization	X													
IXRS system for new dose														X
Complete Physical Exam, including Oropharyngeal and Injection Site Exam[d]												X	X	
Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam[e]	X		X		X		X		X		X			
Weight												X	X	
Vital Signs[g,h]	X		X		X		X		X		X	X	X	X
12-Lead Electrocardiogram (ECG)[h,i]	X				X		X				X	X	X	
Clinical Laboratory Tests[j]	X						X					X	X	
MDS-UPDRS Parts I, II and IV			X		X				X		X			
MDS-UPDRS Part III[h,k]	X		X		X		X		X		X			
In-Clinic Dosing of Study Drug[l]	X		X		X		X		X		X			
Investigator rating of "OFF" or "ON"[m]	X		X		X		X		X		X			
Subject rating of "OFF" or "ON"[n]	X		X		X		X		X		X			

Table 3: Schedule of Assessments – PART B (Continued)

Procedure	Open-Label Crossover Period 1					*3 to 7 Days Washout*	Open-Label Crossover Period 2					End of Study Visit	Early Termination[x]	Dose Reduction Visit[y]
	Clinic Visit 1	Telephone call	Clinic Visit 2	Telephone call	Clinic Visit 3		Clinic Visit 4	Telephone call	Clinic Visit 5	Telephone call	Clinic Visit 6			
Study Visit	**V1**	**T1**	**V2**	**T2**	**V3**		**V4**	**T3**	**V5**	**T4**	**V6**	**EOS**	**ET**	
Day (± 3)	**1**	**10**	**14**	**24**	**28**		**35**	**45**	**49**	**59**	**63**	**71**	**NA**	**NA**
Post-dose Assessment of Dyskinesia[o]	X		X		X		X		X		X			
Self-administration Training	X						X							
Dispense Study Drug for Outpatient Dosing[aa]	X		X				X		X					X
Collect Study Drug and Perform Drug Accountability[aa]			X		X				X		X		X	X
Home Dosing Diary Training[q]	X						X							
Provide Home Dosing Diary[r]	X		X				X		X					X
Collect and Review Home Dosing Diary			X		X				X		X		X	X
Columbia Suicide Severity Rating Scale (C-SSRS)[s,h]	X		X		X		X		X		X	X	X	X
Dyskinesia Questionnaire					X						X		X[w]	
Parkinson's Disease Quality of Life Questionnaire (PDQ-39)[h]	X				X						X		X[w]	
Patient Global Impression of Severity (PGI-S)[h]	X													
Patient Global Impression of Change (PGI-C)[h]					X						X		X[w]	
Clinical Global Impression of Severity (CGI-S)	X													
Clinical Global Impression of Improvement (CGI-I)					X						X		X[w]	

Table 3: Schedule of Assessments – PART B (Continued)

Procedure	Open-Label Crossover Period 1					*3 to 7 Days Washout*	Open-Label Crossover Period 2					End of Study Visit	Early Termination[x]	Dose Reduction Visit[y]
	Clinic Visit 1	Telephone call	Clinic Visit 2	Telephone call	Clinic Visit 3		Clinic Visit 4	Telephone call	Clinic Visit 5	Telephone call	Clinic Visit 6			
Study Visit	**V1**	**T1**	**V2**	**T2**	**V3**		**V4**	**T3**	**V5**	**T4**	**V6**	**EOS**	**ET**	
Day (± 3)	**1**	**10**	**14**	**24**	**28**		**35**	**45**	**49**	**59**	**63**	**71**	**NA**	**NA**
Caregiver Burden (Zarit Burden Interview [ZBI])[t]	X				X						X		X[w]	
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS)[h]	X				X		X				X		X[w]	
European Quality of Life – 5 Dimensions (EQ-5D-5L)[h]	X				X						X		X[w]	
Treatment Satisfaction Questionnaire for Medication (TSQM)[h]					X						X		X[w]	
Treatment Preference Questionnaire											X		X[z]	
Ease of Use Questionnaire					X						X		X[cc]	
Adverse event monitoring	X	X	X	X	X		X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X		X	X	X	X	X	X	X	X
Pharmacokinetic sampling[v]			X		X				X		X			

Abbreviations: IXRS = Interactive X Response System; MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale; NA = not applicable; sc = Subcutaneous; T = telephone call; V = visit.

Note: If a subject attends a clinic visit (except SV1) in the morning after withholding antiparkinsonian medications, including APL-130277 and s.c. apomorphine, from midnight before the visit and the subject's full "OFF" was not identified, the site should wait until full subject is in the full "OFF" state before performing study assessments; to facilitate scheduling, the subject may return to the clinic the following day if it is not possible to remain in clinic until 'OFF'.

[a] All screening procedures to be conducted within 21 days prior to TV1. SV2 must be completed at least 6 days before TV1 in order for the Enrollment Adjudication Committee to review subject data and give go-ahead for subject to be randomized. If TV1 is required to occur more than 21 days after SV1,

medical Monitor approval is required. Screening procedures may occur at either SV1 or SV2, except L-Dopa challenge and related procedures which must be performed at SV2. Screening procedures **must be** performed while subject is in the "ON" state with the exception of the L-Dopa challenge and related procedures.

[b] Subjects will be randomized to the order they receive open-label APL-130277 and s.c. apomorphine. Subjects may not need to attend all titration days/visits or have all telephone calls.

[c] If the site ascertains the dose provides an optimal ON response within 30 minutes and provides an optimal response with respect to onset, magnitude, and duration of response, the subject will return to the clinic for a Dose Confirmation Visit (DCV) within 5-7 days of APL TVI or earlier as determined by the Investigator. The subject cannot move on to the next phase of the study until approval is obtained from the Medical Monitor. If the investigator deems the ON response inadequate during the DCV, the subject may continue uptitration in clinic during the subject's next full OFF state or at home. Following further uptitration at home, additional DCVs should take place within 5 days of one another.

[d] 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 assessment. Skin assessment should include visual inspection of s.c. apomorphine injection sites. 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. Physical examination to be completed by unblinded rater.

[e] During PART A, abbreviated physical examination to include head-eyes-ears-nose and throat; heart; lungs; abdomen; and skin. Subjects will have a predose examination within 30 minutes prior to administration of the first dose and 50 minutes post dosing. During PART B, abbreviated physical examination to include head-eyes-ears-nose and throat; heart; lungs; abdomen; and skin; to be done within 30 minutes prior to dosing and 120 minutes 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. Skin assessment should include visual inspection of s.c. apomorphine injection sites. Assessment to be completed by an unblinded rater.

[f] Both height and weight captured at Screening to calculate BMI; only weight will be recorded at the EOS or ET visit.

[g] Record vital signs (blood pressure [BP], orthostatic hypotension [OH], heart rate [HR], respiratory rate [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 blood pressure and heart rate. 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.
For visits in PART A, vital signs will be measured at t = 0 (just prior to dosing) and 60 minutes post-dose. For visits in PART B, vital signs will be measured at t = 0 (just prior to dosing), 30minutes (or immediately following the final PK draw, if applicable). During PART B, vital signs may be collected at 90 and 120 minutes postdose if clinically necessary in the Investigator's opinion. A window of ± 10 minutes is allowed for vital signs collection. Post-dose ECG may be used as next pre-dose ECG.

[h] Suggested Sequence of Assessments at Pre-Dose: ECG (to be completed within 60 minutes of dosing) → Vitals (to be completed within 60 minutes of dosing) → MDS-UPDRS Part III and Subject "OFF"/"ON" status (to be completed within 30 minutes of dosing).
Suggested Sequence of Assessments Post-Dose when conflict arises: MDS-UPDRS Part III and 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.
The following assessments are to be performed while the subject is in the "ON" state: MMSE, PGI-S, PGI-C, QUIP-RS, TSQM, PDQ-39, C-SSRS, EQ-5D-5L, TPQ, and Ease of Use Questionnaire.

[i] 12-lead ECG will be performed at Screening. For PART A and PART B, ECGs will be performed just prior to dosing and 50 (± 30) minutes post-dose. Unscheduled ECGs may be performed if clinically indicated by changes in vital signs (orthostatic hypotension) or symptoms (new cardiovascular symptoms eg, dizziness, syncope).

[j] Collect blood and urine for clinical laboratory tests (hematology, chemistry, urinalysis and serology [serology collected at the Screening Visit only], and urine drug screening) and serum pregnancy test (for females of child-bearing potential only, [serum pregnancy test collected at the Screening Visit only]). The total volume of blood collected will not exceed 25 mL at each time point.

[k] MDS-UPDRS Part III (Motor Function) to be completed at:
SV2 just prior to dosing with L-Dopa and at 15, 30, 60, 90, and 120 minutes post dosing. At SV2, if the subject does not experience an "ON" within 30 minutes, the site should record the time when the subject turns "ON" and complete the additional MDS-UPDRS Part III assessments up to 120 minutes
In PART A, MDS-UPDRS Part III will be assessed just prior to dosing and at 15, 30, 60, 90, and 120 minutes post-dose (± 5 minutes at each time point) if a subject has a full ON response at 30 minutes. Assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.
NOTE: If the subject turns "ON" before the 30 minute timepoint, the remaining MDS-UPDRS Part III assessments must still be made at the required timepoints up to and including 120 minutes**.** However, if the subject is full OFF at 90 minutes, the 120-minute response is not collected. If the subject is partial ON at 90 minutes, the 120 minute response is collected. If the subject does not turn "ON" by the 30 minute post-dose assessment, the assessments after 30 minutes do not need to be conducted
In PART B, MDS-UPDRS Part III will be assessed just prior to dosing and at 15, 30, 60, 90, and 120 minutes post-dose. Assessments at all timepoints will be collected regardless of response. During PART B the assessment will be completed by a rater blinded to the subject's study drug. Assessments will exclude the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.

[l] Dosing of Study Drug in clinic will be from outpatient supplies, except for placebo dosing.

[m] Investigator will confirm whether subject is "OFF", Full "ON" or Partial "ON" (see Section 11.2.2.1), and note the time the subject changes from "OFF" to Partial "ON" or Full "ON". The Investigator will also record the subject "ON"/"OFF" status prior to performing each MDS-UPDRS Part III assessment just prior to dosing and at 15, 30, 60, 90, and 120 minutes post-dose.

[n] The subject will confirm whether he/she is "OFF", Full "ON" or Partial "ON" (see Section 11.2.2.1), and the staff will ask the subject to notify the staff when he/she changes from "OFF" to Partial "ON" or Full "ON". The subject will also be queried as to their "ON"/"OFF" status prior to performing each MDS-UPDRS Part III assessment just prior to dosing and at 15, 30, 60, 90, and 120 minutes post-dose.
Subjects should also report the time (using 24 hour clock) when the study medication is starting to have an effect (i.e. partial "ON"), if applicable, time of FULL 'ON' and time of "OFF" following dosing (if it occurs within 120 minutes after dosing). These times are to be documented in subject source and in the appropriate form of the EDC.

[o] If the Investigator observes dyskinesia in the subject anytime post-dose (L-Dopa at SV2 and study drug at other visits) through the last time point monitored in clinic, it should be reported as an AE.

[p] These items will only be performed if the subject did not achieve full "ON" in clinic at 30 minutes post-dose of 10 mg APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose.

[q] Home Dosing Diary Training will be performed in PART A at Titration Visit 1. Home Dosing Diary Training will be performed in PART B at Clinic Visit 1 (V1) and Clinic Visit 4 (V4). PART B training will also include training by clinic staff on recognizing troublesome dyskinesia.

[r] Subject Home Dosing Diary to be completed during at-home titration in PART A.
In PART B, the Daily Home Dosing Diary (one diary per day) should be completed.
In PART B, the Expanded Home Dosing Diary (one diary per day) should be completed the 3 days prior to V2, V3, V5, and V6.

[s] C-SSRS "Screening/Baseline" scale to be used at Screening; C-SSRS "Since Last Visit" to be used at all other visits.

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

[u] To be completed ONLY for subjects who did NOT turn fully "ON" within 30 minutes of dosing the dose the subject determined to be the effective dose at DCV or the Investigator decided to uptitrate the subject to the next higher dose.

[v] Blood collection at sites experienced in PK sampling for APL-130277 and s.c. apomorphine PK analyses will occur just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes (± 5 minutes at all time points) post-dose. The samples are to be collected while the subject is in the supine position and just prior to

blood pressure collection for vital signs assessments. The samples may also be used for the additional characterization and/or bioanalytical method development of putative metabolites of apomorphine, if needed. Subjects may be catheterized to facilitate blood collection.

[w] Assessment will not be performed for subjects whose participation was terminated while in PART A.

[x] Subjects whose participation is terminated early will have the procedures/assessments outlined in the ET visit completed as soon as possible.

[y] This visit may occur over multiple days to accommodate receipt of the new dose of study drug (if necessary). Anytime a dose reduction occurs, the reason for dose reduction will be recorded in the eCRF.

[z] Subjects whose participation is terminated 5 days or more after V4 will have this assessment performed.

[aa] Unused Study Drug (as determined by Drug Accountability) to be resupplied to the subject during this visit. Study drug is only to be dispensed via IXRS if deemed necessary as an "Unscheduled visit." Drug accountability performed at Clinic Visit 2, Clinic Visit 3, and Clinic Visit 5 will be captured on the Paper Accountability log. This will not be required to be entered into the EDC.

[bb] Levodopa challenge will be performed at SV2 in clinic in the 'OFF' state. L-Dopa responsiveness is to be confirmed by assessment of the subject's motor function using MDS-UPDRS Part III at t = 0 (just prior to L-Dopa administration), and 15, 30, 60, 90, and 120 minutes after L-Dopa administration. As part of the L-Dopa challenge subjects will take their normal morning dose of L-Dopa in clinic without their normal adjunctive PD medication. The subject should be trained to indicate to site staff once they first note improvement in symptoms (i.e. Partial ON), and when they are in a Full 'ON' state. The Investigator will confirm "OFF" or "ON" state at each timepoint. Subjects who fail to turn Full 'ON' following dosing with L-Dopa as part of the L-dopa challenge may not be re-screened. Subjects who do not turn "ON" by 120 minutes will be considered screen failures.

[cc] Ease of Use Questionnaire to be completed at ET visit only if subject received at least 5 days of treatment.

[dd] If the investigator deems the ON response inadequate during the DCV, uptitration may continue in clinic during the subject's next OFF state or at home (at the investigator's discretion).

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

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LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 4.

Table 4: List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
APL	APL-130277
APOKYN®/APO-go®	apomorphine hydrochloride subcutaneous injection
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
b-SSR	blinded sample size re-assessment
CGI-I	Clinical Global Impression, Improvement
CGI-S	Clinical Global Impression, Severity
CI	Confidence interval
C_{max}	maximum observed plasma concentration
COMT	Catechol O-methyltransferase
C-SSRS	Columbia Suicide Severity Rating Scale
DCV	Dose Confirmation Visit (PART A)
EAC	Enrollment Adjudication Committee
EACF	Enrollment Adjudication Committee Form
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study Visit
EQ-5D-5L	European Quality of Life – 5 Dimensions
ET	Early Termination Visit
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HR	heart rate

Table 4: List of Abbreviations (Continued)

Abbreviation	Term
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPD	Important protocol deviations
IRB	Institutional Review Board
IXRS	Interactive X Response System
L-Dopa	L-3,4-dihydroxyphenylalanine or Levodopa
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
MMSE	Mini-mental State Examination
N	Total number of subjects in a treatment group
OH	Orthostatic hypotension
PD	Parkinson's disease
PDP	Parkinson's disease psychosis
PDQ-39	Parkinson's Disease Questionnaire
PGI-C	Patient Global Impression, Change
PGI-S	Patient Global Impression, Severity
PK	Pharmacokinetic
PT	Preferred term
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard deviation
SEM	Standard error of the mean
sl	Sublingual

Table 4: List of Abbreviations (Continued)

Abbreviation	Term
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard Operating Procedure
SV1	Initial Screening Visit
SV2	Screening Visit 2
T	Telephone call (PART A and PART B)
TV	Titration Visit (PART A)
V	Clinic Visit (PART B)
WBC	white blood cell
ZBI	Zarit Burden Interview

4. INTRODUCTION

4.1. Background

Parkinson's disease (PD) 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 resulting 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 inhibitor, and if necessary combined with dopamine agonists or monoamine oxidase B (MAO-B) inhibitors. However, with disease progression, PD patients develop motor complications that consist of dyskinesia and motor fluctuations. These motor fluctuations represent periods of "OFF" time. The mechanisms by which response fluctuations occur are only partially understood but are thought to include presynaptic neuronal degeneration, postsynaptic changes in dopamine receptor sensitivity or number, fluctuations in plasma levels of L-Dopa occurring due to the short half-life of L-Dopa, and the unpredictable variability of gastric emptying (Mouradian, 1989; Stocchi, 2005).

In general, approximately 40% of patients with PD experience motor fluctuations and/or dyskinesias by 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).

Currently, there are two approved treatments for acute management of "OFF" episodes: apomorphine dosed by subcutaneous (sc) injection (APOKYN, APO-go) and inhaled levodopa (Imbrija) (LeWitt, 2019). Although efficacious, s.c. apomorphine may be difficult for a PD patient to administer and frequently associated with adverse events such as nausea, vomiting, dizziness, dyskinesia, and orthostatic hypotension. As such, there remains an unmet medical need for an easy-to-administer, rapid, safe, and effective, on-demand treatment of "OFF" episodes in PD patients.

4.2. Study Conduct Rationale

There are five main types of "OFF" episodes:

1. End of dose wearing off is the most common "OFF" symptom. With PD progression, levodopa is not fully effective between doses and as a result patients develop "OFF" episodes ahead of his/her next dose.
2. Morning "OFF" episodes and morning akinesia are also related to end of dose wearing off. Patients will take their last dose of dopaminergic drugs late in the evening prior to retiring for the night, but because the patient has little dopaminergic reserve, he/she develops "OFF" in the morning.
3. Delayed "ON" or dose failure sometimes coincides with other "OFF" episodes but may occur alone and represents a delay in the time for the levodopa dose to take effect – usually this occurs within 45-60 minutes after dosing but in some instances this may take 2 hours or longer.

4. Partial "ON" – patient has a benefit following levodopa dose but it is less than is attained with the usual levodopa dose.
5. Unpredictable "OFF" episodes occur random and without waning. Changes in activity level or mood such as agitation or anxiety may further deplete dopamine levels in already dopamine deficit state, precipitating an "OFF" episode.

The precise mechanism of action of apomorphine as a treatment for Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine D_1 and D_2 type receptors within the caudate-putamen in the brain.

After sublingual (sl) administration, the thin film formulation of APL-130277 delivers apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing the extensive first-pass metabolism associated with gastrointestinal absorption of apomorphine.

