Statistical Analysis Plan

Sponsor Name:	Sunovion Pharmaceuticals Inc.
Protocol Number and Title:	CTH-203: A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3-Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)
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I confirm that I have reviewed this document and agree with the content.

APPROVALS	
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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
λ_z	Terminal Elimination Rate Constant
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC_{last}	Area Under the Concentration-time Curve From Time Zero to the Last Measurable Plasma Concentration Using the Linear-Up Log-Down Trapezoidal Rule
AUC_{inf}	Area Under the Concentration-time Curve From Time Zero Extrapolated to Infinity Using the Linear-Up Log-Down Trapezoidal Rule
BMI	Body Mass index
BP	Blood Pressure
CI	Confidence Interval
CL/F	Apparent Total Clearance of the Drug From Plasma After Oral or Subcutaneous Administration
C_{max}	Maximum Observed Plasma Concentration
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
ECG	Electrocardiogram
EOS	End of Study
FDA	Food and Drug Administration
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
L-Dopa	Levodopa
Max	Maximum

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMSE	Mini-Mental State Examination
MRT	Mean Residence Time
P1	Period 1
P2	Period 2
P3	Period 3
PD	Parkinson's Disease
PK	Pharmacokinetic(s)
PT	Preferred Term
QTc	Corrected QT Interval
QTcB	QT Corrected with Bazett's Formula
QTcF	QT Corrected with Fridericia's Formula
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SV	Screening Visit
$t_{½}$	Terminal Phase Half-Life
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
T_{max}	Time at which the highest drug concentration occurs after administration of an extravascular dose
V/F	Apparent Volume of Distribution after extravascular Administration
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

INC Research will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings. Pharmacokinetic parameters will be derived by Nuventra Pharma Sciences (Nuventra) and will be provided to INC Research.

2.2. TIMINGS OF ANALYSES

All final planned analyses identified in this SAP will be performed by INC Research Biostatistics following Sunovion's authorization of this Statistical Analysis Plan, and after the database lock.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the pharmacokinetics (PK) and comparative bioavailability of apomorphine and its metabolites (apomorphine sulfate and norapomorphine) following single doses of APL-130277 sublingual thin film with subcutaneous (s.c.) APO-go® and s.c. APOKYN® in subjects with Parkinson's disease (PD) complicated by motor fluctuations ("OFF" Episodes).

3.2. SECONDARY OBJECTIVE

The secondary objective of this study is to evaluate the safety and tolerability of the study drugs.

3.3. BRIEF DESCRIPTION

This is a multi-center, Phase 2, open-label, randomized, three-way crossover study designed to evaluate the PK and comparative bioavailability of a single dose of APL-130277 sublingual thin film with s.c. APO-go® and s.c. APOKYN® in subjects with PD.

This study will commence with an initial Screening Visit, followed by an open-label, randomized, three-way crossover (Period 1, Period 2, Period 3). Subjects will receive all three treatment arms with a minimum 1-day wash-out period between each visit (excluding the screening visit).

Screening Visit
Before any study procedures are performed on any person, informed consent must be obtained. Subjects who have provided full consent to participate, will arrive at the clinic having taken their usual morning dose of PD medications; but before taking their next dose of medication. Their normally scheduled second dose of L-Dopa (without adjunctive PD medication) will be administered in the clinic following confirmation of an "OFF" episode by the Investigator, to ensure the subject experiences an "ON" response. Eligibility criteria will be assessed by the Investigator. Subjects who are considered eligible, will be scheduled for the Period 1 Visit.

Wash-Out Period
One (1) day prior to the Period 1 Visit, at a minimum, subjects will be required to discontinue use of subcutaneous APOKYN®; this is referred to as the wash-out period. L-Dopa and any other adjunctive PD medication will be permitted during this time. A one (1) day wash-out period will be required prior to each subsequent visit (Period 2, Period 3, End of Study Visit).

Three-Way Open-Label Randomized Crossover (Period 1, Period 2, Period 3)
Subjects will be asked to return to the clinic the morning of Period 1 (P1) after their usual morning dose of PD medications; but before taking their next dose of medication and will be randomized to one of the 6 treatment sequences.

Subjects will be required to wait to take their normally scheduled second dose of PD medications until after confirmation by the Investigator that the subject is in the "OFF" state and will be dosed according to the randomized treatment sequence with either APL-130277, APO-go®, or APOKYN®. All PD medications should be held until 60 minutes after dosing.

Following the same procedures described above, subjects will return to clinic within 3-5 days after Period 1 and will be dosed for Period 2 (P2) with one of the other two treatments. Subjects will return to clinic within 3-5 days after Period 2 and will be dosed for Period 3 (P3) with the third and last treatment.

