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

Study code: CTH-201

Phase II study

STATISTICAL ANALYSIS PLAN

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1 Abbreviations

AAP	All Available Population
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	Area under the concentration-time curve from time zero to the last measurable plasma concentration-time curve using the linear up log down trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to infinity using the linear up log down trapezoidal rule
BLQ	Below the Limit of Quantitation
BP	Blood Pressure
CI	Confidence Interval
CL/F	Plasma clearance
C_{max}	Maximum observed plasma concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of Variation
ECG	Electrocardiogram
HR	Heart Rate
L-Dopa	Levodopa
λ_z	Terminal-phase rate constant
LS	Least Square
M/P	Metabolite to Parent
MDS	Movement Disorders Society
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MMSE	Mini–Mental State Examination
MRT	Mean Residence Time
OH	Orthostatic Hypotension
P1V1	Period 1 Dosing Visit 1
PD	Parkinson's Disease
PK	Pharmacokinetics

Placebo	Placebo for APL-130277
PT	Preferred Term
QTc	Corrected QT interval
QTcB	Corrected QT interval based on the Bazett correction method
QTcF	Corrected QT interval based on the Fridericia correction method
REML	Restricted Maximum Likelihood
RR	Respiratory Rate
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SI	International System of Units
SOC	System Organ Class
SV	Screening Visit
$t_{½}$	Terminal-phase half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Observed time of the maximum concentration
TV	Titration Visit
UPDRS	Unified Parkinson's Disease Rating Scale
WHO-DD	World Health Organization Drug Dictionary

2 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analysis as it is foreseen at the time of planning the study. The SAP will serve as a compliment to the study protocol and supersedes it in case of differences. In case of major differences between the study protocol and SAP (e.g. changes in the analysis related to the primary endpoint), a protocol amendment will be considered. The SAP may be updated during the conduct of the study and will be finalized before breaking the blind.

3 Study objectives

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

The secondary objectives include the evaluation of safety and pharmacokinetics (PK) of APL-130277. A comparison of efficacy of the highest APL-130277 dose and the lowest APL-130277 dose resulting in a full "ON" during the Dose Titration Phase will be included as an exploratory objective.

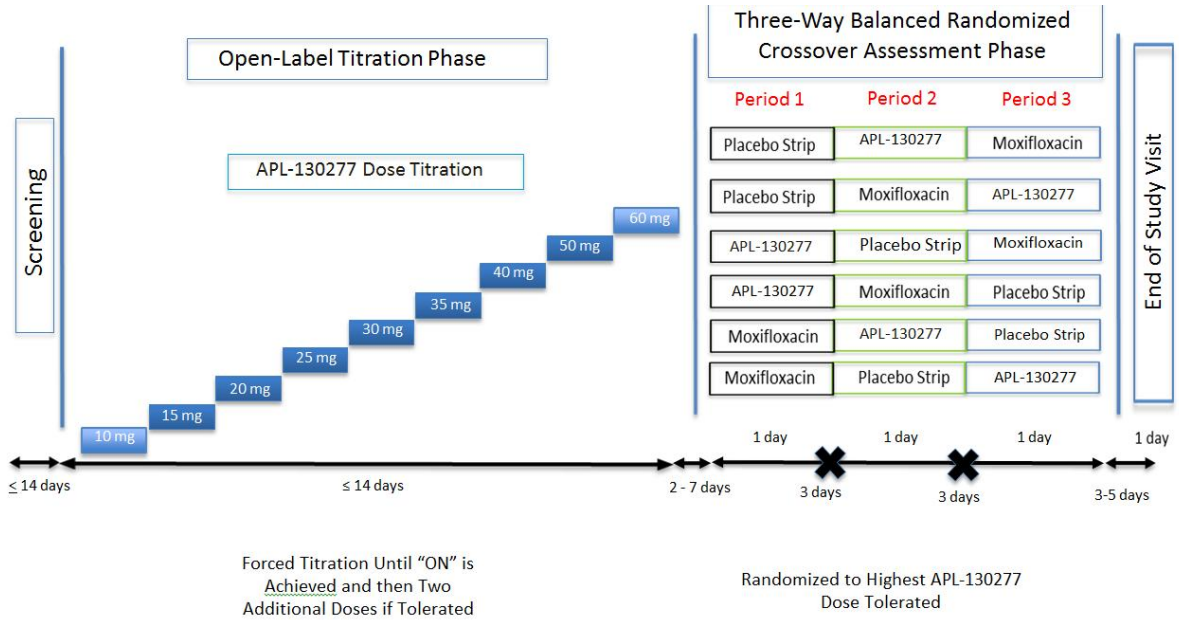
4 Design and type of the study

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

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

The study design is summarized in Figure 1.