In a recent twelve week double-blind placebo-controlled study (CTH-300), APL-130277 was shown to be effective in the treatment of OFF episodes. Significant separation from placebo on the MDS-UPDRS Part III score was determined at 30 minutes post-dose, with a LS Mean Difference of -7.6 favoring APL-130277 at the Week 12 visit. Improvements were observed at all time points, including 15 minutes and 90 minutes post-dose (the first and last time points measured, respectively). Similar patterns of improvement were observed at Weeks 1, 4 and 8. APL-130277 was generally safe and well tolerated. The majority of adverse events, including nausea, vomiting, and dizziness were mild to moderate. Dyskinesia, symptomatic hypotension, hallucinations, impulse control disorder, daytime onset of sleep disorder, and syncope were uncommon events.

The favorable safety profile of APL-130277 suggests that unsupervised titration at home should be generally safe and well tolerated. The current study is designed to compare the efficacy, safety and tolerability of APL-130277 to s.c. apomorphine.

4.3. Rationale for the Dosages

The doses for this study were selected based on the known PK profile of sc administered apomorphine, the PK profile of sl administered APL-130277, and previous studies of APL-130277 in subjects with PD.

4.4. Hypothesis

This study is designed to test the superiority of sublingually administered APL-130277 against subcutaneously injected apomorphine (APO-go®) for the treatment of "OFF" episodes in patients with Parkinson's Disease, as measured by the change from pre-dose to 90 minutes post-dose in MDS-UPDRS Part III score after 4 weeks of dosing in each crossover period.

5. STUDY OBJECTIVES

5.1. Primary Objectives

The primary objective is to demonstrate the efficacy of sublingual (sl) APL-130277 compared to subcutaneous (sc) apomorphine as a treatment of "OFF" episodes in subjects with Parkinson's Disease (PD) as measured by the change from pre-dose to 90 minutes post-dose in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score.

5.2. Secondary Objectives

The secondary objectives are to demonstrate the efficacy of sublingual (sl) APL-130277 compared to subcutaneous (sc) apomorphine as a treatment of "OFF" episodes in subjects with Parkinson's Disease (PD) as measured by:

- Durability of effect, defined as Investigator confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose;
- Subject preference for APL-130277 after the subject has completed both APL-130277 and s.c. apomorphine treatment regimens;
- Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose;
- Patient Global Impression of Change of "OFF" episodes (PGI-C).

5.3. Safety Objectives

To evaluate the safety and tolerability of sl APL-130277 at doses of 10 to 30 mg compared to s.c. apomorphine at doses of 2 to 6 mg during titration and the maintenance treatment period through the assessment of: adverse events (AE) with attention to nausea, vomiting, hypotension, syncope, dyskinesia and impulse control disorders; physical examinations (PE) including oropharyngeal and injection site reactions; electrocardiogram (ECG) derived morphology and conduction parameters; vital signs including orthostatic hypotension (OH); frequency of domperidone use; clinically significant changes in laboratory tests; incidence of suicidal thoughts and actions as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS); and impulsivity as measured by the Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).

5.4. Pharmacokinetic Objectives

To assess the pharmacokinetics (PK) for apomorphine and metabolites (apomorphine sulfate, norapomorphine, and others as deemed necessary) from plasma samples following dosing with sl APL-130277 and s.c. apomorphine.

6. STUDY ENDPOINTS

6.1. Primary Efficacy Endpoint

The primary efficacy variable is the change from pre-dose to 90 minutes post-dose in MDS-UPDRS Part III score after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at V3 and V6 of PART B).

6.2. Secondary Efficacy Endpoints

- Durability of effect, defined as an Investigator confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at V3 and V6 of PART B).
- Subject preference for APL-130277 treatment (either somewhat or definitely prefer APL-103277) as recorded for question 9 of the TPQ. This assessment is scheduled to be performed after the subject has completed both APL-130277 and s.c. apomorphine treatment regimens (assessed in clinic at V6 of PART B).
- Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).
- Patient Global Impression of Change (PGI-C): Subject improvement of "OFF" episodes, defined as very much better, much better or a little better after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).

6.3. Other Efficacy Endpoints (PART B)

- Clinical Global Impression of Improvement (CGI-I): Subject improvement, defined as very much improved, much improved or minimally improved after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).
- Change from pre-dose to 15, 30, 60, 90, and 120 minutes post-dose in MDS-UPDRS Part III score (assessed in-clinic V1, V2, V4, and V5). Change from pre-dose to 15, 30, 60 and 120 minutes post-dose in MDS-UPDRS Part III score (assessed in-clinic V3 and V6).
- Investigator confirmed full "ON" at the 15, 30, 60, 90, and 120 minutes post-dose time points (assessed in-clinic V1, V2, V3, V4, V5, and V6).
- Subject confirmed full "ON" at the 15, 30, 60, 90, and 120 minutes post-dose time points (assessed in-clinic V1, V2, V3, V4, V5, and V6).
- Time to full "ON" and Time to partial "ON" as determined by the subject and Investigator (assessed in-clinic at all visits in PART B).
- Per the Expanded Home Dosing Diary, percent of episodes with a subject-rated full "ON" within 30 and at 90 minutes post-dose based on the 3 consecutive days prior to V2, V3, V5, and V6.

- Level of satisfaction as assessed by the Treatment Satisfaction Questionnaire for Medication (assessed in-clinic at V3 and V6).
- MDS-UPDRS – Part I Score: change from Screening to V2, V3, V5, and V6 (assessed in-clinic at V2, V3, V5, and V6).
- MDS-UPDRS – Part II Score: change from Screening to V2, V3, V5, and V6 (assessed in-clinic at V2, V3, V5, and V6).
- MDS-UPDRS – Part IV Score: change from Screening to V2, V3, V5, and V6 (assessed in-clinic at V2, V3, V5, and V6).
- Improvement in amount of troublesome dyskinesia in the last month per the in-clinic dyskinesia questionnaire; defined as less than usual amount of troublesome dyskinesia after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6).
- Percent of "ON" episodes without troublesome dyskinesia (per expanded home diary) based on the 3 consecutive days prior to V2, V3, V5, and V6.
- Change in the PDQ-39 Total Index Score, and Mobility and Activities of Daily Living subscale scores from pre-dose V1 to after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6).
- European Quality of Life – 5 Dimensions (EQ-5D-5L) (assessed in-clinic at V1, V3, and V6).
- Ease of Use Questionnaire (assessed in-clinic at V3 and V6).

6.4. Safety Endpoints

Evaluation of safety and tolerability of APL-130277 compared to s.c. apomorphine as measured by AEs, physical examination including assessment of oropharyngeal AEs and injection-site related AEs, 12-lead ECGs, vital signs including OH, clinical laboratory tests, and C-SSRS and QUIP-RS assessments.

6.5. Pharmacokinetic Endpoints

Pharmacokinetic concentration-time data for apomorphine and metabolites (apomorphine sulfate, norapomorphine, and others as deemed necessary) will be evaluated and PK parameters (including but not limited to C_{max}, t_{max}, AUC_t, parent-to-metabolite ratios of C_{max} and AUC_t) will be estimated by noncompartmental methods from plasma samples using actual elapsed time from dosing. Details and methodology concerning the analysis of these variables will be provided in a separate PK analysis plan. A separate and stand-alone PK report will be provided.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a two part study: PART A and PART B.

PART A consists of an open label, crossover titration phase where eligible subjects will be randomized to 1 of 2 treatment sequences in a 1:1 ratio to sl APL-130277 followed by s.c. apomorphine or s.c. apomorphine followed by sl APL-130277. Subjects will undergo dose titration with the first assigned study treatment (APL-130277 or s.c. apomorphine) to tolerance and effect, ie, the tolerable dose that turns the subject from the practically defined "OFF" state to the full "ON" state as determined by both the Investigator and subject. The subject will then be crossed over to the other assigned study treatment (APL-130277 or s.c. apomorphine) and similarly titrated to tolerance and effect. The doses of APL-130277 and s.c. apomorphine determined as optimal in PART A will be used during PART B.

The titration of APL-130277 will start in the clinic at 10 mg, and if the subject fails to convert from a practically defined "OFF" to a full "ON" within 30 minutes (per both the Investigator and subject), the subject will be instructed on how to self-administer increasing doses of APL-130277 and continue the titration process at home.

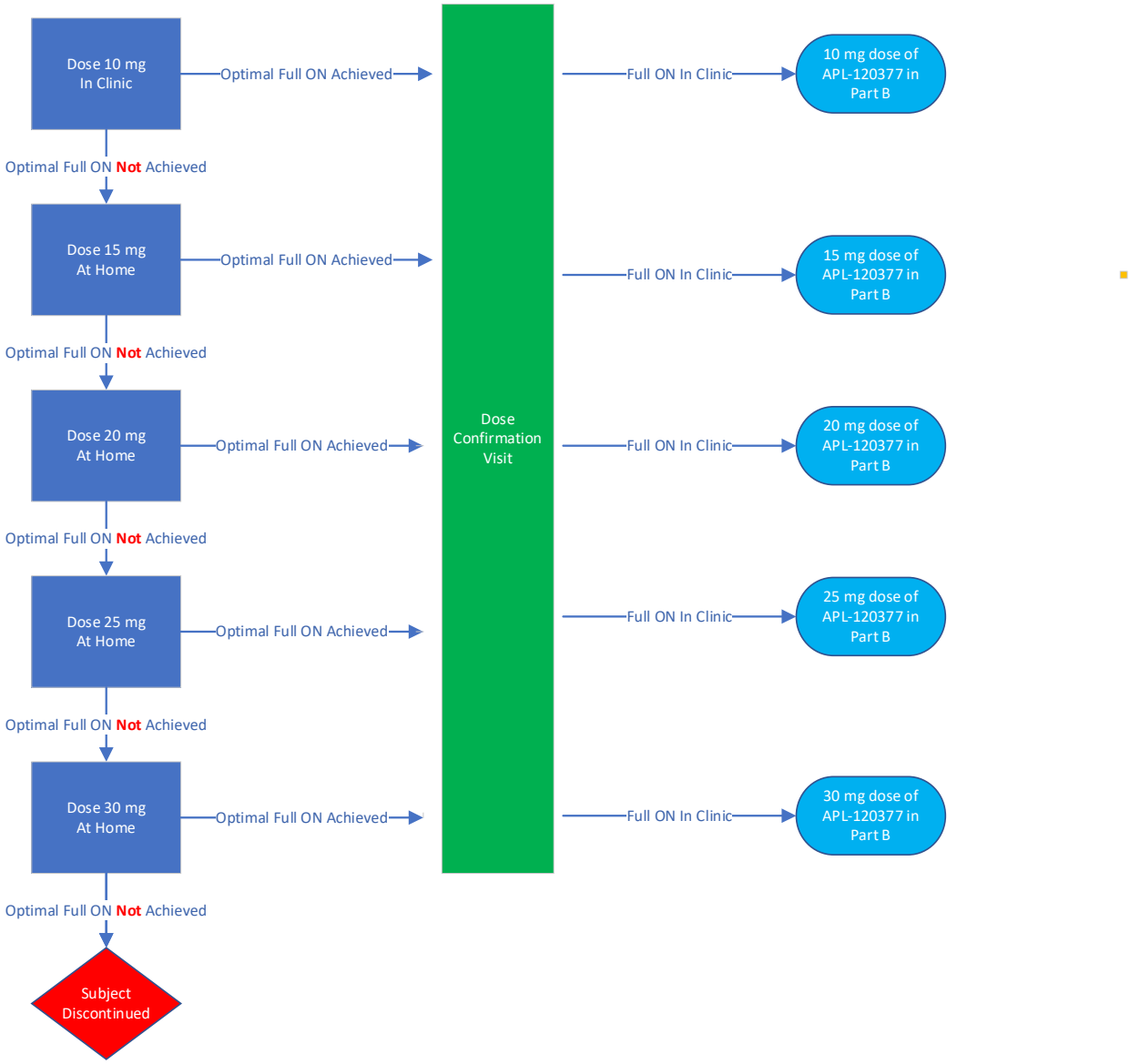
If the 10 mg dose of APL-130277 results in a full "ON" within 30 minutes (per both the Investigator and subject), but not an optimal full "ON" response, unless there are safety/tolerability concerns, the next higher dose, 15 mg, should be administered at home in order to assess for an optimal full "ON" response. The subject should be instructed on how to self-administer increasing doses of APL-130277 and continue the titration process at home. Uptitration in 5 mg increments should continue at home until the subject achieves the optimal full "ON" response.

The site will contact the subject daily to determine titration status and query for tolerability/safety issues. If the site, ascertains the dose of APL-130277 provides an optimal "ON" response, the subject will return to the clinic for a Dose Confirmation Visit (DCV1) 5-7 days of APL TV1, or earlier as determined by the Investigator, to confirm the efficacy and tolerability of the selected dose. If the investigator deems the ON response inadequate during the DCV, the subject may continue uptitration in clinic during the subject's next full OFF state or at home following the procedures for home titration. The next higher dose may be administered no sooner than 2 hours after the previous dose and no later than 5 days of one another. Following further uptitration at home, additional DCVs should take place within 5 days of one another.

If the Investigator determines there are tolerability issues with APL-130277 in the home titration setting, the subject will be instructed to withhold further administration of APL-130277 and come to the clinic for an unscheduled clinic visit.

A schematic showing the flow of APL-130277 titration is provided in Figure 1.

Figure 1: APL-130277 Titration



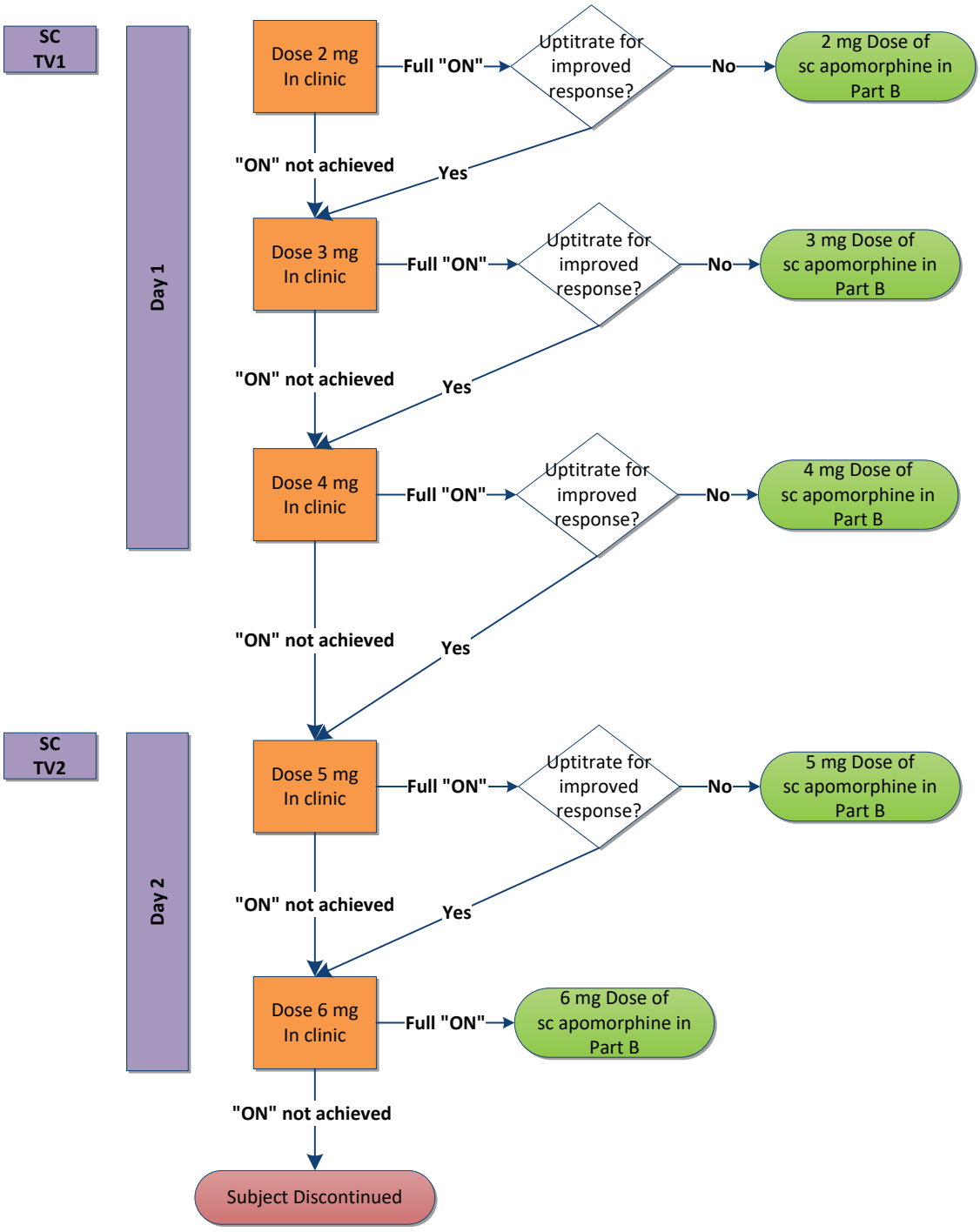
NOTE: Subjects must withhold antiparkinson medications, including APL-130277, beginning at midnight before scheduled visits and be in the "OFF" state prior to dosing.
NOTE: Additional Dose Confirmation Visits can be completed to allow titration in clinic or at home if the initial DCV fails to confirm effective dose.
NOTE: Following dosing with 25 mg, subjects may take the next higher dose (30 mg) of APL-130277 if it is feasible for the subject to remain in clinic. The next higher dose may be administered no sooner than 2 hours after the previous dose.

For de novo subjects, titration with s.c. apomorphine will take place in the clinic only, starting at 2 mg.

Subjects currently taking s.c. apomorohine prior to screening are allowed in the study. Following a washout period of at least 1 day, subjects must enter titration at the dose they were taking prior to screening. The subject may be up-titrated at the investigator's discretion.

Schematics showing the flow of s.c. apomorphine titration are provided in Figure 2 and Figure 3.

Figure 2: De novo s.c. apomorphine Titration



NOTE: Subjects must withhold antiparkinson medications, including s.c. apomorphine, beginning at midnight before scheduled visits and be in the "OFF" state prior to each dosing.

NOTE: Subject may take the next higher dose of s.c. apomorphine (to a maximum of 3 doses per day) if it is feasible for the subject to remain in clinic. The next higher dose may be administered when subject is in a full 'OFF' state no sooner than 1 hour after the previous dose. Subjects may take a maximum of 3 doses per day.

Figure 3: s.c. apomorphine Titration

NOTE: Subjects must withhold antiparkinson medications, including s.c. apomorphine, beginning at midnight before scheduled visits and be in the "OFF" state prior to each dosing.

Depending on the magnitude and duration of the full "ON" response, the Investigator has the option of uptitrating the subject to the next higher dose of either APL-130277 or s.c. apomorphine (not to exceed 30 mg or 6 mg, respectively) in order to assess whether the subject has a faster time to, longer duration, or improved "ON". Further uptitration to higher doses should be performed if the investigator deems the subject's "ON" response is inadequate. The subject must be in a full "OFF" state prior to uptitration.