Subjects will be randomly assigned to one of the following sequences, according to a William's design:

	Period 1	Period 2	Period 3
Sequence 1	APL-130277	APOKYN®	APO-go®
Sequence 2	APL-130277	APO-go®	APOKYN®
Sequence 3	APOKYN®	APL-130277	APO-go®
Sequence 4	APOKYN®	APO-go®	APL-130277
Sequence 5	APO-go®	APL-130277	APOKYN®
Sequence 6	APO-go®	APOKYN®	APL-130277

Treatment Arms:

1. APL-130277 sublingual thin film

2. Subcutaneous APO-go®

3. Subcutaneous APOKYN®

APL-130277 and APO-go® dosing in the Three-Way Crossover will be based on the subjects' current prescribed dose of APOKYN®.

Dose Group	APOKYN® Current Prescribed Dose	APO-go® Study Dose	APL-130277 Study Dose*
1	2 mg	2 mg	15 mg
2	3 mg	3 mg	20 mg
3	4 mg	4 mg	25 mg
4	5 mg	5 mg	30 mg

*These are approximate equivalent doses based on PK.

3.4. SUBJECT SELECTION

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

The study will require approximately 12 subjects to complete the Three-Way Crossover phase. Recruitment will continue until the required number of subjects complete the study. Inclusion criteria and exclusion criteria are described in detail in protocol Section 11.1.1 and 11.1.2.

3.5. DETERMINATION OF SAMPLE SIZE

With a sample size of 12 subjects, a two-sided 90% confidence interval for the difference in paired PK parameter means on the log scale will have an interval that extends no more than 0.221 units from the observed difference with 90% coverage probability. This calculation assumes a coefficient of variation of 35% for the difference on the original scale. If the observed mean difference on the log scale were zero, this would correspond to a 90% confidence interval for the ratio of geometric means of (80.2%, 124.7%) on the original scale.

3.6. TREATMENT ASSIGNMENT & BLINDING

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

Following Sponsor approval, subjects will be randomized centrally at a study level after the Screening Visit has been completed to one of the six randomization sequences using the Williams design (See Section 3.3).

No stratification factors will be used. The randomization scheme will be designed by the study statistician. Once designed, an independent randomization expert will execute the randomization in the IWRS. The randomization number is used to identify the treatment sequence (APL-130277, APO-go®, APOKYN®) of the treatment that will be administered to the subject during the Three-Way Open-Label Randomized Crossover Phase (Period 1, Period 2, Period 3).

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

3.7. STUDY PROCEDURES

All assessments will be performed at each visit according to the schedule of events (Section 17).

4. ENDPOINTS

4.1. PHARMACOKINETIC ENDPOINTS

The primary endpoint of this study is the PK profile (plasma) for apomorphine and its metabolites (apomorphine sulfate and norapomorphine). Apomorphine PK parameters will include: C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{inf}, AUC_{0-24}, MRT, CL/F and V/F. Comparative bioavailability ($F_{T/R}$) of apomorphine between the Test (APL-130277) and Reference (APO-go and APOKYN) products will be evaluated and calculated using C_{max}, AUC_{last}, and AUC_{inf}. In addition, the comparative bioavailability between APOKYN (Reference) and APO-go (Test) will be determined using Cmax, AUClast and AUCinf ($F_{T/R}$_APO-go/APOKYN). Apomorphine metabolites (norapomorphine and apomorphine sulphate) PK parameters will consist of determination of C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{inf}, AUC_{0-24}, and metabolite-to-parent (M/P) ratios of C_{max}, AUC_{inf} and AUC_{last}.

4.2. SAFETY ENDPOINTS

The secondary endpoints are safety and tolerability: evaluation of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including blood pressure [BP], heart rate [HR], respiration rate [RR], body temperature and weight), and adverse events (AEs).

5. ANALYSIS POPULATIONS

5.1. SAFETY POPULATION

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

5.2. PHARMACOKINETIC POPULATION

The PK population includes all subjects who receive at least one dose of study drug and have at least one quantifiable PK concentration. Subjects will be grouped according to the treatment that they received.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

In general, summaries will present data by treatment group and assessment time point where appropriate. Unless stated otherwise, descriptive statistics for continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics for categorical data will include frequency counts and percent. The total number of subjects in the treatment group overall (N) will be used as the denominator for percent calculations, unless stated otherwise. Significance testing will be 2-sided using $\alpha = 0.05$, unless otherwise specified.

All PK analyses will be presented using PK population, while other analyses will be presented using Safety population.

Data from all patients entered into the database will be included in subject data listings.

All statistical procedures will be performed using SAS® Version 9.3 or higher.

Additional programming considerations are presented in Section 12.

6.2. KEY DEFINITIONS

6.2.1. Baseline

6.2.1.1. Study Baseline

Study baseline is defined as the last non-missing measurement in the screening period (SV).