Figure 1 Study Design



4.1 Screening Visits

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

4.2 Dose Titration Phase

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

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

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

During the Dose Titration Phase of the study, subjects will start with a dose of 10 mg APL-130277 and increase in 5 mg increments up to 40 mg and then in 10 mg increments for the 50 mg and 60 mg dose levels until the subject reaches a full “ON” state. Once a full “ON” state is achieved, dosing will continue for 2 additional visits to a maximum dose of 60 mg (i.e., if a subject experiences the first full “ON” at 10 mg, dosing will continue up until a dose of 20 mg).

For those subjects who do not achieve a full "ON" response, titration should continue until the maximum tolerated dose of APL-130277 is determined to a maximum dose of 60 mg.

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

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

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

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

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

Safety and efficacy assessments will be performed at each visit. Efficacy will be assessed using Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part III. Safety assessments will include adverse events (AEs); electrocardiograms (ECGs); and vital signs, including supine and standing blood pressure (BP) to assess OH. ECGs will be obtained using a 12-lead resting ECG device just prior to dosing and 45 minutes after dosing as a safety evaluation and assessed by the

Investigator at each Titration Visit.

4.3 Three-Way Balanced Randomized Crossover Assessment Phase

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

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

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

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

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

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

At P1V1, three (3) sets of triplicate 12-Lead ECGs will be obtained using a continuous 12-lead Holter monitor over approximately 1-hour (prior to dosing) as the baseline assessment.

5 Endpoints

5.1 Primary endpoint

The primary endpoint of this study is the time-matched change from baseline in QTc, placebo-adjusted and corrected for HR based on the Fridericia correction method (QTcF) using delta delta method (ΔΔQTcF). Assay sensitivity will be demonstrated by inclusion of a positive control, moxifloxacin.

Baseline is defined as the mean of the 9 ECGs (3 sets of triplicate ECGs) recorded at baseline (P1V1). In case any of the 9 ECGs is missing, the baseline is defined as the mean of the available baseline values.

The post-dose ECGs are recorded at 15, 30, 45 and 60 minutes and 2, 3, 4, 8, 12 and 24 hours post-dose at Period 1, Period 2 and Period 3. One set of triplicate ECGs (3 ECGs) is obtained at each of the 10 time points. For each of the 10 time points, an average value will be calculated based on the 3 (or all available) ECGs. These average values will be used in all calculations. For the primary analysis, the following 7 time points will be evaluated: 15, 30, 45, 60 minutes and 2, 3, and 4 hours post-dose. The endpoint will be calculated as the difference between each of the 7 post-dose ECGs and baseline (P1V1), separately for each of the 3 periods. For each of the 7 time points, the changes from baseline will be compared between APL-130277 and placebo using the ΔΔQTcF method.

The endpoints for the assay sensitivity comparison will be derived in a similar way. For assay sensitivity, the changes from baseline at 4 selected time points (60 minutes and 2, 3 and 4 hours post-dose) will be compared between moxifloxacin and placebo using the ΔΔQTcF method.

The QTcF will be calculated as follows:

- $QTcF_1 = QT_1/RR_1^{1/3}$, where RR_1 is $60/HR_1$
- $QTcF_2 = QT_2/RR_2^{1/3}$, where RR_2 is $60/HR_2$
- $QTcF_3 = QT_3/RR_3^{1/3}$, where RR_3 is $60/HR_3$
- Mean QTcF = $(QTcF_1 + QTcF_2 + QTcF_3)/3$ (rounded to whole number)

The values provided by the central core laboratory will be used in all calculations.

5.2 Secondary endpoints

The secondary endpoints will be evaluated without any hierarchical order. Due to this, no confirmatory claims will be made on the secondary endpoints.

- PK of apomorphine and apomorphine metabolites

  Blood draws for PK analyses on APL-130277 and placebo treatment days will occur at t = 0 (just prior to dosing), 30, 45, 60 minutes after dosing and at 2, 4 hours after dosing. On the moxifloxacin treatment day, blood draws will occur at t = 0 (just prior to dosing), 30, 60 minutes after dosing and at 2, 3, 4, 6, 8 hours after dosing. The PK endpoints include both the concentration data and PK parameters.

  Concentration levels of apomorphine and metabolites (norapomorphine and apomorphine sulphate) will be measured in plasma using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. PK parameters will be derived using noncompartmental methods employing a validated installation of WinNonlin® Phoenix version 6.3 (Pharsight, St Louis, MO) software.