The effective dose for both APL-130277 and s.c. apomorphine must be approved by the medical monitor based on review of the titration data prior to the subject being randomized into Part B. This dose will be used in PART B of the study.

Antiemetic (domperidone) can be used prophylactically or if clinically warranted, at the Investigator's discretion.

Following a 3 to 7 day washout period, eligible subjects will enter PART B of the study and be randomized to 1 of 2 treatment sequences in a 1:1 ratio; 4-weeks of open-label treatment with sl APL-130277 followed by 4-weeks of open-label treatment with s.c. apomorphine, or 4-weeks of open label treatment with s.c. apomorphine followed by 4-weeks of open-label treatment with sl APL-130277.

Subjects will be instructed to continue with their regular PD medication regimen(s), and to dose themselves with their randomized open-label study treatment (APL-130277 or s.c. apomorphine) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) during the waking day. Subjects will be instructed to dose up to 5 "OFF" episodes per day during the waking period and to complete a daily home dosing diary. Study drug doses (APL-130277 or s.c. apomorphine) must be separated by at least 2 hours.

During the 4-week treatment period, subjects will return to the clinic for safety and efficacy assessments at 2-week intervals. In PART B, the MDS-UPDRS Part III will be assessed by a rater blinded to the subject's study treatment. The rater's blind in PART B will be maintained by:

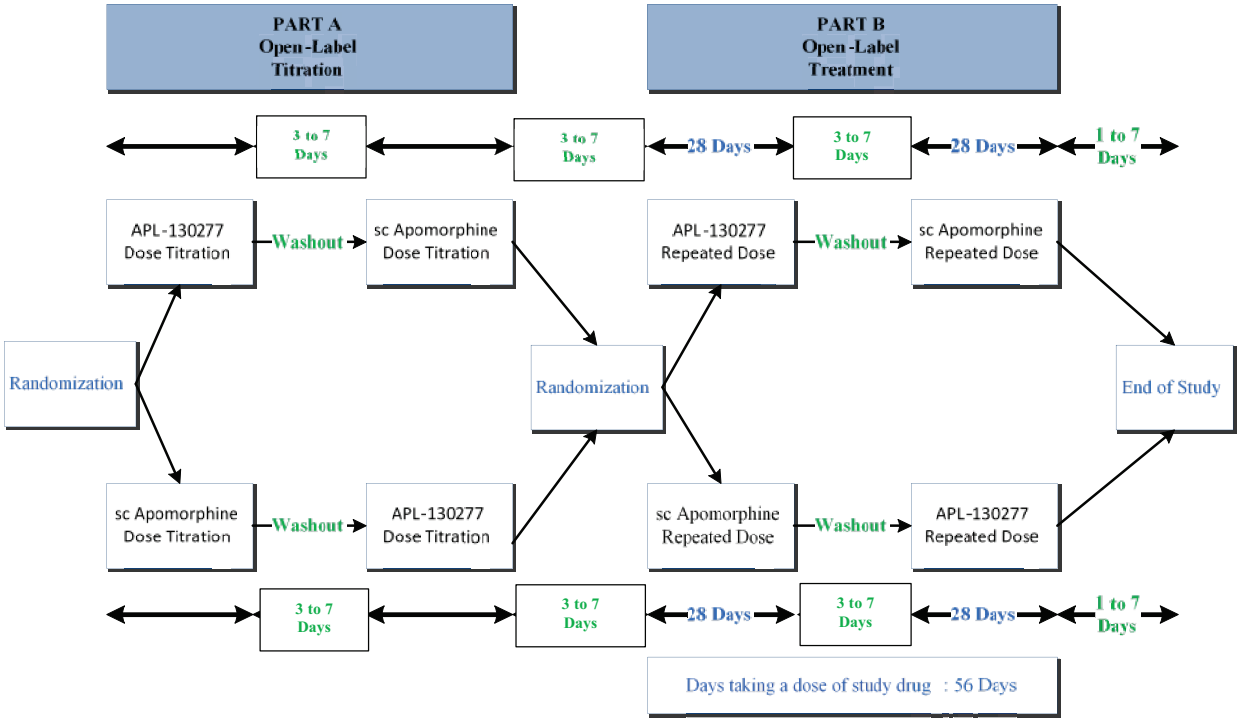
- Ensuring the blinded rater does not witness the in-clinic dosing;
- Ensuring any visible injection sites are covered by the subject's clothing (or other item, eg, hospital gown, robe, etc.);
- Because sublingually dosed APL-130277 can leave blue residue on the subject's tongue, when the subject is dosed in clinic with s.c. apomorphine, he/she will also be sublingually administered Placebo APL-130277;
- The site will take steps to protect source data and eCRFs to ensure the blinded rater does not become aware of the subject's study treatment at any time during the study.

Selected sites will also collect pre- and post-dose samples for pharmacokinetic (PK) analysis for apomorphine and metabolites.

The subject will then be crossed over to the other study treatment (APL-130277 or s.c. apomorphine) for additional 4-weeks of open-label treatment, with subjects returning to the clinic for safety and efficacy assessments throughout the treatment period.

A study schematic is presented in Figure 4. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2 and Table 3, Schedule of Assessments, and Section 11, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

Figure 4: Study Schematic



7.2. Treatment Assignment and Blinding

PART A is an open-label, randomized, crossover titration phase.

PART B is an open-label, randomized, crossover 4-week dosing phase.

7.2.1. Treatment Assignment

At Screening, the interactive X response system (IXRS) 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 IXRS regardless of eligibility in order to obtain a Screening Number. This 7-digit number will consist of a 4-digit site ID followed by a 3-digit number assigned sequentially within each site.

The treatment schedule will be generated by an independent biostatistician. Once a subject is deemed eligible to be randomized, the IXRS will perform the treatment assignment. Blocked randomization will be used with no stratification factors.

In PART A, subjects will be randomized to one of the following treatment sequences in a 1:1 ratio:

- Sequence 1: APL-130277 followed by s.c. apomorphine;
- Sequence 2: s.c. apomorphine followed by APL-130277.

In PART B, subjects will be randomized to one of the following treatment sequences in a 1:1 ratio:

- Sequence 3: APL-130277 followed by s.c. apomorphine;
- Sequence 4: s.c. apomorphine followed by APL-130277.

7.2.2. Blinding

This is an open-label study, and the identity of the study drug will not be blinded to the subject and Investigator.

In PART B, the MDS-UPDRS Part III, CGI-S, CGI-I, and ON/OFF assessment will be assessed by a rater blinded to the subject's study treatment. The rater's blind in PART B will be maintained by:

- Ensuring the blinded rater does not witness the in-clinic dosing;
- Ensuring any visible injection sites are covered by the subject's clothing (or other item, eg, hospital gown, robe, etc.);
- Because sublingually dosed APL-130277 can leave blue residue on the subject's tongue, when the subject is dosed in clinic with s.c. apomorphine, he/she will also be sublingually administered Placebo APL-130277;
- The site will take steps to protect source data and eCRFs to ensure the blinded rater does not become aware of the subject's study treatment at any time during the study.

7.2.3. Prevention of Missing Data

In an effort to minimize the number of subjects who are terminated from the study prior to study completion, the following study design and conduct elements are implemented:

- Open-label titration of study drug to tolerance and effect;
- In PART B, allowance of a dose reduction if the selected dose of study drug is not tolerated;
- Use of study centers with a good track record of enrolling and following eligible subjects;
- Training the study centers on the importance of continued follow-up and on the informed consent process, ensuring prospective subjects understand the commitment they are making, including the intent to complete the study;

- Monitor data collection for adherence during the study.

Please see Section 15.3 for statistical considerations related to missing data.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

The subjects who fulfill the following criteria will be included in the study.

1. The subject (and caregiver, if applicable) must be fully informed of and understand the objectives, procedures, and possible benefits and risks of the study, and give written informed consent prior to performing any study-related activities.
2. Male or female ≥ 18 years of age.
3. Clinical diagnosis of Idiopathic PD, consistent with UK Brain Bank Criteria (excluding the "more than one affected relative" criterion).
4. Clinically meaningful response to levodopa (L-Dopa), as determined by the Investigator.
5. Subjects at Screening must demonstrate an adequate L-Dopa response on the MDS-UPDRS Part III in the "ON" state compared to the MDS-UPDRS Part III in the "OFF" state and on the Hoehn and Yahr, as determined during the review by Enrollment Adjudication Committee (EAC), Sponsor, and Medical Monitor.
6. Receiving stable doses of L-Dopa/carbidopa and/or L-Dopa/benserazide and/or L-Dopa/carbidopa/entacapone (immediate or chronic release) 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 are permitted but must be maintained at a stable dose for at least 4 weeks prior to SV1 with the exception of monoamine oxidase B (MAO-B) inhibitors, which must be maintained at a stable level for at least 8 weeks prior to SV1. Use of Madopar PRN in the 4 weeks prior to screening is permitted. Current use of sc apomorphine by injection at the time of screening is permitted.
7. No planned medication change(s) or surgical intervention anticipated during the course of study.
8. Subjects must experience at least one well defined "OFF" episode per day and have a total daily "OFF" time duration of ≥ 2 hours during the waking day, based on judgment of physician and subject self-assessment.
9. Subject must have predictable morning "OFF" periods, based on judgment of physician and subject self-assessment.
10. Subject, and where appropriate caregiver, must be trained in completing the home dosing diaries and able to recognize "ON" and "OFF" states.
11. Stage III or less on the modified Hoehn and Yahr scale in the "ON" state.
12. Mini–Mental State Examination (MMSE) score > 25.
13. Female subject of childbearing potential and male subject with female partner of childbearing potential must agree to either remain abstinent or use adequate and reliable contraception (see Section 10.4.1 for additional information on acceptable methods of birth control) throughout the study and for at least 7 days after the last dose of study drug

has been taken. Note: Continued use of adequate and reliable contraception is recommended through 30 days after study completion.

14. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.
15. Must be approved as a satisfactory candidate by the Enrollment Adjudication Committee (EAC), Medical Monitor, and Sponsor.

8.2. Subject Exclusion Criteria

The subjects who meet any of the following criteria will be excluded in the study

1. Atypical or secondary parkinsonism.
2. Major focal brain disorders including malignancy or stroke.
3. Prior treatment with any of the following: a neurosurgical procedure for PD; continuous subcutaneous (sc) apomorphine infusion; Duodopa/Duopa; or APL-130277.
4. Subjects who have permanently stopped prior use of sc apomorphine injection.
5. Contraindications to domperidone, subcutaneous apomorphine, or hypersensitivity to apomorphine hydrochloride or any of the ingredients of subcutaneous apomorphine (notably sodium metabisulfite).
6. Female who is pregnant or lactating.
7. Participation in an interventional clinical study and/or receipt of any investigational (ie, unapproved) medication within 30 days prior to SV1.
8. Currently taking selective $5HT_3$ antagonists (ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron), dopamine antagonists (excluding quetiapine or clozapine) or dopamine depleting agents. Subjects receiving anti-depressants must be on a stable daily dose for at least 8 weeks prior to SV1.
9. The subject has a current diagnosis or history of substance abuse (excluding nicotine and caffeine) or alcohol abuse (in the opinion of the investigator) < 6 months prior to SV1.
10. Subject has a positive urine drug screen result. NOTE: Benzodiazepines, opiates, and oxycodone will be allowed provided the subject has been on a stable dose for 4 weeks prior to SV1, provided the subject has a valid prescription. Cotinine is not exclusionary.
11. The recreational use of cannabinoids (including formulations of CBD) and hallucinogenics are excluded, as well any use of a sublingual formulation of any drug.
12. Subject has a history of malignancy within 5 years prior to SV1, except for adequately treated basal cell or squamous cell skin cancer or *in situ* cervical cancer.
13. Subject has a clinically significant abnormality on screening evaluation including physical examination, vital signs, electrocardiogram (ECG), or laboratory tests that the Investigator considers to be inappropriate to allow participation in the study.
14. Subject has screening laboratory test results of: blood urea nitrogen (BUN) value ≥ 1.5 times the upper limit of normal (ULN) for the reference range; serum

creatinine > 1.5 times the ULN for the reference range; or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value ≥ 2 times the ULN for the reference laboratory.

15. Subject has random (non-fasting) screening glucose of ≥ 200 mg/dL (11.1 mmol/L) and HbA1c > 7.0%.
16. Subjects with type 1 diabetes, or insulin-dependent diabetics are excluded. Subjects with type 2 diabetes are eligible for study inclusion if the following conditions are met:
    - Subject's screening glucose is < 200 mg/dL (11.1 mmol/L). Note: Subjects with random (non-fasting) blood glucose at screening ≥ 200 mg/dL (11.1 mmol/L) must be retested in a fasted state; and
    - Subject's hemoglobin A1c (HbA1c) ≤ 7.0%; and
    - If the subject is currently being treated with oral anti-diabetic medication(s), the dose must have been stable for at least 4 weeks prior to SV1. Such medication may be adjusted or discontinued during the study, as clinically indicated.
17. The subject's screening ECG results of corrected QT interval using Fridericia's formula (QTcF) ≥ 450 msec for male subjects or ≥ 470 msec for female subjects. Eligibility will be based on the core laboratory ECG interpretation report.
18. Subject has a positive screening laboratory test result for human immunodeficiency virus (HIV).
19. Subject has a positive screening laboratory test result for hepatitis B surface antigen or hepatitis C antibodies and has liver function test results at screening above the ULN for the reference laboratory.
20. Subject has any other medical disorder that, in the opinion of the Investigator, could interfere with the subject's participation in the study.
21. Subject has major psychiatric disorder(s), including but not limited to: bipolar disorder, psychosis (eg, Parkinson's Disease Psychosis), major depressive episode, or any disorder that, in the opinion of the Investigator, would require treatment that could make study participation unsafe or make treatment compliance difficult.
22. History of clinically significant impulse control disorder(s).
23. History of symptomatic orthostatic hypotension requiring medication.
24. History of severe dyskinesia based on a score of 4 on the MDS-UPDRS Part IV for either "**time spent with dyskinesia**" OR "**the functional impact of dyskinesia**"
25. Current/recent suicidal ideation as evidenced by answering "yes" to "Suicidal Ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Screening (using the "Screening/Baseline Version" scale, in the past 12 months) or attempted suicide within the last 5 years.
26. Presence of canker or mouth sores in the 30 days prior to 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 subject into the study.

8.3. Eligibility Review Process

The Investigator must obtain approval from the EAC, Sponsor, and Medical Monitor prior to enrolling any subject into the study. The EAC, Sponsor, and Medical Monitor will together determine the subject's appropriateness for inclusion in the study.

The Enrolment Adjudication Committee Form (EACF) will be submitted for review, and all SV1 and SV2 data entered into the eCRF within 24 hours of SV2 and at least 6 days prior to the date TV1 is provisionally scheduled to permit time for the review. The eligibility review should be completed within 6 days of submitting a request complete with all required information (including all laboratory and ECG results) available to the reviewers, and the Investigator will be informed of the decision. Following receipt of official approval, the final determination of eligibility for enrollment in the study will be made by the Investigator, who will then submit a request via the IXRS for enrollment into the Dose Titration Phase of the study. In case of refusal, the decision will be accompanied by a rationale. For additional details, please refer to the Enrollment and Randomization Adjudication Process, which is contained in a separate document.

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

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

9.1.1. APL-130277

APL-130277 is a sublingual film that contains the drug substance apomorphine hydrochloride. APL-130277 is intended to be an on demand acute treatment for motor "OFF" episodes experienced by PD subjects. APL-130277 bilayer film is composed of 2 layers: 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 printing.

APL-130277 sublingual films will be provided in 5 strengths: 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg.

9.1.2. Placebo APL-130277

Placebo sublingual films will be used for training and efficacy blinding purposes, and will be identical in appearance, size and color to APL-130277, but contain no active ingredient (ie, apomorphine hydrochloride).

9.1.3. Subcutaneous Apomorphine – APO-go®

Subcutaneous apomorphine will be prescribed by sites as APO-go® as referenced in the SmPC (see Section 23).

9.2. Study Drug Packaging and Labeling

9.2.1. Package Description

During PART A:

- Open-label individual sublingual films of APL-130277 will be supplied packed into unit dose pouches. Individual pouches will be labelled with all applicable information.
- Open-label individual sublingual films of Placebo APL-130277 for training purposes will be supplied packed into unit dose pouches. Individual pouches will be labelled with all applicable information.
- Subcutaneous apomorphine will be supplied from commercially available stock and will be labelled with all applicable information.

During PART B:

- 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.
- Open-label individual sublingual films of Placebo APL-130277 to be administered to ensure the blind is maintained will be supplied packed into unit dose pouches. Individual pouches will be labelled with all applicable information.
- Subcutaneous apomorphine will be supplied from commercially available stock and will be labelled with all applicable information.

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

9.2.2. Labeling Description

Labelling will be implemented as per Annex 13 requirements for Investigational Medicinal Products.

9.3. Study Drug Storage

The Investigator is responsible for ensuring the proper storage of all study drug. Each Investigator is required to keep investigational drug product in a locked cabinet or other secure storage contained with limited access to personnel. Temperature logs must be maintained for the storage room for the entire duration of storage on site.

Subjects must be instructed to store all study medication at room temperature.

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

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.

APO-go®: Cartridges will be stored as per the product insert; do not store above 25°C (77°F).

The Investigator must maintain accurate and adequate records including expiry dates, lot numbers, quantities received, individual usage, etc. At the end of the study, the Investigator must also return unused supplies to the Sponsor giving an account of usage in a trial whether or not the trial is completed or terminated. At the time of return to the Sponsor, the Investigator must verify that all unused or partially used drug supplies have been returned by the 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.

9.4. Dispensing of Study Drug

Investigational product should be maintained under the strict control of qualified site staff at all times. Appropriate guidelines should be followed in proper dispensation to the study participant. Proper handling and storage should be followed. This is outlined in the Pharmacy Manual or Appendices supplied to the site. IXRS drug dispensing guidelines should be followed for dispensing IP to the subject, in addition to all accountability records where required. Proper accountability records must be maintained and up to date capturing all drug dispensing activities. Note: At PART B Clinic Visits 2 and 5 only, drug dispensing refers to re-supply of unused study drug to the subject (which was dispensed from IXRS at Clinic Visit 1 and 4, respectively) which they had brought in to the clinic. If additional study drug is required, IXRS will be used to dispense as an 'Unscheduled Visit'.

9.5. Study Drug Accountability

The Investigator or designee is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/CRO.

To avoid the situation where any expired study drug is dispensed and used, the Sponsor should retrieve all study drug before expiration date. If the study drug is not returned/retrieved from the site before the expiration date, the Investigator or designee should store the expired study drug separately.

The drug will not be dispensed to any person who is not a study subject or caregiver who signed the informed consent under this protocol.