6.2.1.2. Period Baseline

The period baseline is defined as the pre-dose time point within each period.

6.2.2. Study Day

Study day is defined as follows:

- The day when the dosing started is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date – Day 1 date. Thus, study days for screening visit are negative numbers. There is no “Day 0”.

6.3. MISSING DATA

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis population defined in Section 5. No imputation will be done for missing data, except for medication dates (as detailed in section 7.4.3) and PK (detailed in section 8.3). Observed data will be used for analyses.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Summary tables reflecting the number of subjects for the following will be presented overall and by treatment group:

- Screened subjects (overall only)
- Failed screening subjects and reasons for screen failures (overall only)
- Randomized subjects
- Safety population
- PK population
- Subjects who complete the study
- Subjects who early terminate the study and reasons for early termination

Subject disposition and screen failures will be listed.

In addition, the number of randomized subjects will also be summarized by treatment sequence.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics data, such as age, gender, race and ethnicity, and baseline characteristics, such as height, weight, body mass index (BMI), smoking status, MMSE score and baseline modified Hoehn and Yahr scale will be summarized descriptively overall, by treatment group. The following conventions will be implemented:

- Age at Study day 1 = INTCK('year', Subject Birthday, Date of study day 1)
- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536
- BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

Demographic characteristics will also be listed.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history collected at screening will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) version 19.1. Medical history data will be summarized by system organ class (SOC) and preferred term (PT) overall and listed.

Subject's PD history will also be summarized overall and listed. Time since diagnosis of PD (in years) is calculated as the year of screening visit – the year of diagnosis of PD + 1. Time since motor fluctuations started (in years) is calculated as the year of screening visit – the year motor fluctuations started+1.

7.4. MEDICATION

The number and percentage of subjects using each prior or concomitant medication will be summarized using Anatomical Therapeutic Chemical (ATC) classification codes and PT according to the World Health Organization-Drug Dictionary (WHO-Drug) March, 2017. The number and percentage of subjects using each prior medication will be summarized overall, while concomitant medications will be summarized overall and for each treatment group.

Summaries of prior and concomitant PD treatment medications (medications which start with ATC code N04) will be presented in tabular form using the ATC Level 4 and PT. Other prior and concomitant medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and PT. Subjects with multiple uses of a concomitant medication will be counted only once for a given PT in a given ATC term and only once within a given ATC term.

PD medications and other medications will be summarized and listed separately.

7.4.1. Prior Medication

Medications with a stop date before the first date of study drug dosing will be considered prior medications.

7.4.2. Concomitant Medication

Medications with start date or stop date on or after the first date of study drug dosing will be considered concomitant medications. A medication that has a start or stop date anytime on or after Day 1 of a Treatment Period, up through and including the day prior to Day 1 of the next Treatment Period or start and stop dates that span this interval will be assigned to the treatment group associated with the former Treatment Period. A medication that has a start or stop date anytime on or after Day 1 of the last Treatment Period up to EOS in which a subject participates or start and stop dates that span this interval will be assigned to the treatment group associated with this last Treatment Period.

7.4.3. Medications with Missing or Incomplete Start/End Date

If the medication start date is incomplete, then it will be imputed as follows for the purpose of determining concomitant use:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.

- If the start day is missing: Check if month is same as month of first dose date of study treatment. If yes, impute to first dose date of study treatment; else impute first day of the month. However, if the stop date is not missing and is before the date of the first dose of study treatment or the imputed start date, then the stop date will be used instead.

- If the start day and month are missing: Check if year is same as the year of the first dose date of study treatment. If yes, impute to first dose date of study treatment; else impute to first day of the first month (January). However, if the stop date is not missing and is before the date of the first dose of study treatment or the imputed start date, then the stop date will be used instead.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining concomitant use:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used. If resulted imputed stop date is after the latest of last dose date or date of completion/withdrawal, then the latest of last dose date or date of completion/withdrawal will be used.

- If the stop day and month are missing, then the last day of the last month (December) will be used. If resulted imputed stop date is after the latest of last dose date or date of completion/withdrawal, then the latest of last dose date or date of completion/withdrawal will be used.

8. ANALYSIS OF PHARMACOKINETICS

The primary endpoint of this study is the PK profile (plasma) for apomorphine and its metabolites (apomorphine sulfate and norapomorphine). Apomorphine PK parameters will include: C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{inf}, AUC_{0-24h}, MRT, CL/F and V/F. Comparative bioavailability ($F_{T/R}$) of apomorphine between the Test (APL-130277) and Reference (APO-go and APOKYN) products will be evaluated and calculated using dose normalized C_{max}, AUC_{last}, and AUC_{inf}. In addition, the comparative bioavailability between APOKYN (Reference) and APO-go (Test) will be determined using Cmax, AUClast and AUCinf ($F_{T/R}$_APO-go/APOKYN). Apomorphine metabolites (norapomorphine and apomorphine sulphate) PK parameters will consist of determination of C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{inf}, AUC_{0-24h}, and metabolite-to-parent (M/P) ratios of C_{max}, AUC_{inf} and AUC_{last}.