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

- C_{max}: Maximum drug concentration in plasma, determined directly from the concentration-time profile.
- T_{max}: Time of C_{max} in plasma, determined directly from the concentration-time profile.
- AUC_{0-t}: Area under the plasma concentration vs. time curve from time of dosing to last measurable concentration, calculated using the linear up, log down trapezoidal rule.
- AUC_{inf}: AUC extrapolated to infinity (AUC_{last} + last quantifiable concentration/λ_z), calculated using the linear-up/log-down trapezoidal rule.
- λ_z: The terminal phase rate constant; estimated by linear regression through the terminal phase of the log concentration-time profile, using at least 3 data points.
- $t_{½}$: The terminal phase half-life calculated as ln(2) / λ_z.
- CL/F: Plasma clearance, calculated as Dose/AUC_{inf} after single dose (apomorphine only).
- MRT: Mean residence time calculated using the following equation: MRT = $AUMC_{inf}/AUC_{inf}$. $AUMC_{inf}$ is the area under the first moment curve.
- M/P Ratio: Metabolite to Parent exposure ratio (C_{max} and AUC).

- Safety and tolerability of APL-130277 as measured by AEs, physical examination including assessment of oropharyngeal AEs, 12-lead ECGs (resting), vital signs including orthostatic hypotension, clinical laboratory tests, and Columbia Suicide Severity Rating Scale (C-SSRS) assessments.

  The safety endpoints are defined in Section 15 of this SAP.

- Pharmacodynamic assessments including QTc based on the Bazett correction method (QTcB), heart rate (HR), PR interval, QRS interval, uncorrected QT interval, ECG morphology and correlation between the QTcF change from baseline and plasma concentrations of APL-130277

  The continuous ECG endpoints (QTcB, HR, PR interval, QRS interval, uncorrected QT interval) will be derived similarly as QTcF described above. The QTcB will be calculated as QT / $(RR)^{½}$ and rounded to a whole number similarly as QTcF. The rest of the parameters will be calculated as mean values of the available observations without rounding. The values provided by the central core laboratory will be used in all calculations of the continuous ECG endpoints.

  For the ECG morphology, the overall interpretation and the presence of the following abnormalities will be defined by the cardiologist of the central core laboratory:

  - Atrial fibrillation
  - Atrial flutter

- Second degree heart block
- Third degree heart block
- Complete right bundle branch block
- Complete left bundle branch block
- ST segment elevation
- ST segment depression
- T wave abnormalities (negative T waves only)
- Myocardial infarction pattern
- New abnormal U waves.

- Presence of cardiac arrhythmias such as ventricular tachycardia or Torsade de Pointes

  The presence of the cardiac arrhythmias will be defined by the cardiologist of the central core laboratory.

5.3 Exploratory efficacy endpoints

- MDS-UPDRS Part III change from pre-dose to 30, 60, 90 minutes after dosing during the Titration Phase at the highest APL-130277 dose and the lowest APL-130277 dose resulting in a full "ON"

  The MDS-UPDRS Part III score will be calculated as the sum of the individual items of the MDS-UPDRS Part III questionnaire (items 3.1 – 3.18) and will be obtained separately at each assessment time point. Missing individual items will be imputed using the 2 non-missing values at time points adjacent to the missing item on the same date. The maximum of the 2 adjacent values will be assigned as the score for the missing item. However, pre-dose values will not be assigned as post-dose values and if one of the adjacent values for a post-dose value is a pre-dose value, only 1 adjacent value will be used. If there are more than three missing individual items at a given time point, no imputation will be performed for the time point in question and the score will be set as missing. If a pre-dose value is missing, the pre-dose value at the prior visit will be used. The MDS-UPDRS Part III score will be calculated after imputation of the missing item(s) as described above.

- Time to "ON" during Titration Phase at the highest APL-130277 dose and the lowest APL-130277 dose resulting in a full "ON"

  The subjects will report the time when they turned to a full "ON" if it occurs within 90 minutes of dosing. The time to "ON" will be calculated as minutes from the time when the subject received the study medication until the time when turning fully "ON". If the subject did not turn fully "ON" by 90 minutes the data will be censored at 90 minutes.

- Duration of "ON" during Titration Phase at the highest APL-130277 dose and the lowest APL-130277 dose resulting in a full "ON".

The subjects will report the time when they turned "OFF" (in case they first turned fully "ON") if it occurs within 90 minutes of dosing. The duration of "ON" will be calculated as minutes from the time when the subject turned fully "ON" until the time when turning "OFF". If the subject did not turn fully "ON" within 90 minutes the duration of "ON" will be defined as zero minutes. If the subject turned fully "ON" and did not turn "OFF" by 90 minutes, the data will be censored at 90 minutes minus the time when the subject turned fully "ON".

6 Sample size considerations

The study is powered to detect a mean difference in the change in QTcF between APL-130277 and placebo APL-130277 (ΔΔQTcF) of 7 ms, assuming that the true difference between APL-130277 and placebo APL-130277 can be up to 3 ms, adding up to the predefined threshold of 10 ms. The standard deviation of ΔΔQTcF is assumed to be 14 ms. Assuming a one-sided significance level of 0.05, 42 subjects are required for the 3x3 Crossover Phase to achieve approximately 80% power.