9.6. Study Drug Handling and Disposal

A drug inventory record will be supplied from Sponsor/CRO. The Investigator or designee on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned medication. The Investigator or designee is required to return all unused study drug to the Sponsor or designee as instructed. The Investigator or designee is required to maintain copies of medication shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

10. TREATMENT OF SUBJECTS

10.1. Administration of Study Drug

During titration, subjects should be dosed to comparable dose levels for APL-130277 and sc apomorphine using Table 5 as a guide. These are approximate equivalent doses based on pharmacokinetic data. The dose should be optimized for each treatment unless the subject experiences dose-limiting safety or tolerability events. These events should be discussed with the medical monitor.

Table 5: Recommended Sequence of Dosing Titration

Apo-go (apomorphine)	**APL-130277**
2 mg	10/15 mg
3 mg	20 mg
4 mg	25 mg
5/6 mg	30 mg

10.1.1. APL-130277

At TV1 in the APL-130277 Dose Titration Phase, subjects will undergo outpatient self-administration training with clinic staff using Placebo APL-130277. This training is performed in order to familiarize subjects with the self-administration process during PART A and PART B of the study. Staff should demonstrate to subjects the process of opening the individual dose pouches and handling the individual Placebo APL-130277 sublingual films. Subjects will not be dismissed until they have adequately been trained and site staff feels confident the subject understands the full process.

Subjects should be instructed to not cut, swallow or chew the medication. 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. APL-130277 can be administered without regard to food status (ie, either fed or fasted).

Staff will place the product beneath the tongue, with the drug side facing up towards the tongue (ie, the side of the film that <u>does not have</u> an alphanumeric printing), and ask subjects to close their mouth naturally. Subjects should also try not to swallow their saliva for at least 3 minutes. If, upon inspection at the 3-minute mark, the film is not completely dissolved, subjects should be instructed to close their mouth and hold the study drug 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 3-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 drug under their tongue. Staff may verify at regular intervals, as appropriate, for a duration maximum of 4 minutes in total.

During PART A and PART B in-clinic visits, subjects will be dosed by clinic staff. For APL-130277, the time of dosing (t = 0) will be the time when the sublingual film is placed underneath the tongue.

During PART B at home administration, subjects will be provided sufficient study drug in order to self-administer up to 5 "OFF" episodes per day until their next scheduled visit. APL-130277 doses must be separated by at least 2 hours. Unused study drug will be collected by the site and inventoried.

10.1.2. Subcutaneous Apomorphine – APO-go

The method of s.c. apomorphine administration will be as described in the SmPC (see Section 23).

The subject will receive s.c. apomorphine self-administration training with clinic staff using the s.c. apomorphine pen in the open-label crossover period he/she receives s.c. apomorphine (ie, V1 or V4). This training is performed in order to familiarize subjects with the self-administration process. Staff should go through the package leaflet for the s.c. apomorphine pen with the subject to ensure they understand how to administer the injections. Subjects (and/or caregiver) will not be dismissed until they have adequately been trained and the subject (and/or caregiver) understands the entire dosing process. The subject (and/or caregiver) will be required to appropriately perform an administration of s.c. apomorphine (ie, an injection) in the clinic under supervision of the staff prior to the subject (and/or caregiver) being released.

During PART A and PART B in-clinic visits, subjects will be dosed by clinic staff. For s.c. apomorphine, the time of dosing (t = 0) will be the time when the injection is given.

During PART B in-clinic visits, when the clinic staff is dosing s.c. apomorphine to the subject, the staff will also administer Placebo APL-130277 to the subject immediately before / after injection.

During PART B at home administration, subjects will be provided sufficient study drug in order to self-administer for up to 5 "OFF" episodes per day until their next scheduled visit. Subcutaneous apomorphine doses must be separated by at least 2 hours. Unused study drug will be collected by the site and inventoried.

10.2. Study Drug Accountability

In PART B, study drug accountability will be assessed by counting the unused study drug returned by subjects at each in-clinic visit during PART B of this study relative to the amount given at the preceding visit. Discrepancies in the amount taken and that retrieved will be queried by the Investigator and documented, and recorded in the appropriate eCRF.

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

10.3. Prior and Concomitant Medications and Therapies

10.3.1. Prohibited Treatments

As needed use of medications for treating "OFF" episodes during the trial, including Madopar is prohibited.

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

- Any selective $5HT_3$ antagonist (eg, ondansetron, granisetron, dolasetron, palonosetron, alosetron) from 30 days prior to SV1 until study completion.
- Any dopamine antagonists (excluding domperidone) 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.
- Cisapride.
- Dronedarone.
- Neuroleptics.
- Any sublingual medication including vitamin B6.
- Medicinal/recreational marijuana including CBD.

10.3.2. Permitted Treatments

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

- Antiemetic therapy with domperidone is optional and can be initiated prophylactically or if clinically warranted at the Investigator's discretion. If initiated, antiemetic therapy should be stopped when judged clinically appropriate. Domperidone is not typically used for longer than 7 days of continuous use. Domperidone use can exceed 7 days continuous use with approval of the Medical Monitor, where clinically warranted in line with local regulations.

  Domperidone (10 mg t.d.s. or as recommended in the country label) for potential nausea associated with administration of APL-130277 and/or s.c. apomorphine, administered as necessary.

- Stable doses of an L-Dopa formulation with or without other stable adjunctive PD therapies (from at least 4 weeks prior to the initial Screening Visit [SV1] with no planned medication changes during the study).

- Benzodiazepines, opiates, and oxycodone will be allowed provided the subject has been on a stable dose for 4 weeks prior to SV1, provided the subject has a valid prescription.

Any other medications are allowed, apart from those listed in the Prohibited Treatments section, provided they are stable, with no planned medication changes scheduled during the study. If the subject is taking vitamins, ensure the subject does not exceed the recommended daily allowance of vitamin B_6.

Other therapies (eg, for the treatment of an acute condition such as headache or urinary tract infection) can be administered as necessary at the discretion of the Investigator and with the approval from the Medical Monitor. All concomitant medications must be recorded.

10.4. Contraception Requirements

10.4.1. Adequate Contraception

Adequate contraception is defined as surgical sterility, or continuous use of either two barrier methods (eg, condom and spermicide or diaphragm with spermicide) or a hormonal contraceptive. Acceptable hormonal contraceptives include the following:

- contraceptive implant (such as Norplant®) implanted at least 90 days prior to screening;

- injectable contraception (such as medroxyprogesterone acetate injection) given at least 14 days prior to screening; or

- oral contraception taken as directed for at least 30 days prior to screening.

10.4.2. Female Subjects

Female subject of reproductive potential agrees to remain abstinent or use adequate and reliable contraception throughout the study and for at least 7 days after the last dose of study drug has been taken. Continued use of an effective and medically acceptable form of birth control is recommended through 30 days after study completion.

Female subjects who are of non-reproductive potential, ie, subject who is surgically sterile, has undergone tubal ligation, or is postmenopausal (defined as at least 12 months of spontaneous amenorrhea or between 6 and 12 months of spontaneous amenorrhea with follicle stimulating hormone [FSH] concentrations within postmenopausal range as determined by laboratory analysis) are not required to remain abstinent or use adequate contraception.

10.4.3. Male Subjects

Male subjects with female partner(s) of childbearing potential must agree to avoid fathering a child and use acceptable methods of birth control (Section 10.4.1) throughout the study. Continued use of an effective and medically acceptable form of birth control is recommended through 30 days after study completion.

11. STUDY ASSESSMENTS

A study schematic is presented in Figure 3. A summary of assessments to be conducted at each visit is presented in Table 2.

Clinical laboratory evaluations will be performed by a central laboratory. All clinical and laboratory evaluations, procedures related to inclusion/exclusion criteria, or performed during treatment must be reviewed, initialed and dated by the Investigator or appropriate designee.

Study center raters of efficacy and safety assessments will be trained prior to performing any assessments.

If a subject attends a clinic visit (except SV1, ET or EOS) in the morning after withholding antiparkinsonian medications, including APL-130277 and s.c. apomorphine, beginning at midnight the night before the visit and the subject's full "OFF" was not identified, the site should wait until subject is in the full "OFF" state before performing study assessments; to facilitate scheduling, the subject may return to the clinic the following day.

11.1. Demographics and Baseline Characteristics

Demographics (date of birth, sex, ethnicity, race), prior and current medications, and medical and PD history will be collected.

The medical history should assess the subject's current PD medications, including medication name, dose, number of tablets per dose (if applicable), dosage units and frequency per day. Drug, alcohol, and smoking history will also be collected.

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 duration of "OFF" episodes;
- Severity of dyskinesia;
- PD medications previously or currently taken, including:
  - Dopamine agonists;
  - MAO-B inhibitors;
  - COMT inhibitors;
  - Amantadine;
  - Anti-cholinergics.

11.1.1. Modified Hoehn and Yahr

The Modified Hoehn and Yahr scale will be administered at Screening to verify the subject meets the eligibility criteria for this study. The modified Hoehn and Yahr is to be conducted at SV1 in the "ON" state, and twice at SV2 (in the "OFF" state prior to L-Dopa challenge and then in the "ON" state following the L-Dopa challenge).

11.1.2. Mini-Mental State Examination

Mini-Mental State Examination (MMSE) will be administered at Screening to verify the subject meets the eligibility criteria for this study.

The MMSE is to be conducted while the subject is in the "ON" state.

11.2. Efficacy Assessments

11.2.1. MDS-UPDRS Part III

At SV2, MDS-UPDRS Part III will be completed just prior to L-Dopa dosing and at 30 minutes after L-Dopa administration. If the subject does not experience an "ON" within 30 minutes, the site should record the time when the subject turns "ON" and complete an additional MDS-UPDRS Part III assessment at this time.

In PART A, MDS-UPDRS Part III will be completed just prior to dosing and at 15, 30, 60, 90, and 120 minutes post-dose (± 5 minutes at each time point) if a subject has a full ON response at 30 minutes. **NOTE:** If the subject does NOT turn "ON" within and up to the 30 minute timepoint, the remaining MDS-UPDRS Part III assessments should cease. If the subject is full OFF at 90 minutes, the 120-minute response is not collected. If the subject is partial ON at 90 minutes, the 120 minute response is collected.

In PART B, MDS-UPDRS Part III will be assessed just prior to dosing and at 15, 30, 60, 90, and 120 minutes post-dose. During PART B the assessment will be completed by a rater blinded to the subject's study drug.

If the subject turns "OFF" before the 120 minute timepoint, the remaining MDS-UPDRS Part III assessments must still be made at the required timepoints up to and including 120 minutes**. If the subject does not turn 'ON' by the 30 minute post-dose assessment, assessments should continue at each timepoint until 120 minutes.**

All efforts should be made to ensure the same assessor should be used for each subject's MDS-UPDRS assessment during PART B of the study to reduce variability.

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 Screening.

11.2.2. Confirmation of "OFF" or "ON" Episodes

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

At Screening Visit 2 (SV2), subjects will withhold their usual morning L-Dopa dose. While at the clinic, they will receive their usual dose of L-Dopa (**without** adjunctive PD medication) after their normally scheduled second dose of PD medication and study procedures are completed. 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 be instructed on the definitions of "ON" (partial and full ON) and "OFF" states. 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 subject has demonstrated understanding of the "OFF" and "ON" states, the training is complete. Successful completion and understanding of this training should be noted in the appropriate eCRF.

Following dosing with their normal dose of L-Dopa, subjects should also report the time (using 24 hour clock) when the study medication is starting to have an effect (partial "ON", if applicable), time of "Full ON" and time of "OFF" up to and including 120 minutes from dosing. These times are to be documented using the 24 hour clock on the appropriate form of the CRF.

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

11.2.2.1. Definitions of "OFF", Full "ON", and Partial "ON"

The following definitions will be used in this study:

"OFF" (full "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", Note: Not applicable for at-home assessments using the subject dosing diary;
- Confirmed by the subject as "OFF".

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

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

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

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

Partial "ON" as assessed by the **subject** – defined as:

- A period of time where medication is providing some improvement with regard to mobility, stiffness and slowness but where the subject does not feels he/she can yet perform normal daily activities.
- A response that is less than their normal response to PD medications prior to enrolling in the study.

Partial "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 some level of improvement with regard to mobility, stiffness and slowness but subject does yet not have adequate motor function to allow them to perform their normal daily activities.

Investigator Confirmation of the "OFF" state must occur prior to dosing a subject with study drug (or their standard L-Dopa dose at SV2). The same assessor should be used for each subject throughout the study.

Subjects must confirm they are in an "OFF" state prior to dosing with study drug (or their standard L-Dopa dose at SV2).

During Part B, assessment of the subject's "OFF"/"ON" state will be conducted as part of the MDS-UPDRS Part III assessments.

11.2.3. MDS-UPDRS Parts I, II, and IV

Part I (Non-Motor Aspects of Experiences of Daily Living), Part II (Motor Aspects of Experiences of Daily Living), and Part IV (Motor Complications) of the MDS-UPDRS will be completed at Screening and at PART B V2, V3, V5, and V6. The MDS-UPDRS Parts I, II, and IV may be assessed by either a blinded or unblinded rater.

11.2.4. Treatment Satisfaction Questionnaire for Medication (TSQM)

The level of satisfaction or dissatisfaction with the medication will be evaluated using the Treatment Satisfaction Questionnaire for Medication (14-item) at Visit 3 and Visit 6. The assessment will evaluate the effectiveness, side effects, and convenience of the medication over the previous 4 weeks.

The TSQM is to be conducted while the subject is in the "ON" state.

11.2.5. Clinical Global Impression – Severity Scale (CGI-S)

The CGI-S is a clinician-rated assessment of the subject's current illness state ("OFF" episodes associated with PD) on a 7-point scale, where a higher score is associated with greater illness severity. The CGI-S will be administered at Clinic Visit 1. Following a clinical interview, the CGI-S can be completed in 1-2 minutes (Guy, 1976; Williams, 2000). The same blinded study site rater should perform all CGI assessments for a given subject whenever possible.

11.2.6. Clinical Global Impression – Improvement Scale (CGI-I)

The CGI-I is a clinician-rated assessment of the subject's global improvement in which the clinician compares the patient's overall clinical condition ("OFF" episodes associated with PD) to the one week period just prior to the initiation of medication (Baseline visit). The CGI-I is based on a 7-point scale, where a lower score is associated with higher symptom improvement. Following a clinical interview, the CGI-I can be completed in 1-2 minutes (Guy, 1976). The anchored version of the CGI-I, adapted from Kay, 1991, will be used in this study. The CGI-I will be administered on Clinic Visit 3 and 6. The same blinded study site rater should perform all CGI-I assessments for a given subject whenever possible.

11.2.7. Patient Global Impression – Severity Scale (PGI-S)

The PGI-S is a global index that may be used to rate the severity of a specific condition. The PGI-S is based on a 4-point scale, where 1 = normal and 4 = severe. The PGI-S will occur at Clinic Visit 1.

The PGI-S is to be conducted while the subject is in the "ON" state.

11.2.8. Patient Global Impression – Change Scale (PGI-C)

The PGI-C is the patient reported outcome counterpart to the Clinical Global Impressions scale, (CGI), which was published in 1976 by the National Institute of Mental Health (US). It consists of one item taken from the CGI and adapted to the patient. The PGI-C is based on a 7-point scale, where a lower score is associated with higher symptom improvement. The PGI-C will occur at Clinic Visit 3 and 6.

The PGI-C is to be conducted while the subject is in the "ON" state.

11.2.9. Dyskinesia Questionnaire

At V3 and V6 only, the subject will be asked "how would you score the amount of troublesome dyskinesia you had in the last month- less than usual, the same as usual, more than usual". Troublesome Dyskinesia is defined as "Of at least moderate severity such that the dyskinesia impacts activities of daily living to the point that you cannot perform some activities or participate in some social activities during dyskinetic episodes."

If the subject discontinues the study early, the subject will be asked at the Early Termination Visit, "how would you rate the amount of troublesome dyskinesia you had since your last clinic visit - less than usual, the same as usual, more than usual". Troublesome Dyskinesia is defined as "Of at least moderate severity such that the dyskinesia impacts activities of daily living to the point that you cannot perform some activities or participate in some social activities during dyskinetic episodes."

11.2.10. Subject Home Diary

11.2.10.1. PART A Daily Home Dosing Diary

If the subject continues the titration process of APL-130277 at home, the subject will complete a separate PART A Daily Home Dosing Diary for every dose of APL-130277 they self-administer and indicate the date, dose, time of dose, and whether he/she was full "ON" within 30 minutes.

11.2.10.2. PART B Daily Home Dosing Diary

In PART B, the subject will be asked to complete the PART B Daily Home Dosing Diary every day using a paper dosing diary to record the date, time of dose, who administered the dose, and dose.

At each visit, the Investigator will review the completed diary with the subject and assess the number of doses for each day. Missing data or inconsistencies will be reviewed by the clinical site staff with the subject and additional training on diary completion will be provided as needed.

11.2.10.3. PART B Expanded Daily Home Dosing Diary

In PART B, the subject will be asked to complete the PART B Expanded Daily Home Dosing Diary for the 3 days prior to V2, V3, V5, and V6.

The subject will be asked to use a paper dosing diary to record the date, time of dose, who administered the dose, and dose, whether the subject was "ON" within 30 minutes, "ON" at 60, and "ON" at 90 minutes post-dose and whether he/she experienced dyskinesia and whether the dyskinesia was troublesome at any time while he/she was ON.

At each visit, the Investigator will review the completed diary with the subject and assess the number of doses for each day in addition to the "ON" response and dyskinesia. Missing data or inconsistencies will be reviewed by the clinical site staff with the subject and additional training on diary completion will be provided as needed.

11.3. Pharmacokinetic Assessment

For sites participating in the PK collection, blood draws for PK analyses of apomorphine and its metabolites (apomorphine-sulfate, norapomorphine, and others as deemed necessary) will occur during PART B at V2, V3, V5, and V6. Blood draws will occur just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes post-dose (± 5 minutes for each time point). Sampling should occur as close as possible to the target time. The samples are to be collected while the subject is in the supine position and just prior to blood pressure collection for vital signs assessments. Subjects may be catheterized to facilitate blood collection.

Instructions specific to PK draws and sample handling will be outlined in the Laboratory manual.

Plasma samples collected for PK may also be used for the additional characterization and/or bioanalytical method development of putative metabolites of apomorphine, if needed.

11.4. Safety Assessments

11.4.1. Adverse Events

Adverse events will be collected for each subject. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12, Safety Reporting.

AEs and SAEs will be monitored throughout the study at all visits, including telephone assessments.

11.4.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 21. For detailed instructions regarding laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

11.4.3. Vital Signs, Height, and Weight

After rested in the supine position for at least 3 minutes, systolic and diastolic blood pressures, respiratory rate, pulse rate, and body temperature will be collected. Blood pressure and pulse rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study.

If the subject is unable to stand due to orthostatic symptoms such as light-headedness, dizziness, or changes in sensorium upon standing, every attempt should be made to obtain BP and HR in the sitting position.

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

- a systolic BP decrease of ≥ 20 mmHg within 3 minutes of standing up from a supine position; and/or
- a diastolic BP decrease of ≥ 10 mmHg within 3 minutes of standing up from a supine position.