Pharmacokinetic parameters will be derived using noncompartmental methods employing Phoenix WinNonlin® version 6.3 or higher (Certara, Princeton, NJ). Pharmacokinetic analysis will be conducted using actual time elapsed from dosing concentration-time data for apomorphine and metabolites (norapomorphine and apomorphine sulphate).

8.1. PK SAMPLING SCHEDULE

Pharmacokinetic evaluation of APL-130277, subcutaneous APO-go® and APOKYN® will be completed in Period 1, Period 2, and Period 3. Blood draws for PK analyses will occur at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes after dosing and at 1.5, 3, 6 hours after dosing. Sampling should occur as close as possible to the target time. Actual sampling date and time should be recorded in the case report form (CRF).

8.2. PLASMA PK ENDPOINT

Table 1 provides the PK parameters that will be estimated by noncompartmental methods from plasma samples. Actual elapsed time from dosing will be used to determine all individual PK parameters. For APL-130277, the time the sublingual film was placed under the tongue will be used as the start of dosing to calculate the actual elapsed time.

The PK parameters in Table 1 (except M/P $_{Cmax}$, M/P $_{AUClast}$, M/P $_{AUCinf}$) will be calculated and summarized for apomorphine. The same PK parameters, excluding $F_{T/R\ Cmax}$, $F_{T/R\ AUClast}$, $F_{T/R\ AUCinf}$, MRT, CL/F and V/F, will be calculated and summarized for metabolites (norapomorphine and apomorphine sulphate).

All PK parameters will be listed and summarized (AUCext i.e. % extrapolated will only be listed).

Table 1. PK Parameters

C_{max} (ng/mL)	Maximum plasma concentration, observed by inspection of individual subject plots of plasma concentration versus time.
C_{max}/D* (ng/mL)/(mg) (Parent only)	Dose normalized maximum observed concentration
T_{max} (h)	Time from dosing to C_{max}, observed by inspection of individual subject plots of plasma concentration versus time.
AUC_{0-24} (h*ng/mL)	Area under the concentration-time curve from time zero to 24 hours using the linear-up log-down trapezoidal rule.
AUC_{0-24}/D (h*ng/mL)/(mg) (Parent only)	Dose normalized area under the concentration-time curve from time zero to 24 hours using the linear-up log-down trapezoidal rule.
AUC_{last} (hr*ng/mL)	Area under the plasma concentration vs. time curve from dosing to the last measurable concentration, calculated using the linear trapezoidal rule for incremental trapezoids and the log-trapezoidal rule for decremental trapezoids.
AUC_{last}/D (h*ng/mL)/(mg) (Parent only)	Dose normalized area under the plasma concentration vs time curve from time zero to the last measurable concentration.
AUC_{inf} (h*ng/mL)	Area under the plasma concentration vs. time curve from Hour 0.0 to infinity. AUC_{inf} is calculated as the sum of AUC_{0-t} and $AUC_{t-\infty}$. The extrapolated $AUC_{t-\infty}$ is estimated as the ratio of the last measurable plasma concentration and the apparent terminal elimination rate constant (C_t/k_{el}).
AUC_{inf}/D (h*ng/mL)/(mg) (Parent only)	Dose normalized area under the plasma concentration vs time curve from time zero extrapolated to infinity
AUC_{ext}	The percentage (%) of AUC_{inf} extrapolated