7 Statistical hypotheses

The primary objective of this study is to evaluate the effect of APL-130277 compared to placebo on QTc intervals in subjects with PD complicated by motor fluctuations.

The hypothesis of no difference in QTc time between APL-130277 and placebo will be evaluated by observing if any of the evaluation time points have a two-sided 90% upper confidence bound (i.e. one-sided 95%) which is equal to, or exceeds, 10 ms. If the upper limits of the two-sided 90% confidence intervals (CIs) for APL-130277 versus placebo fall below 10 ms, it will be concluded that APL-130277 does not prolong the QTc interval to a clinically significant degree.

If the upper bound of only 1 or 2 of the 7 time points just exceeds 10 ms, a determination of whether this is a false positive response will be based on all of the study findings with special emphasis on the PK-Pharmacodynamics evaluation.

The assay sensitivity will be evaluated by comparing moxifloxacin and placebo. The hypothesis of assay sensitivity will be rejected if the lower bound of the one-sided (Bonferroni-corrected) 95% confidence interval is below 5 ms at all of the 4 evaluation time points (60 minutes and 2, 3 and 4 hours). The assay sensitivity is considered to be demonstrated if there is at least one time point where the lower confidence bound of the mean difference of moxifloxacin and placebo APL-130277 is greater than or equal to 5 ms. The Bonferroni-corrected CIs will be calculated by using the coverage of 0.05/4=0.0125 for the 4 CIs.

8 Analysis sets

The following analysis sets will be used for the analysis of the disposition and ECG (holter), efficacy, safety and PK data.

8.1 All Available population

The All Available Population (AAP) includes all subjects who consented for the study, including screening failures. Unless specified otherwise, the AAP will be used for subject listings and for the summary of subject disposition.

8.2 ECG population

The ECG population includes all randomized subjects who have evaluable baseline ECG (holter) data from P1V1 and at least one evaluable post-dose ECG (holter) assessment during the Crossover Phase. The ECG population will be used for the analysis of the primary endpoint and secondary endpoints related to ECG (holter) data. The treatment (APL-130277, placebo or moxifloxacin) actually received during each crossover period will be used to group the patients.

8.3 Completer population

The Completer population includes all randomized subjects who have any evaluable pre-dose and post-dose ECG (holter) data from all three periods of the Crossover Phase. The Completer population will be used for a sensitivity analysis of the primary endpoint. The treatment (APL-130277, placebo or moxifloxacin) actually received during each crossover period will be used to group the patients.

8.4 Efficacy population

The Efficacy population includes all subjects who have efficacy assessments at the lowest dose level resulting in a full “ON” and at a higher dose level during the Dose Titration Phase. The patient is regarded as having reached full “ON” based on the Case Report Form assessing the time when the patient turned “ON”. The efficacy population will be used for the analysis of the efficacy data.

8.5 Safety population

The Safety population includes all subjects who were enrolled and received at least one dose of APL-130277. The Safety population will be used for the analysis of the safety data from the Dose Titration Phase and for the pooled data from Dose Titration Phase and Randomized Crossover Phase.

8.6 Crossover Phase Safety population

The Crossover Phase Safety population includes all randomized subjects who received at least one dose of study medication (APL-130277, placebo or moxifloxacin) after the randomization. The Crossover Phase Safety population will be used for the analysis of the safety data from the Randomized Crossover Phase. The treatment (APL-130277, placebo or moxifloxacin) actually received during each crossover period will be used to group the patients.

8.7 PK population

The PK population includes all subjects with sufficient data for PK analysis and will be used for the analysis of the PK data.

9 General statistical considerations

All data from the APP entered into the database will be included in subject data listings. The listings will be generally sorted by center and subject number (and by visit and by time point, if applicable), unless specified otherwise. All applicable data will be summarized by treatment group (APL-130277, placebo or moxifloxacin). 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. Additionally, geometric mean and geometric coefficient of variation (CV%) will be included in the summaries of the PK data. Descriptive statistics for categorical data will include frequency counts and percents. 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 statistical analyses and summaries will be produced using SAS version 9.3 or higher. Deviations from the statistical plan will be reported in the clinical study report, including the rationale for change.

9.1 Adjustment for covariates

For the analysis of ECG (holter) endpoints, the baseline ECG value (average value of the pre-dose ECGs at P1V1) of the endpoint in question will be included as a baseline covariate (for continuous endpoints). For the analysis of the continuous efficacy endpoints, the assessment at SV2 will be used as the covariate.

9.2 Handling of drop-outs or missing data

All observed data will be included in the primary analysis. The missing and incomplete data will be managed using likelihood-based mixed effects modeling. Sensitivity analysis will be conducted in subjects with complete data from all study periods.