During PART A, vital signs will be collected just prior to dosing and at 60 minutes postdose. During PART B, vital signs will be collected just prior to dosing and at 30 minutes postdose. During PART B, vital signs may be collected at 90 and 120 minutes postdose if clinically necessary in the Investigator's opinion. A window of ± 10 minutes is allowed for vital signs collection.

Weight and height should be measured in indoor clothing with no shoes. Height will only be recorded at Screening.

11.4.4. Electrocardiograms (ECGs)

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 10 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. The time the ECG is performed will be recorded (using a 24-hour clock). See Section 20, Appendix I for additional details on ECG collection and reporting.

For Part A and Part B, ECGs will be performed just prior to dosing and 50 (± 30) minutes post dose. Unscheduled ECGs may be performed if clinically indicated by changes in vital signs (orthostatic hypotension) or symptoms (new cardiovascular symptoms eg, dizziness, syncope).

A central facility will be used in this study for interpretation and analysis of ECGs.

The PI or a qualified designee must review, initial, and date the ECG, which must be filed in the subject's study chart. Results will be captured in the subject's study chart, not in the eCRF.

Clinically significant findings at the screening ECG must be captured in the medical history. Any clinically significant changes compared with screening must be captured as AEs in the eCRF.

11.4.5. Physical Examinations

Complete physical examinations at all scheduled time points must include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including the oral cavity; musculoskeletal system; central and peripheral nervous system; and skin; to be done at SV1 (or may be completed at SV2) and End of Study Visit (EOS).

Abbreviated physical examinations at all scheduled time points must include head-eyes-ears-nose and throat; cardiovascular system; respiratory system; abdomen; and evaluation for local irritation or injection site reactions following administration of s.c. apomorphine and oropharyngeal cavity examination following administration of APL-130277; to be done at all clinical visits in Part A and Part B except for the EOS and ET visits at which time a complete physical examination will occur.

All examinations performed in this study, whether complete or abbreviated at all scheduled timepoints, will include an oropharyngeal cavity examination by the unblinded 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(s):

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

Grade:

- Mild
- Moderate
- Severe

All examinations performed in this study, whether complete or abbreviated, will include a visual inspection of s.c. apomorphine injection sites by the unblinded Investigator (or designate trained to perform this examination). Each location within the skin assessment will be scored and graded as follows:

Dermal response:

0 = no evidence of irritation

1 = minimal erythema, barely perceptible

2 = definite erythema, readily visible; minimal edema or minimal papular response

3 = erythema and papules

4 = definite edema

5 = erythema, edema, and papules

6 = vesicular eruption

7 = strong reaction spreading beyond test site.

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

In the event of either local irritation or injection site reactions, IP may be discontinued at Investigator discretion and contact the Medical Monitor.

All oral AESIs are considered immediately reportable events and must be reported to the Sponsor within 1 business day of the Investigator or study center staff becoming aware of the event. An SAE/ Adverse Event of Special Interest Reporting form is to be completed and submitted to PPD Pharmacovigilance within 1 business day

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

11.4.6. Post-dose Assessment of Dyskinesia

If the Investigator observes dyskinesia in the subject anytime post-dose up through the last time point monitored, it should be reported as an AE.

11.4.7. Safety Scales

11.4.7.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal adverse events (suicidal behavior and suicidal ideation) for 12 months prior to the Screening visit and throughout the study. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The scale takes approximately 5 minutes to administer. The C-SSRS will be administered by a trained rater at the study center.

The C-SSRS Screening/Baseline Version will be used at Screening and the C-SSRS Since Last Visit Version will be used at all visits in PART A and PART B. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional. The same study center rater should perform all C-SSRS assessments for a given subject whenever possible.

The C-SSRS is to be conducted while the subject is in the “ON” state.

11.4.7.2. Other Safety and Quality of Life Assessments

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

- Parkinson's Disease Questionnaire (PDQ-39), to be performed while subject is in the "ON" state (Part B V1, V3 and V6).
- Zarit Burden Interview (ZBI) – Optional; to be completed if caregiver is present and consent is provided (Part B V1, V3 and V6).
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS), to be performed while subject is in the "ON" state (Part B V1, V3, V4 and V6).
- European Quality of Life – 5 Dimensions (EQ-5D-5L), to be performed while subject is in the "ON" state (Part B V1, V3 and V6).
- Ease of Use Questionnaire, to be performed while subject is in the "ON" state (Part B V3 and V6).

11.5. Recommended Sequence of Clinical Assessments

Table 6 outlines the relevant clinical assessments that will be performed by the study center. It is recommended that the assessments noted in Table 6 are ordered in the following way:

Table 6: Recommended Sequence of Clinical Assessments

Prior to Dosing	**After Dosing**
1. ECG	1. Subject "OFF"/"ON" Status
2. Vital Signs	2. MDS-UPDRS Part III
3. Subject "OFF"/"ON" status	3. ECG
4. MDS-UPDRS Part III	4. Vital Signs

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

ECG and vital sign predose assessments are to be completed within 60 minutes prior to dosing. MDS-UPDRS Part III and Subject "OFF"/"ON" status predose assessments are to be completed within 30 minutes prior to dosing.

A window of ± 30 minutes is allowed for the 50-minute postdose ECGs. A window of ± 10 minutes is allowed for vital signs collection. A window of ± 5 minutes is allowed for all other assessments during clinic visits.

11.6. Study Visits and Assessments

A study schematic is presented in Figure 3. A summary of assessments to be conducted at each visit is presented in Table 2 and Table 3.

Assessments will be conducted within the time frames specified. All times are relative to the time of dosing for individual subjects unless otherwise specified.

11.6.1. Screening Visits

All screening assessments must be performed within 21 days before Titration Visit 1 (TV1). If TV1 is required to occur more than 21 days after SV1, Medical Monitor approval is required. Subjects who fail the screening process will be allowed to rescreen once if agreed by the Medical Monitor.

11.6.1.1. Screening Visit 1 (SV1)

Before any study procedures are performed on any subject, written informed consent must be obtained at the initial Screening Visit (SV1). Following receipt of subject consent and completion of SV1 assessments, the subject will be instructed to return to the clinic for SV2.

The investigator may perform procedures/assessments scheduled for SV1 at SV2 except for the L-Dopa challenge, MDS-UPDRS Part III, and subject "OFF" versus "ON" training.

The following procedures will be performed by study staff at SV1:

- Written Informed Consent.
- Review Entry Criteria.
- Modified Hoehn and Yahr (in the "ON" state).
- MDS-UPDRS Part I, II and IV.
- Medical History/Demographics. Record demographics and detailed medical history, including review of medications taken within 6 months prior to SV1, current treatment regimens, drug, alcohol and smoking history.
- Complete Physical Exam, including Oropharyngeal Site Exam. 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.
- Body Mass Index (BMI), weight and height. Measure height and weight; calculate BMI.
- 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 blood pressure and heart rate. 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.
- 12-Lead Electrocardiogram (ECG).
- Clinical Laboratory Tests. Collect blood and urine for clinical laboratory tests (hematology, chemistry, urinalysis and serology [serology collected at the Screening Visit only], and urine drug screening) and serum pregnancy test (for females of

childbearing potential only, [serum pregnancy test collected at the Screening Visit only]). The total volume of blood collected will not exceed 25 mL at each time point.

- Mini-mental State Examination (MMSE). Perform a MMSE.
- Columbia Suicide Severity Rating Scale (C-SSRS). Assess suicidal ideation using C-SSRS. The "Screening" scale should be used at this visit.
- Prior/concomitant medication review.
- Record adverse events.

11.6.1.2. Screening Visit 2 (SV2)

Subjects will be instructed to attend Screening Visit 2 (SV2) after withholding their normal morning dose of L-dopa (ie, in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior).

Definitions of "OFF", Full "ON", and Partial "ON" are in Section 11.2.2.1.

The following procedures will be performed by study staff at SV2 (note: a window of ± 30 minutes is allowed for post dose ECGs; a window of ± 10 minutes is permitted for Vital Signs assessments and a window of ± 5 minutes of scheduled time is allowed for all other timed assessments):

- Review Entry Criteria.
- Modified Hoehn and Yahr (in the "OFF" state). Assess subject using the Modified Hoehn and Yahr scale.
- Subject "OFF" versus "ON" Training. Perform subject training in order to distinguish "OFF" versus "ON".
- MDS-UPDRS Parts I and II. Assess subject using MDS-UPDRS Parts I and II.
- MDS-UPDRS Part III. Assess subject motor function using MDS-UPDRS Part III at just prior to L-Dopa administration and 30 minutes after L-Dopa administration. If the subject does not experience an "ON" within 30 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. If the subject does not turn 'ON' by the 30 minute post-dose assessment, assessments should continue at each timepoint until 120 minutes.
- Levodopa (L-Dopa) Challenge. Subjects will take their normal dose of L-Dopa ***without*** their normal adjunctive PD medication. Levodopa challenge will be performed at SV2 in clinic in the 'OFF' state. As part of the L-Dopa challenge subjects will take their normal morning dose of L-Dopa in clinic without their normal adjunctive PD medication. L-Dopa responsiveness is to be confirmed by assessment of the subject's motor function using MDS-UPDRS Part III at t = 0 (just prior to L-Dopa administration), 15, 30, 60, 90, and 120 minutes after L-Dopa administration. The subject should be trained to indicate to site staff once they first note improvement in symptoms (i.e. Partial ON), and when they are in a Full 'ON' state. The Investigator will confirm "OFF" or "ON" state at each timepoint. Subjects who fail to

turn Full 'ON' following dosing with L-Dopa as part of the L-dopa challenge may not be re-screened.

- Modified Hoehn and Yahr (in the "ON" state). Assess subject using the Modified Hoehn and Yahr scale.
- Investigator rating of "OFF" or "ON". Investigator will confirm whether subject is "OFF", Full "ON" or Partial "ON" (see Section 11.2.2.1), and note the time the subject changes from "OFF" to Partial "ON" or Full "ON". The Investigator will also record the subject "ON"/"OFF" status prior to performing each MDS-UPDRS Part III assessment.
- Subject rating of "OFF" or "ON". The subject will confirm whether he/she is "OFF", Full "ON" or Partial "ON" (see Section 11.2.2.1), and the staff will ask the subject to notify the staff when he/she changes from "OFF" to Partial "ON" or Full "ON". The subject will also be queried as to their "ON"/"OFF" status prior to performing each MDS-UPDRS Part III assessment.
- Post-dose Assessment of Dyskinesia.
- Adverse event monitoring.
- Prior/concomitant medication review.

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.

SV2 must be completed, and all data entered into the EDC at least 6 days prior to TV1 in order for the Enrollment Adjudication Committee (EAC) to review subject data and give go-ahead for subject to be randomized. Sites should enter the subject's SV2 MDS-UPDRS Part III data in the eCRF as soon as possible following SV2. The EAC will review subject data from SV1 and 2 to assess subjects' suitability to be entered into the Dose Titration Phase (PART A). Subjects will not be entered into Dose Titration (PART A) until approved by the EAC, Sponsor, and Medical Monitor.

Once the site has been informed the subject has been approved to enroll, the site will contact the IXRS and determine the randomization for PART A. Subjects will be randomized to 1 of 2 treatment sequences in a 1:1 ratio. Depending on the subject's random treatment assignment, dose titration will begin with either APL-130277 or s.c. apomorphine.

11.7. PART A – Dose Titration Phase

Eligible subjects will be instructed to return to clinic on Dose Titration Visit 1 (TV1) after withholding their normal morning dose of L-dopa (i.e., in the practically defined "OFF" state with no anti-parkinsonian medication after midnight the night prior).

If the subject's random treatment assignment is APL-130277, APL TV1 will continue in Section 11.7.1.1; if the subject's random treatment assignment is s.c. apomorphine, SC TV1 will continue in Section 11.7.2.1.

In general, the following procedures should be followed during titration:

- For APL-130277 and sc apomorphine, subjects are to be titrated to a dose that is tolerable and effective as deemed by the investigator and subject.
- Uptitration should continue until a full ON is achieved at 30 minutes. The dose should also be optimized such that it provides the best ON response with respect to time to effect, the magnitude of response and its duration. Once a full ON is confirmed at 30 minutes, assessments should continue up to 120 minutes unless the subject is in a full OFF at 90 minutes,
- Assessments of response should be done when the subject is in a practically defined full OFF state, not in a partial ON state.
- APL titration is to be done at home in 5 mg increments following the initial dose of 10 mg, which is done in clinic. Uptitration should continue at home until the best possible response has been achieved (faster time to, longer duration, or improved "ON"). A DCV is to be scheduled 5-7 days of APL TV1, or earlieras determined by the Investigator. Subsequent uptitration, if necessary, can be done in clinic or at home
- For de novo subjects, sc apomorphine titration is to be done in clinic starting at 2 mg and up to 6 mg as tolerated over 2 days. However, subjects currently taking s.c. apomorphine prior to screening may enter titration at that dose following at least 1 day washout. Uptitration can be done at the investigator's discretion.
- The final dose for APL 130277 and sc apomorphine must be approved by the medical monitor prior to randomization for Part B and within 24 hours of receipt of the MDS-UPDRS part III and ON/OFF data.
- Domperidone can be used prophylactically and as clinically warranted at the discretion of the investigator.

11.7.1. Titration of APL-130277

The titration of APL-130277 will start in the clinic at 10 mg, and if the subject fails to convert from a practically defined "OFF" to a full "ON" within 30 minutes (per both the Investigator and subject) or the Investigator selects to uptitrate to assess whether the subject has a more optimal "ON", the subject will be instructed on how to self-administer increasing doses of APL-130277 and continue the titration process at home.

If the 10 mg dose, results in a full "ON" within 30 minutes (per both the Investigator and subject), but not in an optimal ON response (determined by the onset, magnitude and duration of effect as measured by the MDS-UPDRS part III and ON/OFF response), unless there are safety/tolerability concerns, the next higher dose, 15 mg, should be administered at home in order to assess for an improved full "ON" response. The subject should be instructed on how to self-administer increasing doses of APL-130277 and continue the titration process at home. Uptitration in 5 mg increments should continue at home until the subject achieves an optimal ON response as determined by subject and investigator.

The site will contact the subject daily by telephone to determine titration status and query for tolerability/safety issues. If the site, ascertains the dose of APL-130277 provides an optimal "ON" response, the subject will return to the clinic for a Dose Confirmation Visit 5-7 days of APL TV1, or earlier as determined by the investigator, to confirm the efficacy and tolerability of

the selected dose. If the investigator deems this dose to be the most effective dose in eliciting an optimal "ON" response, this dose will be used in Part B of the study.

If a full "ON" response within 30 minutes is not achieved, or the investigator deems the response is not optimal at the DCV, uptitration may continue in clinic during the subject's next full OFF state or at home (at the investigator's discretion). Following further uptitration at home, additional DCVs should take place within 5 days of one another.

If at any time, the Investigator determines there are tolerability issues with APL-130277 during home titration the subject will be instructed to withhold further administration of APL-130277 and come to the clinic for an unscheduled clinic visit.

A schematic showing the flow of APL-130277 titration is shown in Figure 1.

The effective dose for APL-130277 must be approved by the medical monitor based on review of the titration data.

11.7.1.1. APL-130277 Titration Visit 1 (APL TV1) – Study Day 1

Site staff will perform the following procedures at APL-130277 Titration Visit 1, Day 1 (note: ECG and vital sign predose assessments are to be completed within 60 minutes prior to dosing. MDS-UPDRS Part III and Subject "OFF"/"ON" status predose assessments should be completed within 30 minutes prior to dosing. A window of ± 30 minutes is allowed for the 50-minute postdose ECG, a window of ± 10 minutes is allowed for vital signs collection, a window of ± 5 minutes is allowed for all other timed assessments):

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic Dosing of Study Drug.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.
- Dispense Study Drug for Outpatient Dosing. (**Note:** only if the subject did not achieve full "ON" at 30 minutes post-dose of 10 mg APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose.)
- APL-130277 self-administration Training. (**Note:** only if the subject did not achieve full "ON" at 30 minutes post-dose of 10 mg APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose.)

- Home Dosing Diary Training. (**Note:** only if the subject did not achieve full "ON" at 30 minutes post-dose of 10 mg APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose.)
- Provide Home Dosing Diary. (**Note:** only if the subject did not achieve full "ON" at 30 minutes post-dose of 10 mg APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose.)
- Postdose (60 minutes postdose) 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 blood pressure and heart rate. 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.
- Postdose 12-lead ECG (50 minutes ± 30 minutes postdose)
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Prior/concomitant medication review.

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 their standard dosage, or at a dosage considered appropriate by the Investigator to achieve a full "ON" state. If this occurs, the subject may return to the clinic on another day to resume the titration with the next highest dose. However, if the subject cannot tolerate the "OFF" state and does not respond efficaciously to a dose of APL-130277, the subject will be terminated from the study. If a subject requires rescue medication, efficacy assessments **will not be performed**.

Subjects who respond to APL-130277 10 mg dose with a full "ON" response within approximately 30 minutes (per both the Investigator and subject) should continue assessments up to 120 minutes. Details of dose and subject tolerability should be sent to the Medical Monitor for review. Upon approval from the Medical Monitor, they will be considered complete and their visit for s.c. apomorphine Dose Titration or PART B will be scheduled as applicable.

The titration of APL-130277 will start in the clinic at 10 mg, while the subject is in a practically defined "OFF" state after withholding Parkinson's disease medication beginning at midnight the night before. If the subject fails to convert from a practically defined "OFF" to a full "ON" within 30 minutes, the subject will be instructed on how to self-administer increasing doses of APL-130277 and will continue the titration process at home.

If the 10 mg dose of APL-130277 results in a full "ON" within 30 minutes (per both the Investigator and subject), but not an optimal full "ON" response, unless there weres safety/tolerability issues with the 10 mg dose, the next higher dose, 15 mg, should be administered at home in order to assess for an optimal full "ON" response. Uptitration in 5 mg increments should continue at home until the subject achieves the optimal "ON" response.

The Part A Home Dosing Diary will be dispensed, and the subject will be instructed on how to complete the daily diary and how to self-administer increasing doses of APL-130277. Uptitration in 5 mg increments should continue at home until the subject achieves an optimal ON response as determined by subject and investigator.

11.7.1.2. Telephone Call 1 (T1) – Day 2 (if needed)

On Day 2, the subject should treat their first morning "OFF" episode with a single dose of 15 mg APL-130277, after withholding their usual anti-parkinsonian medications from midnight the night prior. The subject should complete their home dosing diary on each day of at-home dose titration. The subject can resume their usual anti-parkinsonian medications (including long-acting dopamine agonists) approximately 60 minutes after they take their dose of APL-130277.

The site will contact the subject by telephone to determine if the 15 mg dose was effective in the subject achieving the "ON" state at 30 minutes post-dose, and to query for adverse events experienced during dosing.

- If the 15 mg dose provides a full "ON" response, depending on the AEs, robustness, time to effect, and duration of the "ON" response reported by the subject, at the investigator's discretion, the next higher dose could be assessed to see if an improved full "ON" can be achieved. The subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day (Day 3), the subject should treat the first morning "OFF" episode with a single dose of 20 mg APL-130277.