λ_z (h^{-1})	Apparent terminal elimination rate constant, determined by log linear regression of the plasma concentration versus time data that was judged to be in the log-linear elimination phase. At least 3 data points in the terminal phase will be used in the determination of the rate constant.
$t_{½}$ (h)	Terminal phase half-life, as calculated by the following equation: $t_{½} = \ln(2)/\lambda_z$.
MRT (h) (parent only)	Mean residence time during one dosing interval calculated using the following equation: MRT = $AUMC_{inf}/AUC_{inf}$. $AUMC_{inf}$ is the area under the first moment (time.plasma concentration vs. time) curve.
$F_{T/R\ Cmax}$ (parent only)	The comparative bioavailability calculated as the ratio of the Test/Reference (APOGO and APOKYN) formulation PK parameter (Dose normalized C_{max}). Ratio of APO_go/APOKYN will be determined
$F_{T/R\ AUClast}$ (parent only)	The relative bioavailability calculated as the ratio of the Test/Reference (APOGO and APOKYN) formulation PK parameter (Dose normalized AUC_{last}). Ratio of APO_go/APOKYN will be determined
$F_{T/R\ AUCinf}$ (parent only)	The relative bioavailability calculated as the ratio of the Test/Reference (APOGO and APOKYN) formulation PK parameter (Dose normalized AUC_{inf}). Ratio of APO_go/APOKYN will be determined
M/P $_{Cmax}$ (metabolite only)	Metabolite to Parent exposure ratio, C_{max}, corrected for molecular weight differences.
M/P $_{AUClast}$ (metabolite only)	Metabolite to Parent exposure ratio, AUC_{last}, corrected for molecular weight differences.
M/P $_{AUCinf}$ (metabolite only)	Metabolite to Parent exposure ratio, AUC_{inf}, corrected for molecular weight differences.
CL/F (L/h) (parent only)	Apparent total clearance of the drug from plasma extravascular administration, calculated as Dose/AUC_{inf}.
V/F (L) (parent only)	Apparent volume of distribution after extravascular administration, calculated as Dose/(AUC_{inf} * λ_z).

8.3. HANDLING OF DROPOUTS, MISSING DATA OR DATA BELOW THE LOWER LIMIT OF QUANTIFICATION

For PK concentration analyses:

For calculation of mean concentrations and generation of mean concentration time profiles, all BLQ values will be set to zero except when an individual BLQ falls between two quantifiable values, in which case it will be treated as missing data. PK concentration listing will list original values without any data handling adjustments.

For APL-130277, time when sublingual film was placed under the tongue will be use as time zero. For APOKYN and APOGO, start of dosing time will be used as time zero.

For PK parameter calculation:

For the PK analysis, a concentration that is BLQ will be assigned a value of zero if it occurs in a profile before the first measurable concentration. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ will be treated as missing data. BLQ values occurring at the end of the collection interval (after the last quantifiable concentration) will be treated as missing data. If two BLQ values occur in succession after Cmax, the profile will be deemed to have terminated at the first BLQ value and any subsequent concentrations will be omitted from PK calculations.

All PK parameter calculations will use actual times relative to time of dosing. APL-130277 apomorphine and its metabolite PK data from subjects who experience emesis for a given study treatment dose may be excluded from statistical analysis if vomiting occurs at or before two times of median T_{max}. These APL-130277 PK concentration and parameter data may be excluded from descriptive and mixed effect model analyses but will be included in individual listings.

PK analysis will be performed for individual profiles with at least 4 quantifiable results following BLQ imputation unless noted otherwise in the study report.

For APL-130277, time when sublingual thin film was placed under the tongue will be used as time zero. For APOKYN and APOGO, start of dosing time will be used as time zero.

Reporting of AUCinf and AUCinf-dependent parameters is contingent on the percent of the total area obtained by extrapolation as follows:

• AUCinf values with <20% of the total area coming from Clast/ λ z are acceptable to report.

• Individual plasma concentration-time profiles for which the extrapolated areas are >20% of AUCinf will be identified in the report.

• It is unacceptable to use AUCinf data if >40% of the AUC has been extrapolated, except in specific situations.

The percentage of AUCinf obtained by extrapolation (AUC%Extrap) will be calculated as follows:

AUC%Extrap (AUCext) = [(AUCinf – AUClast) / AUCinf] x 100

8.4. PK CONCENTRATION ANALYSIS

Apomorphine and metabolite concentration-time data will be summarized descriptively in tabular formats by dose level for each treatment group using the following summary statistics: n, mean, SD, coefficient of variation (CV)%, median, minimum, maximum. In addition, dose normalized apomorphine concentration (PK concentration/dose level) will be summarized descriptively.

Figures illustrating the time course of mean drug concentration vs. time for apomorphine and its metabolites separately will be presented for relevant comparisons on linear and semi-logarithmic scales by dose level with treatment groups overlaid, and by treatment group with dose levels overlaid. Plots illustrating dose normalized concentration data may be included as appropriate. In addition, the individual subject concentration-time data will be listed and displayed graphically on linear and semi-log scales by overlaid treatment group and dose level.

8.5. PK PARAMETER ANALYSIS

Individual PK parameters from the noncompartmental PK analysis will be tabulated, where calculable, and summarized descriptively by treatment group and dose level. The following summary statistics will be presented for PK parameters: n, arithmetic mean, CV%, SD of the arithmetic mean, median, minimum, maximum, geometric mean and CV% of the geometric mean. T_{max} will be presented as n, median, minimum and maximum.

Other analyses such as exploring the relationship between PK parameters and dose will be conducted, as appropriate.