9.3 Interim analyses and data monitoring

No interim analyses are foreseen.

9.4 Multiple comparison/multiplicity

This study has a single primary endpoint, ΔΔQTcF. The primary endpoint will be evaluated at 7 different time points for non-inferiority (no meaningful difference between APL-130277 and placebo) using the intersection-union testing approach. This is a conservative approach, as non-inferiority must be met at each of the 7 time points.

Assay sensitivity may be demonstrated at any of the 4 time points. Due to this, Bonferroni-adjustment will be used for this analysis.

The secondary endpoints will be evaluated without any hierarchical order. Due to this, no confirmatory claims will be made on the secondary endpoints.

9.5 Examination of subgroups

At least the following subgroup analyses have been pre-planned. The subgroup analyses will be performed for selected ECG (holter) endpoints (at least the primary endpoint) and for adverse events. Selected baseline data will be presented for the subgroups as well.

- Non-elderly (<65 years) versus elderly (≥65 years) subjects
- Male versus female subjects
- Region (US versus non-US)
- Subjects who had final dose level (i.e. the dose to which the subject was randomized to) of <35 mg of less versus subjects with final dose level of ≥35 mg. The dose level documented on the Case Report Form page "Randomization" will be used for this classification.

In addition, for the clinical efficacy endpoints (MDS-UPDRS scores, time to "ON" and duration of "ON"), additional exploratory subgroup analyses may be conducted based on the observed patient characteristics. These additional subgroup analyses will not be included in the clinical study report.

10 Disposition

The subject disposition will be summarized as follows. The percentages will be calculated based on the number of enrolled subjects, unless otherwise specified.

- The number of subjects screened (i.e. the number of subjects in the AAP)
- The number (%) of subjects who failed screening (% calculated from the AAP), including the distribution of reasons for failing the screening. In case the subject fails the screening multiple times, all reasons leading to the exclusion will be summarized as event count (i.e. there can be multiple reasons for the same subject).
- The number (%) of subjects enrolled into the study (% calculated from the AAP)

- The number (%) of subjects who received at least one dose of study medication (Safety Population)
- The number (%) of subjects in the Efficacy population
- The number (%) of subjects who discontinued the study prematurely before Randomization, presented by highest dose level received, including the distribution of reasons for discontinuations
- The number (%) of subjects randomized to the Crossover Phase
- The subjects who were randomized to the Crossover Phase will be presented by the final randomized dose level (% calculated from all randomized subjects)
- The number (%) of subjects who received at least one dose of study medication during the Crossover Phase, i.e. Crossover Phase Safety Population (% calculated from all randomized subjects)
- The number (%) of subjects in the ECG Population (% calculated from all randomized subjects)
- The number (%) of subjects in the Completer Population (% calculated from all randomized subjects)
- The number (%) of subjects who completed the study (% calculated from all randomized subjects)
- The number (%) of subjects who discontinued the study prematurely after Randomization including the distribution of reasons for premature discontinuations after Randomization (% calculated from all randomized subjects); presented by the treatment group (APL-130277, placebo or moxifloxacin). The APL-130227 group will be further broken down by dose level.

11 Demographic and other baseline characteristics

Demographics and baseline characteristics will be summarized descriptively for the ECG and Safety populations. The following variables will be summarized:

- Demographics: (age (continuous), age categorized as <65 years versus ≥65 years, gender, ethnicity, race, height, weight, BMI, country)
- Smoking history
- PD history (time since diagnosis of PD measured in years at time of first dose at TV1, presence of a rest tremor at the time of diagnosis, time since initiation of L-Dopa treatment, time since onset of motor fluctuations, type of OFF episodes experienced, number of OFF episodes/day, typical length of OFF episodes)
- Cognitive status: Mini–Mental State Examination (MMSE) total score (as categorical, % of subjects with a score of 30, 29, 28, 27, 26 or <26)
- Modified Hoehn and Yahr scale in “ON” state

- Baseline MDS-UPDRS Part III (Motor Examination) assessed in an "OFF" state prior to L-Dopa administration at SV2
- Change in MDS-UPDRS part III (Motor Examination) at SV2 from pre-dose to 30 minutes post-dose
- Total daily L-Dopa dose at screening.

12 Concomitant medication/treatment

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD).

Medications with a stop date before the first date of study drug dosing will be considered prior medications. Medications with start date or stop date on or after the first date of study drug dosing will be considered concomitant medications. The prior medications will be listed and the concomitant medications will be summarized.

Summaries of concomitant PD treatment medications (medications which start with ATC code N04) will be presented in tabular form using the ATC Level 4 and preferred term. Other concomitant medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and Preferred Term (PT). The tables will be sorted by overall descending frequency of ATC Level(s) and then, within an ATC Level, by overall descending frequency of PT.