  If the investigator believes the optimal ON response has been achieved, the subject should not administer any additional APL-130277 doses. The subject will return to the clinic for Dose Confirmation Visit (APL DCV) 5-7 days of APL TV1, or earlier as determined by the investigator, and he/she should attend the visit in the practically defined "OFF" state.
- If the 15 mg dose does not provide a full "ON" response, the subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day (Day 3), the subject should treat the first morning "OFF" episode with a single dose of 20 mg APL-130277.

The following safety assessments will be conducted on the telephone call:

- Adverse event monitoring.
- Prior/concomitant medication review.

11.7.1.3. Telephone Call 2 (T2) – Day 3 (if needed)

On Day 3, the subject should treat their first morning "OFF" episode with a single dose of 20 mg APL-130277, after withholding their usual anti-parkinsonian medications from midnight the night prior. The subject should complete their home dosing diary on each day of at-home dose titration. The subject can resume their usual anti-parkinsonian medications (including long-acting dopamine agonists) approximately 60 minutes after they take their dose of APL-130277.

The site will contact the subject by telephone to determine if the 20 mg dose was effective in the subject achieving the "ON" state at 30 minutes post-dose, and to query for adverse events experienced during dosing.

- If the 20 mg dose provides a full "ON" response, depending on the AEs, robustness, time to effect, and duration of the "ON" response reported by the subject, at the investigator's discretion, the next higher dose could be assessed to see if an improved full "ON" can be achieved. the subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day (Day 3), the subject should treat the first morning "OFF" episode with a single dose of 25 mg APL-130277.

  If the investigator believes the optimal ON response has been achieved, the subject should not administer any additional APL-130277 doses. The subject will return to the clinic for Dose Confirmation Visit (APL DCV) no later than 5-7 days of APL TV1, or earlier as determined by the investigator, and he/she should attend the visit in the practically defined "OFF" state.
- If the 20 mg dose does not provide a full "ON" response, the subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day (Day 4), the subject should treat the morning "OFF" episode with a single dose of 25 mg APL-130277.

The following safety assessments will be conducted on the telephone call:

- Adverse event monitoring.
- Prior/concomitant medication review.

11.7.1.4. Telephone Call 3 (T3) – Day 4 (if needed)

On Day 4, the subject should treat their first morning "OFF" episode with a single dose of 25 mg APL-130277, after withholding their usual anti-parkinsonian medications from midnight the night prior. The subject should complete their home dosing diary on each day of at-home dose titration.

The site will contact the subject by telephone to determine if the 25 mg dose was effective in the subject achieving the "ON" state at 30 minutes post-dose, and to query for adverse events experienced during dosing.

- If the 25 mg dose provides a full "ON" response, depending on the AEs, robustness, time to effect, and duration of the "ON" response reported by the subject, at the investigator's discretion, the next higher dose could be assessed to see if an improved full "ON" can be achieved. the subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day (Day 3), the subject should treat the first morning "OFF" episode with a single dose of 30 mg APL-130277.

  If the investigator believes the optimal ON response has been achieved, the subject should not administer any additional APL-130277 doses. The subject will return to the clinic for Dose Confirmation Visit (APL DCV) no later than 5-7 days of APL

TV1, or earlier as determined by the investigator, and he/she should attend the visit in the practically defined "OFF" state.

- If the 25 mg dose does not provide a full "ON" response, the subject will be instructed to resume their usual anti-parkinsonian medications (including long-acting dopamine agonists) and treat their next "OFF" episode (that occurs at least 2 hours after the first dose of APL-130277) with a single dose of 30 mg APL-130277.
  - If no other "OFF" episode occurs on Day 4, the subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day (Day 5), the subject should treat the first morning "OFF" episode with a single dose of 30 mg APL-130277.
  - If the 30 mg dose provides a full "ON" response, the subject should not administer any additional APL-130277 doses. The subject will return to the clinic for DCV no later than 5-7 days of TV1, or earlier as determined by the investigator, and should attend the visit in the practically defined "OFF" state.
  - If the 30 mg dose DOES NOT provide a full "ON" response, the subject should not administer any additional APL-130277 doses. The subject will return to the clinic for DCV no later than 5-7 days of TV1, or earlier as determined by the investigator, and should attend the visit in the practically defined "OFF" state.

The following safety assessments will be conducted on the telephone call:

- Adverse event monitoring.
- Prior/concomitant medication review.

11.7.1.5. APL Dose Confirmation Visit (APL DCV) (Additional Visits if needed)

If a full "ON" response within 30 minutes is not achieved in clinic, or the investigator deems the response is not optimal during DCV1, the next higher dose could be evaluated in-clinic no sooner than 2 hours after the previous dose and no later than 5 days once the subject is in a full OFF state.

Alternatively, uptitration may continue at home following home titration procedures. Additional DCV(s) following a optimal "ON" response will be performed no later than 5 days of one another. The subject must be in an "OFF" state prior to uptitration.

In the event of safety/tolerability concerns, a lower dose could be assessed in-clinic no sooner than 2 hours after the previous dose and not later than 5 days.

11.7.1.5.1. For Subjects who Achieved a Full "ON" with At-home Titration

With the subject at the clinic in the "OFF" state, the site will confirm the response to the dose that was effective achieving the "ON" state (ie, 15 mg, 20 mg, 25 mg, or 30 mg) and evaluate the effect by confirming the time to "ON" state.

Site staff will perform the following procedures at APL DCV1 (note: ECG and vital sign predose assessments are to be completed within 60 minutes prior to dosing. MDS-UPDRS Part III and Subject "OFF"/"ON" status predose assessments are to be completed within 30 minutes prior to dosing. A window of ± 30 minutes is allowed for the 50-minute postdose ECG, a window of

± 10 minutes is allowed for vital signs collection, a window of ± 5 minutes of scheduled time is allowed for all other timed assessments):

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic Dosing of Study Drug.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.
- Collect Study Drug and Perform Drug Accountability.
- Dispense Study Drug for Outpatient Dosing. (**Note:** only if the subject did not achieve full "ON" at 30 minutes of dosing the dose the subject determined to be the effective dose of APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose at home.)
- APL-130277 self-administration Training. (**Note:** only if the subject did not achieve full "ON" at 30 minutes of dosing the dose the subject determined to be the effective dose of APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose at home.)
- Home Dosing Diary Training. (**Note:** only if the subject did not achieve full "ON" at 30 minutes of dosing the dose the subject determined to be the effective dose of APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose at home.)
- Provide Home Dosing Diary. (**Note:** only if the subject did not achieve full "ON" at 30 minutes of dosing the dose the subject determined to be the effective dose of APL-130277, or the Investigator decided to uptitrate the subject to the next higher dose at home.)
- Collect and Review prior Home Dosing Diary.
- Postdose vital signs (60 minutes postdose) (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 blood pressure and heart rate. 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.

- Postdose 12-lead ECG (50 minutes ± 30 minutes postdose)
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Prior/concomitant medication review.

Subjects who respond to the APL-130277 15 mg, 20 mg, 25 mg, or 30 mg dose (as appropriate) with a full "ON" response within approximately 30 minutes should continue assessments up to 120 minutes. Details of dosing and subject tolerability are to be sent to the Medical Monitor. Upon Medical Monitor approval they will be considered complete and their visit for s.c. apomorphine Dose Titration or PART B will be scheduled as applicable.

The subject may not move on with dosing until approval is obtained from the Medical Monitor.

11.7.1.5.2. For Subjects Who Did Not Achieved a Full "ON" During At-home Titration

With the subject at the clinic in the "OFF" state, the site will administer 30 mg of APL-130277 to the subject and evaluate the effect.

Site staff will perform the following procedures at APL DCV1 (note: ECG and vital sign predose assessments are to be completed within 60 minutes prior to dosing. MDS-UPDRS Part III and Subject "OFF"/"ON" status predose assessments are to be completed within 30 minutes prior to dosing. A window of ± 30 minutes is allowed for the 50-minute postdose ECG, a window of ± 10 minutes is allowed for vital signs collection, a window of ± 5 minutes of scheduled time is allowed for all other assessments):

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic-Dosing of Study Drug.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.
- Collect Study Drug and Perform Drug Accountability.
- Collect and Review Home Dosing Diary.

- Postdose vital signs (60 minutes postdose) (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 blood pressure and heart rate. 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.
- Postdose 12-lead ECG (50 minutes ± 30 minutes postdose)
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Prior/concomitant medication review.

Subjects who do respond to the APL-130277 30 mg dose with a full "ON" response within approximately 30 minutes will be considered complete and their visit for s.c. apomorphine Dose Titration or PART B will be scheduled as applicable.

If the subject does not achieve "ON" within approximately 30 minutes at a dose of 30 mg (as confirmed by both the Investigator and subject), he/she will be considered a non-responder to the doses examined in CTH-302, and will be withdrawn from the study and have the Early Termination (ET) procedures performed.

11.7.1.6. Telephone Call (Following APL DCV1) (Additional, if needed)

If the investigator deems the ON response inadequate during the APL DCV1 the following procedures may take place through telephone calls. Multiple telephone calls may take place before an additional DCV is needed.

The subject should treat their first morning "OFF" episode with a single dose of APL-130277 (at the dose higher than the dose from the APL DCV1), after withholding their usual anti-parkinsonian medications from midnight the night prior. The subject should complete their home dosing diary on each day of at-home dose titration. The subject can resume their usual anti-parkinsonian medications (including long-acting dopamine agonists) approximately 60 minutes after they take their dose of APL-130277.

The site will contact the subject by telephone to determine if the dose was effective in the subject achieving the "ON" state at 30 minutes post-dose, and to query for adverse events experienced during dosing.

- If the dose provides a full "ON" response, depending on the AEs, robustness, time to effect, and duration of the "ON" response reported by the subject, at the investigator's discretion, the next higher dose could be assessed to see if an improved full "ON" can be achieved. The subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day, the subject should treat the first morning "OFF" episode with a single dose of APL-130277 (next higher).

  If the investigator believes the optimal ON response has been achieved, the subject should not administer any additional APL-130277 doses. The subject will return to

the clinic for the next DCV within 5 days of DCV1, , and he/she should attend the visit in the practically defined "OFF" state.

- If the dose does not provide a full "ON" response, the subject will be instructed to withhold their usual anti-parkinsonian medications beginning at midnight. The next day, the subject should treat the first morning "OFF" episode with a single dose of APL-130277.

The following safety assessments will be conducted on the telephone call:

- Adverse event monitoring.
- Prior/concomitant medication review.

11.7.2. Titration of s.c. apomorphine

For de novo subjects, titration with s.c. apomorphine will take place in the clinic only, starting at 2 mg.

Subject taking s.c. apomorphine prior to screening are allowed. Subjects can enter titration at the dose they were taking following a washout period of at least 1 day. Uptitration may take place at the investigator's discretion.

Schematics showing the flow of s.c. apomorphine titration is shown in Figure 2 and Figure 3.

Depending on the magnitude and duration of the full "ON" response observed, the Investigator has the option of uptitrating the subject to the next higher dose or s.c. apomorphine (not to exceed 30 mg or 6 mg, respectively) in order to assess whether the subject has a faster time to, longer duration, or improved "ON". Further uptitrations to higher doses are allowed if the investigator deems the subject's "ON" responses are inadequate. The subject must be in an "OFF" state prior to uptitration. If this next higher dose of s.c. apomorphine is deemed more effective and is also tolerated by the subject, this dose will be used in PART B of the study. The effective dose for s.c. apomorphine must be approved by the medical monitor based on review of the titration data.

11.7.2.1. SC Titration Visit 1 (SC TV1) – Day 1

Site staff will perform the following procedures at SC Titration Visit 1, Day 1 (note: a window of ± 15 minutes is allowed for predose ECGs, a window of ±30 minutes is allowed for the 50-minute postdose ECG, a window of ± 10 minutes is allowed for vital signs collection, a window of ± 5 minutes of scheduled time is allowed for all other assessments):

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG).

- MDS-UPDRS Part III.
- In-Clinic Dosing of 2 mg s.c. apomorphine.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.
- Postdose vital signs (60 minutes postdose) (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 blood pressure and heart rate. 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.
- Postdose 12-lead ECG (50 minutes ± 30 minutes postdose).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Prior/concomitant medication review.

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 their standard dosage, or at a dosage considered appropriate by the Investigator to achieve a full "ON" state. If this occurs, the subject may return to the clinic on another day to resume the titration with the next highest dose. However, if the subject cannot tolerate the "OFF" state and does not respond efficaciously to a dose of s.c. apomorphine the subject will be terminated from the study. If a subject requires rescue medication, efficacy assessments **will not be performed**.

Subjects who respond to the s.c. apomorphine 2 mg dose with a full "ON" response within approximately 30 minutes (per both the Investigator and subject) and the Investigator does not believe uptitration will elicit a better response may be considered complete, pending approval by the Medical Monitor. The next visit for Dose Titration or PART B will be scheduled as applicable.

Subjects who do not respond to the 2 mg dose with a full "ON" response within approximately 30 minutes (per both the Investigator and subject) will be given the 3 mg dose of s.c. apomorphine no earlier than 60 minutes after the 2 mg dose. Uptitration will only occur if subject is in a full OFF state.

Site staff will perform the following procedures for the 3 mg dose of s.c. apomorphine:

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- 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 blood pressure and heart rate. 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.

- 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic Dosing of 3 mg s.c. apomorphine.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.

If, in the opinion of the subject and the Investigator, the subject has turned fully "ON" within 30 minutes of dosing the 3 mg dose of s.c. apomorphine and the Investigator does not believe uptitration is needed, the subject's participation in PART A (s.c. apomorphine Dose Titration) will be considered complete, pending approval by the Medical Monitor. The next visit for PART A (APL-130277 Dose Titration) or PART B, will be scheduled as applicable.

Subjects who do not respond to the 3 mg dose with a full "ON" response or per Investigator discretion an uptitration is warranted within approximately 30 minutes will be given the 4 mg dose of s.c. apomorphine no earlier than 60 minutes after the 3 mg dose. Uptitration will only occur if subject is in a full OFF state.

Site staff will perform the following procedures for the 4 mg dose of s.c. apomorphine:

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- 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 blood pressure and heart rate. 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.
- 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic Dosing of 4 mg s.c. apomorphine.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.

If, in the opinion of the subject and the Investigator, the subject has turned fully "ON" within 30 minutes of dosing the 4 mg dose of s.c. apomorphine and the Investigator does not believe uptitration is needed, the subject's participation in PART A (s.c. apomorphine Dose Titration)

will be considered complete, pending approval by the Medical Monitor. The next visit for PART A (APL-130277 Dose Titration) or PART B, will be scheduled as applicable.

Subjects who do not respond to the 4 mg dose with a full "ON" response or per Investigator discretion an uptitration is warranted within approximately 30 minutes will be asked to return to the clinic the next day (Day 2) to resume titration.

11.7.2.2. SC Titration Visit 2 (SC TV2) – Day 2 (if needed)

The subject will arrive for SC Titration Visit 2 (TV2) Day 2 after withholding their normal morning medication in the practically defined "OFF" state.

Site staff will perform the following procedures at SC TV2 Day 2 (note: a window of ± 15 minutes is allowed for predose ECGs, a window of ± 30 minutes is allowed for the 50-minute postdose ECG, a window of ± 10 minutes is allowed for vital signs collection, a window of ± 5 minutes of scheduled time is allowed for all other assessments):

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic Dosing of 5 mg s.c. apomorphine.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.
- Postdose vital signs (60 minutes postdose) (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 blood pressure and heart rate. 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.
- Postdose 12-lead ECG (50 minutes ± 30 minutes postdose).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Prior/concomitant medication review.

If, in the opinion of the subject and the Investigator, the subject has turned fully "ON" within 30 minutes of dosing the 5 mg dose of s.c. apomorphine and the Investigator does not believe uptitration is needed, the subject's participation in PART A (s.c. apomorphine Dose Titration) will be considered complete, pending approval by the Medical Monitor. The next visit for PART A (APL-130277 Dose Titration) or PART B, will be scheduled as applicable.

Subjects who do not respond to the 5 mg dose with a full "ON" response or per Investigator discretion an uptitration is warranted within approximately 30 minutes (per both the Investigator and subject) will be given a 6 mg dose of s.c. apomorphine no earlier than 60 minutes after the 5 mg dose. Uptitration will only occur if subject is in a full OFF state.

Site staff will perform the following procedures for the 6 mg dose of s.c. apomorphine:

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- 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 blood pressure and heart rate. 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.
- 12-Lead Electrocardiogram (ECG).
- MDS-UPDRS Part III.
- In-Clinic Dosing of 6 mg s.c. apomorphine.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.

If, in the opinion of the subject and the Investigator, the subject has turned fully "ON" within 30 minutes of dosing the 6 mg dose of s.c. apomorphine and the Investigator does not believe uptitration is needed, the subject's participation in PART A (s.c. apomorphine Dose Titration) will be considered complete, pending approval by the Medical Monitor. The next visit for PART A (APL-130277 Dose Titration) or PART B, will be scheduled as applicable.

If, in the opinion of the subject and the Investigator, the subject has NOT turned fully "ON" within 30 minutes of dosing at the in-clinic 6 mg dose of s.c. apomorphine, the subject will be withdrawn from the study and have the Early Termination (ET) procedures performed. Subjects who successfully complete the titration phase are considered completers for PART A.

11.8. PART B – Open-label Crossover Periods

Subjects will be randomized to 1 of 2 treatment sequences in a 1:1 ratio. Depending on the subject's random treatment assignment, PART B will begin with either APL-130277 or s.c. apomorphine. PART B consists of at home dosing with APL-130277 for 4 weeks and then at home dosing with s.c. apomorphine for 4 weeks, or the reverse sequence depending on the subject's random treatment assignment.

Subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with their study treatment (APL-130277 or s.c. apomorphine) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) during the waking day while on their current treatment regimen. Subjects will be instructed to dose up to 5 "OFF" episodes per day during the waking period. Study drug doses (APL-130277 or s.c. apomorphine) must be separated by at least 2 hours.

Antiemetic therapy with domperidone during the Open-label Crossover Period is optional and can be initiated prophylactically or if clinically warranted at the Investigator's discretion. If initiated, antiemetic therapy should be stopped when judged clinically appropriate. Domperidone use can exceed 7 days continuous use with approval of the Medical Monitor, in line with local regulations.

11.8.1. Clinic Visit 1 (V1, Day 1) and Clinic Visit 4 (V4, Day 33)

V1 will occur 3 to 7 days after the last PART A visit, and V4 will occur 3 to 7 days after V3.

Subjects will be asked to arrive at the clinic after withholding their normal morning medication in the practically defined "OFF" state.