A mixed effects model with fixed effects for treatment and period, with subject nested within sequence as a random effect will be used to analyze the natural-log transformed dose normalized AUC_{last}, AUC_{0-24}, AUC_{inf}, and C_{max}. The Kenward-Roger method will be used for the model. For each treatment comparison, a point estimate and 90% CIs will be provided for the geometric mean ratio upon back-transformation. T_{max} will be analyzed by dose level for each treatment group using a non-parametric test (Wilcoxon test); two-sided p-value will be presented. $t_{½}$ will be analyzed by dose levels for each treatment group using a t-test; t-statistics score, two-sided p-value, mean difference and

corresponding 90% CIs will be presented. These tests will only be performed if there are more than 5 subjects at a dose level. Descriptive statistics will be presented for all PK parameters by dose level for each treatment group.

9. SAFETY

Safety will be assessed on the basis of clinical laboratory tests, 12-lead ECGs, physical examinations, vital signs (including BP, HR, RR, body temperature and weight), and AEs.

9.1. STUDY DRUG EXPOSURE

A summary of subjects receiving any dose of study drug, subjects that had a confirmed "OFF" episode prior to dose, the dose administered, subjects that experienced an "ON" response, subjects that were rescued with L-Dopa or other PD medications will be presented overall for each treatment. The time from the start of dosing to an "ON" response (in hours) will be summarized descriptively.

Study drug administration will be provided in subject listings.

Note that for APL-130277, time when sublingual thin film was placed under the tongue will be used as start of dosing time.

9.2. ADVERSE EVENTS

Adverse events will be recorded from the time of signing of the ICF by the subject through to study completion or earlier, if warranted by a subject discontinuation. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 and summarized by SOC and PT.

AEs that occur on or after Day 1 of a Treatment Period, up through and including the day prior to Day 1 of the next Treatment Period will be assigned to the treatment group associated with the former Treatment Period and considered a treatment-emergent adverse event (TEAE). An AE that occurs on or after Day 1 of the last Treatment Period up to EOS in which a subject participates will be assigned to the treatment group associated with this last Treatment Period and considered a TEAE.

AEs that are associated with injection site reactions reported on the injection site CRF will be directly assigned to the last treatment they received (APOKYN or APOGO) regardless of the AE onset date.

Pre-treatment emergent AEs are defined as any AEs with a start date prior to the start of dosing in Period 1.

An overall summary of the number and percentages of subjects reporting any TEAEs, drug-related TEAEs, severe TEAEs, serious TEAEs, non-serious TEAEs, TEAEs leading to study treatment discontinuation, leading to death, drug-related TEAEs leading to study treatment discontinuation and drug-related serious TEAEs will be presented. Corresponding event counts will also be provided.

TEAEs will be summarized (number of events and number of subjects having experienced at least one event) overall and by treatment group, SOC and PT. TEAEs will also be summarized by maximum severity (in the order of mild, moderate and severe) and by relationship to study drugs (related and unrelated). Subjects with multiple TEAEs at the same SOC or PT within an SOC level will only be counted once at the maximum severity. Subjects with multiple TEAEs at the same SOC or PT within an SOC level and at least one is related, will only be counted once as related. An AE with missing relationship to study drug will be considered as related to study drug. Serious adverse events (SAEs) and TEAEs leading to drug discontinuation will also be summarized.

Pre-treatment AEs will be summarized (number of events and number of subjects having experienced at least one event) overall and by SOC and PT.

All AEs will be listed.

9.2.1. Adverse Event with Missing or Incomplete Start/End Date

Missing or incomplete AE start and stop dates will not be imputed. The treatment period for which the AE was treatment-emergent will be determined using the following rules:

- If the day of the AE start date is missing, the month is on or after the month of first dose in Period 1 and the end date is on or after the first dose date in Period 1, then this AE will be considered treatment emergent. The TEAE will be considered a Period 1 TEAE if based on the available partial date information, the TEAE could have started prior to the first dose in Period 2. The TEAE will be considered a Period 2 TEAE if based on the available partial date information, the TEAE could have started on or after the first dose in Period 2 but prior to the first dose in Period 3. The TEAE will be considered a Period 3 TEAE if based on the partial date information, the TEAE could have started on or after the first dose in Period 3 up to the EOS. If based on the available partial date information, the TEAE couldn't be assigned to any specific treatment period, then this TEAE will be assigned to APL-130277.

- If the day and month of the AE start date is missing but the year is on or after the year of first dose in Period 1, then this AE will be assigned as Period 1 TEAE or Period 2 TEAE or Period 3 TEAE, assuming any available AE end date information does preclude inclusion into one or more of the periods. If based on the available partial date information, the TEAE couldn't be assigned to any specific treatment period, then this TEAE will be assigned to APL-130277.

- If the AE start date is completely missing, then this AE will be assigned as Period 1 TEAE or Period 2 TEAE or Period 3 TEAE, assuming any available AE end date information does preclude inclusion into one or more of the periods. If based on the available partial date information, the TEAE couldn't be assigned to any specific treatment period, then this TEAE will be assigned to APL-130277.