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 the same as the month of the first dose. If this is the case, use the first dose date as start date. Otherwise the first day of the month will be used.
    - However, if the stop date is not missing and is before the first dose date or the imputed start date (as defined above), then the stop date will be used instead.
- If the start day and month are missing: check if year is the same as the year of the first dose. If this is the case, use the first dose date as start date. Otherwise the first month of the year (January) will be used.
    - However, if the stop date is not missing and is before the first dose date or the imputed start date (as defined above), 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 the stop day and month are missing, then the last day of the last month (December) will be used.

The summary of concomitant medications will be done for the Safety population.

13 Medical history

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The medical history data will be summarized with frequencies and percentages of subjects with at least one medical history item, and subject frequencies and percentages on the System Organ Class (SOC) and PT levels. The number of events will also be summarized. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The summary of medical history data will be done for the Safety population.

14 Analysis of Primary and Secondary Endpoints

14.1 Primary endpoint

14.1.1 Central Tendency Analysis

The primary analysis for the QTcF data in this study is the central tendency analysis which is based on the time-matched comparisons using the ΔΔQTcF approach with a mixed model, as proposed by Tao et al (2015), with the exception of the covariance structure. The mixed model includes treatment group (APL-130227, placebo or moxifloxacin; actual treatment received will be used), time (15, 30, 45 and 60 minutes and 2, 3 and 4 hours), interaction between treatment group and time, period (1, 2 or 3), sequence (ABC, ACB, BCA, BAC, CAB or CBA, randomized sequence will be used), region (US versus non-US) and gender as fixed factors. The baseline QTcF (average of the pre-dose assessments at P1V1) will be included as a covariate. Restricted Maximum Likelihood (REML) estimation method will be used. The subject nested within sequence will be included as a random effect and a spatial power covariance structure for the unequally spaced time points will be assumed for the repeated measures over the time points. The denominator degrees of freedom will be calculated with Kenward-Rogers algorithm. All observed change from baseline values from the 7 time points will be used as response variables. The ECG population will be used for the primary analysis. The SAS code used for the modelling is outlined below.

```
proc mixed;
class TRTA ATPTN APERIOD TRTSEQP USUBJID SEX CNTRYGR1;
model CHG = BASE TRTA ATPTN TRTA*ATPTN APERIOD TRTSEQP SEX CNTRYGR1 / ddfm=kr;
```

```
random USUBJID(TRTSEQP);
repeated ATPTN / subject=TRTA*USUBJID(TRTSEQP) type=sp(pow)(atptn2);
where 0 < ATPTN <= 4;
run;
```

In case the model does not converge, the fixed factors for gender and region will be excluded. If the model still does not converge, a more simple covariance structure will be used, e.g. AR(1) or CS.

The least square (LS) mean, standard error, and LS mean difference between APL-130277 and placebo at all 7 time points along with the 2-sided 90% CIs for the treatment difference will be provided. The descriptive statistics will be presented for the absolute values by treatment group and time point, changes from baseline by treatment group and time point and within-subject differences between APL-130277 and placebo by time point.

Subgroup analyses will be performed for factors defined in section 9.5 of this document. Each subgroup will be summarized separately with descriptive statistics. In addition, for each of the subgroup factors, a mixed model similar to the primary model will be used, including additional fixed factors for the subgroup variable and the interactions between the treatment group and subgroup variable, time point and subgroup variable and the three-way interaction term between subgroup variable, treatment group and time point. However, if the three-way interaction term is not statistically significant ($p>0.05$) or if the model does not converge, the three-way interaction term will be excluded from the model. The influence of each subgroup factor will be investigated using the p-value for the interaction terms (treatment group x time point x subgroup variable (if applicable), treatment group x subgroup variable) calculated with this model. In addition, the treatment difference (APL-130277 versus placebo) will be estimated using confidence intervals with similar coverage as for the primary analysis.

14.1.2 Assay sensitivity

Moxifloxacin will be included as a positive control to validate the sensitivity of the assay to detect small increases from baseline for QTcF. The assay sensitivity will be evaluated by comparing moxifloxacin and placebo. To establish the assay sensitivity, there should be at least one time point where the lower confidence bound of the mean difference of moxifloxacin and placebo is greater than or equal to 5 ms. This analysis will use the same model as described for the time-matched central tendency analysis. The difference along with 2-sided 90% CIs (Bonferroni-corrected) between moxifloxacin and placebo will be estimated for the 4 evaluation time points (60 minutes and 2, 3 and 4 hours) from the model which includes all 7 time points, as specified above.

14.1.3 Sensitivity analyses of the primary endpoint

The following sensitivity analyses will be performed for the primary endpoint.