The following procedures will take place at these visits except where explicitly stated. Note: ECG and vital sign predose assessments are to be completed within 60 minutes prior to dosing. MDS-UPDRS Part III and Subject "OFF"/"ON" status predose assessments are to be completed within 30 minutes prior to dosing. A window of ± 30 minutes is allowed for the 50-minute postdose ECG, a window of ± 10 minutes is allowed for post dose vital signs collection, a window of ± 5 minutes of scheduled time is allowed for all other assessments. If a subject requires rescue medication, efficacy assessments will not be performed.

- Randomization (V1 only).
- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG).
- Clinical Laboratory Tests.
- MDS-UPDRS Part III.
- In-Clinic Dosing of Study Drug.
- Investigator rating of "OFF" or "ON".
- Subject rating of "OFF" or "ON".
- Post-dose Assessment of Dyskinesia.

- Self-administration Training.
- Dispense Study Drug for Outpatient Dosing.
- Home Dosing Diary Training.
- Provide Home Dosing Diary.
- Postdose vital signs (30 minutes postdose) (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 blood pressure and heart rate. 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. If clinically necessary in the Investigator's opinion, vital signs may be collected at 90 and 120 minutes postdose.
- Postdose 12-lead ECG (50 minutes ± 30 minutes postdose).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Parkinson's Disease Quality of Life Questionnaire (PDQ-39; To be assessed pre-dose at V1 only).
- Patient Global Impression of Severity (PGI-S; V1 only).
- Clinical Global Impression of Severity (CGI-S; V1 only).
- Caregiver Burden (Zarit Burden Interview [ZBI]; To be assessed pre-dose at V1 only).
- Questionnaire for Impulsive-Compulsive- Disorders in Parkinson's Disease Rating Scale (QUIP-RS; To be assessed pre-dose at V1 only).
- European Quality of Life – 5 Dimensions (EQ-5D-5L; To be assessed pre-dose at V1 only).
- Adverse event monitoring.
- Concomitant medication review.

11.8.2. At-home Assessments

During the 4-week periods of at home dosing, subjects will be instructed to continue with their regular PD medication regimen(s), but should dose themselves with study drug (APL-130277 or s.c. apomorphine) if they experience an "OFF" episode (eg, morning akinesia, wearing "OFF", dose failure, sudden "OFF", etc.) during the day while on their current treatment regimen. Subjects should treat up to 5 "OFF" episodes a day with study drug. Study drug doses (APL-130277 or s.c. apomorphine) must be separated by at least 2 hours.

After Clinic Visit 1 (V1), Clinic Visit 2 (V2), Clinic Visit 4 (V4), and Clinic Visit 5 (V5), subjects will be requested to complete the Home Dosing Diary.

For the 3 days prior to Clinic Visit 2 (V2), Clinic Visit 3 (V3), Clinic Visit 5 (V5), and Clinic Visit 6 (V6), subjects will be requested to complete the Expanded Home Dosing Diary.

Subjects will complete these diaries for every self-administration of study drug they perform.

11.8.3. Telephone Call (T1, T2, T3, and T4)

Sites will follow-up- with subjects 4 days before each scheduled in-clinic visit in order to remind subjects to complete the Expanded Home Dosing Diary for 3 days prior to each in-clinic visit (telephone calls to be performed on Day 10, Day 24, Day 43, and Day 57). If the dose of study drug needs to be adjusted because of safety concerns or tolerability, subjects will be asked to return to the clinic for additional evaluations at an unscheduled Dose Reduction Visit (Section 11.11).

The following safety assessments will be conducted on the telephone call:

- Adverse event monitoring.
- Prior/concomitant medication review.

11.8.4. Clinic Visit 2 (V2, Day 14), Clinic Visit 3 (V3, Day 28), Clinic Visit 5 (V5, Day 47), and Clinic Visit 6 (V6, Day 61)

Subjects will be asked to arrive at the clinic after withholding their normal morning medication in the practically defined "OFF" state.

The following procedures will take place at these visits except where explicitly stated. Note: ECG and vital sign predose assessments are to be completed within 60 minutes prior to dosing. MDS-UPDRS Part III and Subject "OFF"/"ON" status predose assessments are to be completed within 30 minutes prior to dosing. A window of ± 30 minutes is allowed for the 50-minute postdose ECG, a window of ± 10 minutes is allowed for post dose vital signs collection, a window of ± 5 minutes of scheduled time is allowed for all other assessments. If a subject requires rescue medication, efficacy assessments **will not be performed**.

- Abbreviated Physical Exam, including Oropharyngeal and Injection Site Exam.
- Predose 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 blood pressure and heart rate. 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.
- Predose 12-Lead Electrocardiogram (ECG at V3 and V6).
- MDS-UPDRS Parts I, II, and IV.
- MDS-UPDRS Part III.
- In-Clinic Dosing of Study Drug.
- Investigator rating of "OFF" or "ON".

- Subject rating of “OFF” or “ON”.
- Post-dose Assessment of Dyskinesia.
- Collect Study Drug and Perform Drug Accountability. (V2 and V5 only: Record in Paper Accountability Log only, not to be recorded in eCRF) (V3 and V5: full drug accountability to be recorded in Paper Accountability Log and eCRF).
- Dispense Study Drug for Outpatient Dosing (V2 and V5 only: Unused Study Drug (as determined by Drug Accountability) to be re-supplied to the subject. Study drug is only to be dispensed via IXRS at these visits if deemed necessary as an ‘Unscheduled visit.’)
- Provide Home Dosing Diary (V2 and V5 only).
- Collect and Review Home Dosing Diary.
- Postdose vital signs (30 minutes postdose) (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 blood pressure and heart rate. 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. If clinically necessary in the Investigator’s opinion, vital signs may be collected at 90 and 120 minutes postdose (within a window of ± 10 minutes).
- Postdose 12-lead ECG at V3 and V6 (50 minutes ± 30 minutes postdose).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Dyskinesia Questionnaire (V3 and V6 only).
- Parkinson’s Disease Quality of Life Questionnaire (PDQ-39; V3 and V6 only).
- Patient Global Impression of Change (PGI-C; V3 and V6 only).
- Clinical Global Impression of Improvement (CGI-I; V3 and V6 only).
- Caregiver Burden (Zarit Burden Interview [ZBI]; V3 and V6 only).
- Questionnaire for Impulsive-Compulsive- Disorders in Parkinson’s Disease Rating Scale (QUIP-RS; V3 and V6 only).
- European Quality of Life – 5 Dimensions (EQ-5D-5L; V3 and V6 only).
- Treatment Satisfaction Questionnaire for Medication (TSQM; V3 and V6 only).
- Treatment Preference Questionnaire (V6 only).
- Ease of Use Questionnaire (at V3 and V6 only).
- Adverse event monitoring.
- Concomitant medication review.

- Pharmacokinetic sampling. Collect blood samples just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes (± 5 minutes at all time points) postdose. Samples are to be collected while the subject is in the supine position and just prior to blood pressure collection for vital signs assessments.

11.9. End of Study Visit (EOS, Day 68)

Within 7 days following the completion of PART B V6, subjects will be asked to return for a final safety assessment visit at the End of Study Visit. The Investigator will ensure appropriate follow-up care is in place for the subject. The following procedures will take place at this visit:

- Complete Physical Exam, including Oropharyngeal and Injection Site Exam.
- Weight.
- 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 blood pressure and heart rate. 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.
- 12-Lead Electrocardiogram (ECG).
- Clinical Laboratory Tests.
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Concomitant medication review.

11.10. Early Terminations

Every effort should be made to have subjects complete all study visits. The Investigator will ensure appropriate follow-up care is in place for the subject. All subjects who are terminated early in the study will all undergo the following assessments:

- Complete Physical Exam, including Oropharyngeal and Injection Site Exam.
- Weight.
- 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 blood pressure and heart rate. 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.
- 12-Lead Electrocardiogram (ECG).
- Clinical Laboratory Tests.

- Collect Study Drug and Perform Drug Accountability.
- Collect and Review Home Dosing Diary.
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Dyskinesia Questionnaire (**Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Parkinson's Disease Quality of Life Questionnaire (PDQ-39; **Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Patient Global Impression of Change (PGI-C; **Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Clinical Global Impression of Improvement (CGI-I; **Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Caregiver Burden (Zarit Burden Interview [ZBI]; **Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS; **Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- European Quality of Life – 5 Dimensions (EQ-5D-5L; **Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Treatment Satisfaction Questionnaire for Medication (**Note**: Assessment will not be performed for subjects whose participation was terminated while in PART A.)
- Treatment Preference Questionnaire (**Note**: Subjects whose participation is early terminated 5 days or more after V4 will have this assessment performed.)
- Ease of Use Questionnaire (only for subjects who had a minimum of 5 days of treatment).
- Adverse event monitoring.
- Concomitant medication review.

11.11. Unscheduled Dose Reduction Visits

If at any time during the study, it is determined that a dose reduction is required, the subject will return for an unscheduled Dose Reduction Visit. The following will be performed:

- IXRS system for new dose.
- 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 blood pressure and heart rate. 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.

- Dispense Study Drug for Outpatient Dosing.
- Collect Study Drug and Perform Drug Accountability.
- Provide Home Dosing Diary.
- Collect and Review Home Dosing Diary.
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Adverse event monitoring.
- Concomitant medication review.

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 or tolerability, the Investigator may reduce the scheduled dose of study drug to the next dose (eg, to the 10 mg dose if the subject is receiving 15 mg). The Investigator should make all attempts to maintain subjects on a stable dose. Where possible, the Medical Monitor should be contacted in order to discuss dose reductions prior to their implementation.

Any subject whose dose has been reduced at a Dose Reduction Visit will self-administer study drug using the new dosage at home and at all in-clinic visits for the remainder of the study. If, in the opinion of the Investigator, use of this dose cannot be tolerated by the subject, he/she should be discontinued from the study.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the ICF and first drug administration are pre-treatment events. Those that occur after first administration of study drug are considered AEs.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. AEs will be collected from after first administration of study drug to the last study visit/EOS visit.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term “severe” is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.4); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported

as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the eCRF.

12.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for APL-130277 pertaining to irritation of the oral mucosa require immediate reporting (see Section 12.5.3) no matter if the event is serious or non-serious. 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

Note: Per their discretion, Investigators may use other terminology and/or descriptors pertaining to oral events that are related to APL-130277 administration.

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 12.5.3. 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.

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

- Orthostatic Hypotension.

12.3. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign

(eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

All on-site ECG tracings and ECG over-read reports will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

12.4. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice. All pre-treatment events and AEs/all AEs must be recorded on the eCRF.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** - Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** - Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** - Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.

- **Dose Reduced.**
- **Dose Not Changed**
- **Not Applicable.**
- **Unknown**

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**
  - **Not related -** Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Related**
  - **Possible** - occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** - occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** - occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.5. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE;
- Pregnancy;
- Oral AESIs;
- AESIs of OH that leads to the discontinuation of the subject from the study.

- Nodules associated with s.c. apomorphine dosing.

Emergency contact information can be found in Table 1.

12.5.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after first administration of study drug through 7 days following the last dose of the study drug, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the eCRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs "spontaneously" to PPD-PVG if considered at least possibly related 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 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) or Independent Ethics Committee (IEC) by the Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

12.5.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 7 days following the last dose of the study drug will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to commence discontinuation of the study drug. Further, the subject (or female partner of male subject) will be instructed to return promptly of the first notification of pregnancy to the study center and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study drug. All pregnancies, whether or not the subject received any additional study drug, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG within 24 hours of the Investigator or study center staff becoming aware of the pregnancy. The Sponsor will provide the Pregnancy Event Form.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

12.5.3. Adverse Events of Special Interest

All oral AESIs (Section 12.2) must be reported immediately to the Sponsor regardless of seriousness or presumed relationship to study drug. All oral AESIs are considered immediately reportable events and must be reported within 1 business day of the Investigator or study center staff becoming aware of the event.

In the event of either local irritation or injection site reactions, IP may be discontinued at Investigator discretion and contact the Medical Monitor.

All oral AESIs are considered immediately reportable events and must be reported to the Sponsor within 1 business day of the Investigator or study center staff becoming aware of the event. An SAE/ Adverse Event of Special Interest Reporting form is to be completed and submitted to PPD Pharmacovigilance within 1 business day.

Similarly, any AESI (Section 12.2) of OH that leads to the discontinuation of the subject from the study, regardless of presumed relationship to study drug, must be reported within 1 business day of the Investigator or study center staff becoming aware of the event.

13. TERMINATION OF SUBJECT FROM STUDY/ DISCONTINUATION OF STUDY DRUG

13.1. Criteria for Subject Termination

Subjects may be discontinued from the study drug at any time during the treatment period. The possible reasons for discontinuation of study drug are as follows:

- Adverse event
- Lack of efficacy (specify)
- Lost to follow-up (specify)
- Non-compliance with study drug (specify)
- Protocol violation (specify)
- Pregnancy
- Withdrawal by subject (specify)
- Other (specify)

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study treatment.

In addition, if at any time during the study the subject answers “yes” to item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment, the subject must be discontinued from the study and referred to a mental health professional.

The reason for discontinuation and information on the epoch will be recorded on the appropriate eCRF. In case of death, the date of death should be captured on the eCRF.

Subjects who prematurely terminate the study participation will not be replaced.

13.2. Clinical Assessments After Study Drug Discontinuation

Every effort should be made for all treated subjects prematurely discontinuing the study drug, regardless of cause, to:

- Undergo final evaluation procedures, in accordance with the ET Visit as described in Section 11.10.

Subjects withdrawn/terminated during PART A of the study will have fewer assessments performed than those withdrawn/terminated during PART B (refer to Schedule of Events for additional details on the procedures to be performed).

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at one study center or at multiple centers for safety or administrative reasons at any time while safeguarding that early termination does not compromise subject's safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study drugs pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or study center termination, subjects will be required to return for a final study assessment as described in Section 11.10 and then provided with access to standard care.

15. STATISTICS

Full statistical considerations, table mock-ups and complete analysis of safety and efficacy data collected in this study will be specified in a formal Statistical Analysis Plan (SAP). The SAP will be finalized prior to locking the database.

This section of the protocol prospectively defines the primary and secondary analysis methods. Methodology concerning the analysis of other efficacy variables will be provided in the SAP. All applicable data will be summarized separately for PARTs A and B, unless stated otherwise. Where appropriate, data will be summarized by visit week and/or time point in addition to treatment group. For PART B analyses by visit week, data from V1 and V4 will be labeled as Week 0; V2 and V5 will be labeled as Week 2; and V3 and V6 will be labeled as Week 4. Unscheduled or repeat assessments will not be included in summary tables, but will be included in listings. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Standard error of the mean (SEM) will also be provided for summaries of efficacy data, if relevant. Descriptive statistics for categorical data will include frequency counts and percentages. The total number of patients in the treatment group overall (N) will be used as the denominator for percent calculations, unless stated otherwise. Significance testing will be 2-sided at the 0.05 level, unless otherwise specified.

15.1. Sample Size

The initial sample size calculation is based on the primary endpoint of the study, the mean change from pre-dose in MDS-UPDRS Part III Motor Examination score at 90 minutes post-dose, evaluated at V3 and V6 for each treatment in PART B. Assuming that the discontinuation rate is 25% in PART A, a total of 106 subjects will be randomized into PART A, so that at least 80 subjects are randomized into PART B. Assuming a 30% discontinuation rate in PART B, approximately 55 subjects are expected to complete PART B. With 55 subjects, the study has 90% power to detect a mean treatment difference between APL-130277 and s.c. apomorphine of 5.5 points for the change in MDS-UPDRS Part III score, assuming a standard deviation of 12 points for the period differences in PART B. The expected mean treatment difference of at least 5.5 points for the change in MDS-UPDRS Part III score was based on the results of the CTH-300 study.

A blinded sample size re-assessment (b-SSR) will be performed to assess assumptions regarding nuisance parameters in the above calculation for the primary endpoint. After approximately 37 randomized patients have completed PART B (67% of the targeted number of completers), an overall aggregate estimate of the standard deviation of the period differences (SD) will be made from the available completer data. This estimate will be made in a completely blinded fashion without regard to treatment group membership. The overall aggregate drop-out rates for PART A and B will also be assessed for subjects whose disposition status is known at the time. The b-SSR will be performed by an external, independent statistician who is not involved in the final analysis of this study. If it does not appear that the magnitude of the variability and drop-out is consistent with the assumptions used in the sample size calculation above, the sponsor will consider increasing the target sample size. Only increasing, not decreasing, the initial target sample size will be allowed. If the target sample size is to be increased, the independent statistician will only report the aggregate estimates of the nuisance parameters to the sponsor, along with the revised sample size estimate. The revised sample size calculation would be

identical to the original calculation above except that the estimate of the SD and/or drop-out rates would be revised based on the b-SSR. As there is no treatment comparison involved, no inflation of the type I error from this procedure is expected, and no adjustment to the significance levels for the final analysis is necessary.

Based on the observed aggregated standard deviation at the time of b-SSR, the sample size will be adjusted for the target number of completers. The table below displays the pre-specified target number of completers for each observed range of SD estimates. For illustration, we also show the total sample size based on the initial drop-out assumptions, however, this number will be adjusted according to the observed drop-out rates at the time of b-SSR. In any case, the maximum total sample size is set at 164 subjects.

Re-estimated SD for Primary Endpoint	**Target Number of Completers for Power Calculation**	**Total Sample Size Under Current Drop-out Assumptions**
≤ 12	55	106
> 12 to ≤ 12.5	58	110
> 12.5 to ≤ 13	62	118
> 13 to ≤ 13.5	66	126
> 13.5 to ≤ 14	71	136
> 14 to ≤ 14.5	75	143
> 14.5 to ≤ 15	81	155
> 15	86	164

15.2. Analysis Populations

15.2.1. All Subjects Enrolled Population

The all subjects enrolled (ENR) population will contain all subjects who provide informed consent for this study.

15.2.2. Safety Populations

The following safety populations will be defined:

- PART A Safety Population: The PART A Safety Population includes all subjects who received at least one dose of either study drug in PART A. The PART A Safety Population will be used for the safety analysis of PART A according to treatment received.
- PART B Safety Population: The PART B Safety Population includes all subjects who received at least one dose of either study drug in PART B. The PART B Safety Population will be used for the safety analysis of PART B according to treatment received.

15.2.3. Modified Intent-to-Treat (mITT) Populations

The following modified Intent-to-Treat (mITT) populations will be defined:

- PART A mITT Population: The PART A mITT Population includes all subjects who were randomized and received at least one dose of either study drug in PART A. This population will be used for any efficacy analysis of PART A data according to randomized treatment.
- PART B mITT Population: The PART B mITT Population includes all subjects who were randomized and received at least one dose of either study drug in PART B. This population will be used for the efficacy analysis of PART B data according to randomized treatment.

15.3. Data Analysis

15.3.1. Subject Disposition

The number and percentage of subjects who are randomized, treated, and completed or discontinued, with reason for discontinuation, will be presented by treatment sequence and overall for each study part.

15.3.2. Drug Exposure

Duration of exposure and number of doses taken will be summarized by treatment for each study part in the Safety populations.