AEs with missing time will not be imputed.

9.3. LABORATORY EVALUATIONS

All clinical laboratory parameters will be converted to consistent units according to the International System of Units (SI) before summarization.

Laboratory data will be summarized by the type of laboratory test. Normal reference ranges and abnormal results will be used in the summary of laboratory data. Data will be flagged according to the reference limits (high or low) if applicable.

Descriptive statistics will be calculated for each numeric laboratory test parameter at study baseline and end of study (EOS) visit overall. Changes from study baseline results will be presented descriptively. For chemistry and hematology lab tests, shift tables showing baseline and EOS visit will be performed for the following categories: low, normal, and high. A listing of subjects with any laboratory results outside the reference ranges will be provided.

9.4. VITAL SIGNS

Descriptive summaries of actual values and changes from study baseline will be calculated for vital signs by treatment group and time points (study baseline and EOS will be summarized overall), which includes blood pressure (BP), heart rate (HR), respiration rate (RR), and body temperature.

Vital sign results for each parameter will then be tabulated for actual and change from period baseline values by treatment group and time points. The proportion of subjects with orthostatic hypotension will be tabulated by treatment group and time point (screening and EOS will be summarized overall).

Actual values and change from study baseline for weight will be summarized separately by treatment group and visit (study baseline and EOS will be summarized overall).

All vital sign data will be listed by subject and time of measurement.

9.5. ECG

A standard 12-lead ECG will be performed at all time points outlined in Table 2. A triplicate 12-lead ECG will be performed at the Screening Visit and the median value will be used for summary purposes. ECGs will be performed in a semi-recumbent position and after 5 minutes of rest. All ECGs should be assessed by the Investigator and deemed “Normal”, “Abnormal, not clinically significant” and “Abnormal, clinically significant”. A shift table showing period baseline to 60 minutes post-dose by treatment group and a shift table showing study baseline to EOS visit will be performed for the above categories. The ECG variables that will be analyzed are heart rate, RR interval, PR interval, QRS interval, QT interval, QT corrected with Bazett’s formula (QTcB), and QT corrected with

Fridericia's formula (QTcF). The actual value and change from study baseline of ECG measurements will be summarized by treatment group and time point (study baseline and EOS will be summarized overall). The same ECG results will then be summarized for change from period baseline by treatment group.

All-important abnormalities from the ECG readings that, in the opinion of the Investigator are deemed clinically significant should be reported as AEs and will be listed in the AE listing.

9.6. PHYSICAL EXAMINATION

A complete physical examination including the oropharyngeal cavity examination will be performed at the screening and EOS visit. Findings of the oropharyngeal cavity examination will be tabulated by treatment group for the treatment period assessments and overall for the Screening and EOS Visit assessment.

Examination for injection site reactions will be completed just prior to dosing and 2 hours after dosing in P1, P2, and P3, as well as the EOS Visit. The findings will be summarized by treatment group for the treatment period assessments and overall for the EOS Visit assessment. All findings will be listed.

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

All physical examination data will be listed.

9.7. 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.

10. INTERIM ANALYSES

Two unplanned interim analyses were conducted for regulatory submissions.

11. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

AUC 0-24 for apomorphine and apomorphine metabolites parameters were added to primary analyses.

Analysis of raw PK concentration and parameter data will only be conducted by dose level as different dose levels will have different PK profiles and cannot be combined together for analysis without dose-normalization.

The analysis on log-transformed AUC_{last}, AUC_{inf}, and C_{max} has been changed to a mixed effect model on dose-normalized log-transformed PK parameters.

REFERENCE LIST

12. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

PK parameters will be derived using noncompartmental methods employing Phoenix WinNonlin® version 6.3 or higher (Pharsight, St Louis, MO).

12.1. GENERAL CONSIDERATIONS

- Each output will be stored in a separate file.
- Output files will be delivered in Rich Text Format.
- Numbering of TFLs will follow ICH E3 guidance.

12.2. TABLE, LISTING, AND FIGURE FORMAT

12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:
  Sunovion Pharmaceuticals Inc.
  Protocol CTH-203
- All output should have Page n of N at the top or right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). The title is centered. The analysis population will be identified on the line immediately following the title. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Safety Population

12.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- When appropriate the variable (or characteristic) column will be on the far left followed by the treatment group or sequence columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, the “unit” in column or row heading will be included when appropriate.
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis population.
- For tables presented by treatment group, the order of treatments will be APL-130277, APOKYN® and APO-go®, followed by an overall column. For tables presented

by treatment sequence, the order will following sequentially, followed by an overall column.

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category will be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as “0” and not as “0 (0%)”.