- Completer analysis: The analysis as specified above will be repeated for the Completer population

- Time-averaged analysis: In this analysis, the mean of all baseline ECGs is subtracted from the mean of all on-treatment ECG values through 4 hours post-dose for a given subject at a given visit. The mean will be calculated as mean of the 7 time points (i.e., the mean of the replicates at each time point is calculated prior to calculating the mean across the 7 time-points). These data will be analyzed with a mixed model similar to the one used for the primary analysis, but without the fixed effect for time and treatment group by time interaction term. The overall difference between APL-130227 and placebo APL-130277 will be estimated from this model. This analysis will use the ECG population.

14.1.4 Graphical summaries of the primary endpoint

The differences between APL-130277 and placebo estimated with the mixed model will be presented using forest plots. Each of the 7 time points will be presented in one graph showing the placebo-adjusted estimates and 2-sided 90% CIs. In addition, the placebo-adjusted estimates and Bonferroni-corrected 2-sided 90% CIs for moxifloxacin will be presented similarly.

14.1.5 Outlier analysis

An outlier or categorical analysis supplements the central tendency analysis by determining if there were subjects who had an exaggerated effect on any ECG interval that would not be revealed in a mean change from baseline central tendency analysis.

The following criteria are defined for the outlier analysis. The criteria will be tested separately for each time point. The number and proportion of subjects with outlier events will be tabulated by treatment, time point and overall (number of subjects with an outlier value at least once). Each outlier category will be tabulated separately. In addition, the number of subjects with abnormality in at least one category will be tabulated. For all the criteria listed below, the baseline refers to the average of the pre-dose assessments at P1V1. The ECG population will be used for the outlier analysis.

- Heart rate (HR):
  - Bradycardic event: Post-dose HR <50 bpm and a decrease of at least a 25% from the baseline
  - Tachycardic event: Post-dose HR >100 bpm and an increase of at least a 25% from the baseline
  - Either bradycardic or tachycardic event.
- PR interval: Post-dose PR interval >200 ms and an increase of at least a 25% from the baseline.
- QRS interval: Post-dose QRS interval >100 ms and an increase of at least a 25% from baseline.
- QT interval: Post-dose QT interval >500 ms and the subject's baseline is ≤500 ms.
- QTcF:

- Post-dose QTcF interval >500 ms and the subject's baseline ≤500 ms
- Post-dose QTcF interval >480 ms and the subject's baseline is ≤480 ms
- Post-dose QTcF interval >450 ms and the subject's baseline is ≤450 ms
- Change from baseline >30-60 ms
- Change from baseline >60 ms
- Any of the criteria above for QTcF.

- QTcB:
  - Post-dose QTcB interval >500 ms and the subject's baseline ≤500 ms
  - Post-dose QTcB interval >480 ms and the subject's baseline is ≤480 ms
  - Post-dose QTcB interval >450 ms and the subject's baseline is ≤450 ms
  - Change from baseline >30-60 ms
  - Change from baseline >60 ms
  - Any of the criteria above for QTcB.

14.2 Secondary endpoints

The following secondary endpoints will be analyzed.

- PK of apomorphine and metabolites

  The non-compartmental analysis of the apomorphine plasma concentration data methods and results will be described in detail in a separate PK document(s).

- Safety of APL-130277, including orthostatic BP and oral irritation (assessed with oropharyngeal examination)

  See Section 15 of the SAP.

- Pharmacodynamic assessments including QTc based on the Bazett correction method (QTcB), heart rate (HR), PR interval, QRS interval, uncorrected QT interval, ECG morphology and correlation between the QTcF change from baseline and plasma concentrations of APL-130277

  The continuous ECG endpoints (QTcB, HR, PR interval, QRS interval, uncorrected QT interval) will be analyzed similarly as the primary endpoint, using the central tendency approach, i.e. by calculating 90% confidence intervals using the mixed model. The ECG population will be used for these analyses.

  The number and proportion of subjects with ECG morphology will be tabulated by treatment group. Each morphology category will be tabulated separately. In addition, the number of subjects with

abnormality in at least one category will be tabulated. The ECG population will be used for the morphology analysis.

The details on the PK-Pharmacodynamic analysis (correlation between the QTcF change from baseline and plasma concentrations of APL-130277 will be provided in a separate document.

- Presence of cardiac arrhythmias such as ventricular tachycardia or Torsade de Pointes

  The number and proportion of subjects with cardiac arrhythmias will be tabulated by treatment group. Each type of event will be tabulated separately. In addition, the number of subjects with at least one event will be tabulated. The ECG population will be used for the analysis of cardiac arrhythmias.

14.3 Exploratory efficacy endpoints

- MDS-UPDRS Part III change from pre-dose to 30, 60, 90 minutes after dosing during the Titration Phase at the highest APL-130277 dose compared to the lowest APL-130277 dose resulting in a full "ON".