15.3.3. Protocol Deviations

Protocol deviations will be identified and documented during the conduct of the study. Protocol deviations will be categorized by type, and whether major or minor based on clinical review. Individual deviations will be presented in a data listing. The number and percentage of subjects will be summarized by type of deviation and treatment group for Parts A and B.

15.3.4. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the mITT and Safety populations by treatment sequence and overall.

15.3.5. Efficacy Analyses

The efficacy analyses will be performed using the mITT populations (PART A mITT Population, PART B mITT Population).

The primary and secondary efficacy endpoints will be tested in hierarchical order to maintain on overall type I error rate of 0.05 (i.e. in a fixed sequential manner).

The primary endpoint will be tested first at the 5% significance level. If there is a statistically significant treatment difference, the first secondary endpoint will be tested and declared statistically significant if the p-value is less than 0.05. The testing will continue in this manner for each secondary endpoint in the hierarchical order shown below:

1. Durability of effect, defined as an Investigator confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed by the blinded-rater in-clinic at V3 and V6 of PART B);
2. Subject preference for APL-130277 treatment (either somewhat or definitely prefer APL) as recorded for question 9 of the TPQ. This assessment is scheduled to be performed after the subject has completed both APL-130277 and s.c. apomorphine treatment regimens (assessed in clinic at V6 of PART B);
3. Subject confirmed durability of effect, defined as subject confirmed full "ON" within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B);
4. Patient Global Impression of Change (PGI-C): Subject improvement of "OFF" episodes, defined as very much better, much better or a little better after 4 weeks of dosing in each crossover period (assessed in-clinic at V3 and V6 of PART B).

15.3.5.1. Primary Efficacy Endpoint

Primary analysis: The primary endpoint is the change from pre-dose to 90 minutes post-dose in MDS-UPDRS Part III Motor Examination score. The primary endpoint is evaluated at V3 and V6, after 4 weeks of dosing of each treatment in each crossover period of PART B, and a blinded rater will be used for this assessment. The primary endpoint will be analyzed in the PART B mITT population and compared between the treatment groups using a linear mixed model (SAS Mixed procedure), as described by Tao et al. (2015). The mixed model for the change from pre-dose to 90 minutes in the MDS-UPDRS Part III score as the response outcomes, includes the following variables: treatment group, visit week (0, 2, 4), treatment by visit week interaction, PART B sequence and period as fixed factors. The Week 0 visit pre-dose UPDRS motor score will be used as a covariate. Subject nested within the PART B sequence will be included as a random effect and an AR(1) covariance structure will be used for the repeated measures over time (visit week). The Kenward-Roger (KR) method will be used to calculate degrees of freedom. The least square (LS) mean, standard error, and LS mean treatment difference, along with the 95% confidence interval (CI) and p-value will be provided.

Sensitivity Analysis: If the primary analysis significantly favors APL-130277, a missing not at random (MNAR) sensitivity analysis of the primary endpoint will be conducted in the PART B mITT population. This analysis will use a tipping point approach with multiple imputation (MI) for the missing outcome data. The trajectories of the patients in the APL-130277 group after withdrawal are assumed to be worse by an amount of delta. After the MI using the missing at random (MAR) assumption, the amount of delta will be added to each imputed Week 4 value in the APL-130277 group. Successively harsher deltas will be imposed on the imputed values in the APL-130277 group only, starting with an increment (worsening) of 1.0 point. The delta is further increased in the steps of 0.5 points (1.5, 2.0, 2.5…) until the statistical significance is lost, i.e. until the p-value becomes > 0.05. For the s.c. apomorphine group, the MI using MAR assumption will be used. Additional sensitivity analyses may be specified in the SAP.

Supplementary Analyses: Two supplementary analyses of the primary endpoint in the PART B mITT population will be conducted. First, an analysis of just the Week 4 outcome data using ANCOVA will be performed. The ANCOVA model would include the following variables:

treatment group, PART B sequence, and period as fixed effects. The Week 0 visit pre-dose UPDRS-III score will be used as a covariate. Subject nested within sequence will be included as a random effect. Missing Week 4 data within each period will be imputed using LOCF for this analysis. If there are convergence or other numerical issues that prevent fitting the primary repeated measures model analysis specified above, this supplementary ANCOVA analysis will be used instead for primary inference.

Second, a supplementary responder analysis will be performed. A responder is defined as a subject with a > 4 point improvement in the change from pre-dose to 90 minutes post-dose in MDS-UPDRS Part III Motor Examination score. Response will be compared between the treatment groups in the PART B mITT population using a generalized linear random effects model with logit link function. The model includes the binomial variables as the response outcomes, and the following independent variables: treatment group, visit week (0, 2, 4), treatment by visit week interaction, PART B sequence and period as fixed factors. Subject nested within the PART B sequence will be included as a random effect and an AR(1) covariance structure will be used for the repeated measures over time (visit week). The Kenward-Roger (KR) method will be used to calculate degrees of freedom. The SAS Glimmix procedure will be used for this analysis. The predicted response rates, treatment odds ratio, 95% confidence interval and p-value will be presented.

15.3.5.2. Secondary Efficacy Endpoints

15.3.5.2.1. Durability of Effect Endpoints

For these endpoints, response will be compared between the treatment groups in the PART B mITT population using a generalized linear random effects model with logit link function. The model includes the binomial variables as the response outcomes, and the following independent variables: treatment group, visit week (0, 2, 4), treatment by visit week interaction, PART B sequence and period as fixed factors. Subject nested within the PART B sequence will be included as a random effect and an AR(1) covariance structure will be used for the repeated measures over time (visit week). The Kenward-Roger (KR) method will be used to calculate degrees of freedom. The SAS Glimmix procedure will be used for this analysis. The predicted response rates, treatment odds ratio, 95% confidence interval and p-value will be presented. This method of analysis will be utilized for the following secondary endpoints:

- Durability of effect, defined as an Investigator confirmed full “ON” within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each PART B crossover period.
- Subject confirmed durability of effect, defined as subject confirmed full “ON” within 30 minutes post-dose and at 90 minutes post-dose, after 4 weeks of dosing in each PART B crossover period.

15.3.5.2.2. Subject Preference for APL-130277 Endpoint

Patient reported preference for APL-130277 or s.c. apomorphine is based on question 9 of the TPQ and assessed on a 5-point scale. The number and percent of subjects in each response category will be summarized descriptively. The main analysis will evaluate the proportion of subjects with preference for APL. Responses will be dichotomized as follows for statistical

analysis: preference for APL (responses of either definitely or somewhat prefer APL) versus no preference for APL (responses of no preference, or somewhat/definitely prefer s.c. apomorphine). This endpoint will be analyzed in the PART B mITT population with preference data. The preference assessment is scheduled to be performed upon completion of both treatments in PART B. For subjects who terminate the study early, the assessment at the ET visit will be used for analysis if available. If in this case, the ET assessment is not available, the last treatment received prior to termination will be considered the treatment that is not preferred (i.e. the alternative treatment, whether received or not, will be considered preferred for analysis).

The proportion of subjects preferring the APL-130277 treatment (either somewhat or definitely prefer APL) and two-sided 95% confidence interval for this proportion will be calculated. The p-value from a 1-sample, 2-sided test of the null hypothesis that the true proportion is 50% will be calculated to evaluate if a significantly higher proportion of the subjects prefer APL-130277 or not. The confidence interval and p-value will be calculated using the binomial distribution with normal approximation (Wald asymptotic confidence interval). As a supportive analysis, the PART B sequence effect (the order in which the treatments were given in PART B) will be assessed by summarizing the proportion of subjects preferring the APL-130277 treatment within each of the two sequences.

15.3.5.2.3. Patient Global Impression of Change (PGI-C):

Subject improvement of "OFF" episodes, defined as very much better, much better or a little better at Week 4 in each PART B crossover period will be analyzed using a generalized linear random effects model with logit link function. The model includes the following independent variables: treatment group, PART B sequence, and period as fixed effects. Subject nested within sequence will be included as a random effect. If the Week 4 PGI-C assessment is missing, the assessment at the ET visit for that treatment period will be used if available for analysis. The predicted response rates, treatment odds ratio, 95% confidence interval and p-value will be presented.

15.3.5.3. Other Efficacy Endpoints

The other PART B efficacy endpoints will be summarized descriptively, including paired treatment differences and 95% confidence intervals as appropriate. PART A efficacy endpoints may be summarized as needed.

These analyses will be defined in more detail in the SAP.

15.3.6. Safety Analysis

15.3.6.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse Events (AEs) are untoward medical occurrences that start after the subject receives the first dose of study treatment. PART A AEs are defined as all AEs that start on or after the date of the first dose of study drug (APL-130277 or s.c. apomorphine) in PART A, but before the date of the first dose of study drug in PART B. PART B AEs are defined as all AEs that start on or after the date of the first dose of study drug in PART B. Within each part of the study, the AE will be assigned to the study treatment (APL-130277 or s.c. apomorphine) that was given during the day of the

AE onset (or the last study treatment that was given before the onset of the AE). Events will be classified as drug-related if the AE is classified as possibly, probably, or definitely related to study drug. Separate summaries will be generated for AEs of special interest (described below). AEs will be summarized by SOC and PT and by treatment group. AEs with onset after the last dose of the study treatment are attributed to the treatment received during the last treatment period. Both event and subject counts, where applicable, will be summarized. The counts will be complemented by percentages calculated for the subject counts unless otherwise specified. The following summaries will be done separately for PART A and PART B:

- An overall summary of the number and percentage of subjects reporting AEs and the number of AEs, drug-related AEs, severe AEs, serious AEs, non-serious AEs, AEs leading to study treatment discontinuation, AEs leading to dose interrupted/reduced/temporary withdrawal, and AEs leading to death;
- AEs by SOC and PT, both as event and subject counts;
- AEs by PT, both as event and subject counts;
- Severe AEs by SOC and PT, both as event and subject counts;
- AEs by SOC, PT and severity, as event counts
- AEs by SOC, PT and relationship to study drug;
- Serious AEs by SOC and PT, both as event and subject counts;
- AEs leading to study treatment discontinuation by SOC and PT, both as event and subject counts;
- AEs leading to dose interrupted/reduced/temporary withdrawal by SOC and PT, both as event and subject counts;
- For each AESI category, AESIs will be presented by PT. AESIs will be further defined within the SAP.

In addition, the following tables will be summarized by dose level of APL-130277: Serious AEs, AEs leading to study treatment discontinuation, AEs of special interest. The actual dose level prior to the AE onset will be used for this analysis.

15.3.6.2. Clinical Laboratory Variables

All clinical laboratory parameters will be converted to consistent units according to the International System of Units (SI) before summarization. The laboratory parameter values and change from baseline (screening) to the end of study for each parameter will be summarized with descriptive statistics.

15.3.6.3. Vital Signs

Vital sign measurements include heart rate (HR), respiratory rate (RR), blood pressure (BP) and body temperature. The BP values will be assessed both in supine and standing position. In addition to the vital signs captured on the Case Report Form, the standing minus supine values (standing minus supine systolic BP, standing minus supine diastolic BP) will be evaluated.

The following summaries will be done for PART A and PART B:

- Actual values and changes from both baseline (screening) and visit pre-dose to post-dose time point, at each visit for each parameter (including the standing minus supine values), by treatment group.
- Orthostatic hypotension will be defined as a reduction in systolic BP of 20 mmHg or more, and/or a reduction in diastolic BP of 10 mmHg or more, for the standing measurement compared to the supine measurement. The proportion of subjects with orthostatic hypotension will be tabulated by visit and time point, by treatment group.

15.3.6.4. ECG

The ECG data will be centrally over-read and interpreted, and the following ECG parameters will be reported: Heart rate, PR interval, QRS interval, RR interval, QT interval, QTc Interval (Fridericia's correction) and QTc Interval (Bazett's correction).

The following summaries will be done for PART A and PART B:

- Actual values and changes from both baseline (screening) and visit pre-dose to the post-dose time point, at each visit for each parameter (including the standing minus supine values), by treatment group

The ECGs will be centrally over-read and abnormal readings will be tabulated by visit and time point.

In addition, the QTc Intervals fulfilling the following criteria will be tabulated separately using Fridericia's correction and Bazett's correction:

- Values > 500 msec
- Values increasing > 15% from baseline if baseline value is ≥ 440 msec
- Values increasing > 30% from baseline if baseline value is < 440 msec
- Values increasing > 30 msec from baseline
- Values increasing > 60 msec from baseline
- At least one of the abnormalities listed above.

15.3.6.5. Other Safety Variables

- The Columbia Suicide Severity Rating Scale (C-SSRS) is a measure of suicidal ideation and behavior. The rating scale has 4 general categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts. All C-SSRS data will be listed. The frequency and percentage of patients with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized as appropriate by treatment group and visit for PART A and B.
- The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) is an instrument used to measure the extent of impulsive and compulsive behaviors in PD patients. The QUIP-RS consists of four questions which have to be answered for each disorder (gambling, sex, buying, eating, hobbyism, punding and PD medication use) on a 5-point Likert scale. Scoring range for each scale (ie, disorder) is 0–16. The frequency and percentage of patients with positive

response ("rarely" or higher) for each disorder will be summarized by treatment group and visit for the Titration phase and the Maintenance phase. Furthermore, the total Impulsive Control Disorder (ICD) score and the total QUIP-RS score will be summarized with descriptive statistics by treatment group and visit (both absolute values and changes from baseline) for PART A and B.

- The frequency and percentage of patients with each type of oropharyngeal cavity and injection site examination finding will be summarized by treatment group, visit, time point (when applicable) and location.

15.3.7. Pharmacokinetic Analysis

Pharmacokinetic parameters (including but not limited to C_{max}, t_{max}, AUC_t, parent-to-metabolite ratios of C_{max} and AUC_t) will be derived using noncompartmental methods employing Phoenix WinNonlin® version 6.3 or higher (Certara, St Louis, MO). Pharmacokinetic analysis will be conducted using actual elapsed time from dosing concentration-time data for apomorphine and metabolites (apomorphine sulfate, norapomorphine, and others as deemed necessary). The complete PK analyses to be performed will be specified and results reported in a separate document. The PK results will also be described in the clinical study report.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL/ DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results, electrocardiogram results and IXRS data) will be recorded in the subject's eCRF. The study centers will use an electronic data capture (EDC) system (Medidata Rave). Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed electronic Case Report Forms (eCRFs) must be reviewed and electronically signed and dated by the Investigator.

16.2. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

16.3. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

16.4. Study Documentation

Study records are comprised of source documents, eCRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

16.5. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis of the clinical laboratory tests for this study. The central laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director's curricula vitae and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the "Investigator Approval" page.

17.2. Institutional Review Board/Independent Ethics Committee

Documented approval for conducting the study from appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s), and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB/IEC chairman or designee identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB/IEC complies with the requirements in 21 CFR Part 56 for a study conducted under a US Investigational New Drug (IND) or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. All informed consent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, permitted to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study drug, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject, and will record the date of the informed consent on the eCRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent form must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

The Sponsor, Sponsor representative, or any designees affirms to uphold the subject's confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

If any cases are identified where the subject's confidentiality has been breached, this must be rectified immediately. All subject identifiable information should be removed and the Sponsor notified.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 25 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor standard operating procedures (SOPs). The Investigator/study center should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor, its representative, and the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion Pharmaceuticals Inc. sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

The Sponsor will disclose the study results, in the form of a clinical study report synopsis, as required, to any IEC/IRBs and applicable regulatory authorities within one year of the end of the study. The format of this synopsis and that of the clinical study report should comply with ICH E3 guidelines for structure and content of a clinical study report.

18. REFERENCES

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

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

Guy W. EDCEU Assessment Manual for Psychopharmacology – Revised (DHEW Publ No ADM 76-338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976:534-7.

Kay SR. Positive and negative symptoms in schizophrenia: Assessment and research. 1st ed. Clinical and Experimental Psychiatry (Book 5). Routledge; 1991.

LeWitt PA, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Neurol 2019; 18(2): 145-54.

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

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.

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

Tao J, Kiernan K, Gibbs P. Advanced Techniques for Fitting Mixed Models Using SAS/STAT® Software. SAS Institute white paper number SAS1919; 2015.

Williams JBW. Mental health status, functioning, and disabilities measures. In: Handbook of Psychiatric Measures. Washington, D.C.: American Psychiatric Association, 2000, p. 93-115.

19. INVESTIGATOR APPROVAL

I have read the protocol, CTH-302, Version 4.02, "An Open-Label, Randomized, Crossover Trial utilizing a Single-Blinded Rater to evaluate APL-130277 compared to s.c. Apomorphine in Levodopa Responsive Subjects with Parkinson's Disease Complicated by Motor Fluctuations", 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 approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested 10 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study.
- ECGs will be reviewed, signed and dated by the Investigator after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- The ECG tracing will be kept with subject's source documentation unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the study center.

4. Data Standardization

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

21. APPENDIX II. CLINICAL LABORATORY TESTS

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)
Hemoglobin, Hematocrit, Platelet Count (or estimate), RBC Count, RBC Indices, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), WBC, including differential

BLOOD CHEMISTRIES: albumin, bilirubin (total, direct, indirect), total protein, bicarbonate (HCO3), alkaline phosphatase, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, glucose, calcium (Ca), hemoglobin A1c, sodium, magnesium (Mg), phosphorus (P), potassium (K), uric acid, globulin, vitamin B_6

URINALYSIS: pH, specific gravity, blood, glucose, protein, ketones, leukocyte esterase, microscopic examination, nitrites

URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Cotinine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

NOTE: Benzodiazepines, opiates, and oxycodone will be allowed provided the subject has been on a stable dose for 4 weeks prior to SV1, provided the subject has a valid prescription. Cotinine is not exclusionary if the subject is a current smoker.

SEROLOGY PANEL: Hepatitis B Ag, Hepatitis C Ab, HIV-1 Ab, HIV-2 Ab.

OTHER TESTS: Serum Pregnancy (β-hCG) (in female subjects only), Urine Pregnancy Test (in female subjects only)

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

22. APPENDIX III. PHARMACOKINETIC SAMPLING AND HANDLING GUIDELINE

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

Samples are to be collected while the subject is in the supine position and just prior to blood pressure collection for vital signs assessments. Subjects may be catheterized to facilitate blood collection.

All collection devices, labels, and requisitions will be provided by the central laboratory. Blood must be collected from all subjects at the time points indicated below.

PART B Visit No.	**Day No.**	**PK Blood Sample Collection Times:**
V2	14	Just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes (± 5 minutes at all time points) post-dose
V3	28	Just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes (± 5 minutes at all time points) post-dose
V5	47	Just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes (± 5 minutes at all time points) post-dose
V6	61	Just prior to dosing and at t = 15, 30, 60, 90, 120, 180 and 240 minutes (± 5 minutes at all time points) post-dose

23. APPENDIX IV. APO-GO® SUMMARY OF PRODUCT CHARACTERISTICS

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

24. APPENDIX V. 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 1:

- 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 10 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.