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups will be included.
- An Unknown or Missing category will be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	XX
Mean (SD)	XX.X (XX.XX)
Median	XXX.X
Min, Max	XX.X, XX.X

- P-values will be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as “<0.001”.

- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as "100%", without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the overall column in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

12.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

13. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. INC Research SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

INC Research SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output.

14. INDEX OF TABLES

Please see table shell attachment 1.

15. INDEX OF FIGURES

Please see figure shell attachment 2.

16. INDEX OF LISTINGS

Please see listing shell attachment 3

17. APPENDICES

Table 2. Schedule of Events Tables

Procedures	Screening Visit[1]	Telephone Contact[2]	Wash-Out	Period 1 Visit	Telephone Contact[2]	Wash-Out	Period 2 Visit	Telephone Contact[2]	Wash-Out	Period 3 Visit	Telephone Contact[2]	Wash-Out	End of Study Visit
Study Visit	SV	TC	W/O	P1	TC	W/O	P2	TC	W/O	P3	TC	W/O	EOS
Day	-21 to -3	1 day prior to W/O	1 day prior to P1	1	1 day prior to W/O	1 day prior to P2	3-5 days after P1	1 day prior to W/O	1 day prior to P3	3-5 days after P2	1 day prior to W/O	1 day prior to EOS	3-5 days after P3
	-21 to -3	-2	-1	1	2	3	4-6	7	8	9-11	12	13	14-16
Outpatient Visit	X			X			X			X			X
Written Informed Consent	X												
Reconfirmation of Consent				X			X			X			X
Review Entry Criteria	X												
Review Prohibited Treatment & Study Restrictions	X			X			X			X			X
Medical History/Demographics	X												
Complete Physical Exam, including Oropharyngeal Exam & Injection Site Reaction[3]	X												X
Abbreviated Physical Exam, including Oropharyngeal Exam & Injection Site Reaction[4]				X			X			X			
BMI, Weight and Height[5]	X			X			X			X			X

Procedures	Screening Visit[1]	Telephone Contact[2]	Wash-Out	Period 1 Visit	Telephone Contact[2]	Wash-Out	Period 2 Visit	Telephone Contact[2]	Wash-Out	Period 3 Visit	Telephone Contact[2]	Wash-Out	End of Study Visit
Study Visit	SV	TC	W/O	P1	TC	W/O	P2	TC	W/O	P3	TC	W/O	EOS
Day	-21 to -3	1 day prior to W/O	1 day prior to P1	1	1 day prior to W/O	1 day prior to P2	3-5 days after P1	1 day prior to W/O	1 day prior to P3	3-5 days after P2	1 day prior to W/O	1 day prior to EOS	3-5 days after P3
	-21 to -3	-2	-1	1	2	3	4-6	7	8	9-11	12	13	14-16
Vital Signs (BP, HR, RR and Temp)[6,7]	X			X			X			X			X
12-Lead ECG[7,8]	X			X			X			X			X
Clinical Laboratory Tests[9]	X												X
PK[7,10]				X			X			X			
MMSE	X												
Modified Hoehn and Yahr[11]	X												
C-SSRS[12]	X												X
Clinical Confirmation of "OFF" or full "ON"	X			X			X			X			
Randomization				X									
In-Clinic Dosing				X			X			X			
AEs/Serious AEs (SAEs)				X			X			X			X
Previous/Current Concomitant Medications	X			X			X			X			X

[1] All screening procedures to be conducted within 21 days prior to dosing (Period 1).

[2] Telephone contact as a reminder for subject to discontinue APOKYN® a minimum of 1-day prior to each study visit for the wash-out period (excluding SV).

[3] Physical examinations 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; skin; and injection site. 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. Examination for injection site reaction will be completed at the End of Study Visit (EOS).

[4] Abbreviated physical examinations to include head-eyes-ears-nose and throat; heart; lungs; abdomen; skin; mouth – oral cavity and injection site to be done at t= 0 (just prior to dosing) and 2 hours after dosing at Period 1, Period 2, and Period 3. The oropharyngeal cavity examination should include a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

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

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

[7] Suggested Sequence of Assessments: PK – ECG – Vitals.

[8] 12-lead ECG: Obtain in triplicate at the Screening Visit. Period 1, Period 2 and Period 3 obtain at t = 0 (just prior to dosing) and 60 minutes after dosing. Obtain at the End of Study Visit.

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

[10] PK will be assessed in Period 1, Period 2 and Period 3 at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes and 1.5, 3, 6 hours after dosing.

[11] The modified Hoehn and Yahr will be used during the Screening Visit in the “ON” state to determine eligibility.

[12] C-SSRS “Screening” scale to be used at the Screening Visit; “Since Last Visit” scale to be used at End of Study Visit.