  A Mixed Model for Repeated Measures (MMRM) will be used for analysis of the MDS-UPDRS Part III scores. Separate model will be used for each time point (30 minutes, 60 minutes and 90 minutes). Response data include data from two study days: day when the lowest APL-130277 dose resulting in a full "ON" was given (Day 1) and day when the highest APL-130277 dose level was given (Day 2). The model will include the changes from pre-dose to the analysis time point (30 minutes, 60 minutes or 90 minutes) as the response variables. The study day (Day 1 or Day 2) will be included as a fixed factor and the change from pre-dose to the respective analysis time point at SV2 as a covariate. The difference between the study days will be estimated with 2-sided 95% confidence intervals. An unstructured covariance structure will be applied for MMRM. The Kenward-Roger method will be used to compute degrees of freedom. The Efficacy population will be used for the analysis of the MDS-UPDRS data.

- Time to "ON" during Titration Phase at the highest APL-130277 dose and the lowest APL-130277 dose resulting in a full "ON"

  The time to "ON" will be described using Kaplan-Meier plots. Separate Kaplan-Meier analysis will be done for the day when the lowest APL-130277 dose resulting in a full "ON" was given (Day 1) and for the day when the highest APL-130277 dose was given (Day 2). The median time to "ON" along with 25% and 75% quartiles (if applicable) will be estimated with the Kaplan-Meier analysis. In addition, the number of subjects who turned "ON" will be summarized. The Efficacy population will be used for the analysis of the time on "ON".

- Duration of "ON" during Titration Phase at the highest APL-130277 dose and the lowest APL-130277 dose resulting in a full "ON".

The duration of "ON" will be evaluated similarly as the time to "ON". The Efficacy population will be used for the analysis of the duration on "ON".

15 Analysis of safety and tolerability

The population used for safety analyses will be the Safety Population and Crossover Phase Safety Population. In general, the safety data will be presented separately for the Dose Titration Phase (where applicable, using the Safety Population) and for the Crossover Phase (using the Crossover Phase Safety Population). The safety analysis of the Dose Titration Phase will summarize the safety data for the total Safety population while the analysis of the Crossover Phase will focus on the comparison of the APL-130277 treated subjects versus placebo and moxifloxacin. In addition, separate summaries will be prepared for all subjects receiving APL-130277 either during the Dose Titration Phase or Crossover Phase by pooling the data from the two phases during the APL-130277 exposure (using the Safety Population).

15.1 Extent of exposure

The following information will be summarized by treatment group (for the Crossover Phase) and overall. In addition, these summaries will be broken down by the dose level of APL-130277.

- The number of subjects exposed to study treatment, defined separately for the Dose Titration Phase and for the Crossover Phase.
- A cross-tabulation of the highest dose level received during the Dose Titration Phase and the randomized dose level.
- A cross-tabulation of the highest dose level received and the lowest dose level received resulting in a full "ON" during the Dose Titration Phase.

15.2 Compliance

As this is a single-dose study, no analysis of compliance will be done.

15.3 Adverse events

All AEs will be coded using MedDRA version 19.1. Treatment-emergent adverse events (TEAEs) are defined as all AEs that start after the subject receives the first dose of study treatment. Events will be classified as drug-related if the AE is classified as possibly, probably, or certainly related to study drug.

Events with a missing start time, but with a start date equal to the date of first dose of study treatment will be considered treatment-emergent. If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE:

- If the start date is completely missing, the start date will be equal to the date of the first dose of study treatment. However, if the stop date is not missing and is before the date of the first dose of study treatment, then the stop date will be used instead.
- If the start day is missing: check if month is the same as the month of the first dose. If this is the case, use the first dose date as start date. Otherwise the first day of the month will be used.
    - However, if the stop date is not missing and is before the first dose date or the imputed start date (as defined above), then the stop date will be used instead.
- If the start day and month are missing:check if year is the same as the year of the first dose. If this is the case, use the first dose date as start date. Otherwise the first month of the year (January) will be used.
    - However, if the stop date is not missing and is before the first dose date or the imputed start date (as defined above), then the stop date will be used instead.

For the Crossover Phase, the AE will be assigned to the period that corresponds to the latest treatment received prior to the onset.

The original date and time will be shown on all listings of AEs. Listings will be provided for all AEs, serious AEs, AEs leading to study treatment discontinuation and deaths. The listings will display study day, calculated as the AE start date – date of first dose in the relevant study phase (first dose in the Dose Titration Phase or the date of the dose of the relevant study medication in the Crossover Phase) + 1 for events occurring on or after the first dose in the Dose Titration phase, and as AE start date – date of first dose in the Dose Titration phase for AEs occurring prior to the first dose in the Dose Titration Phase.

TEAEs will be summarized by SOC and PT and by treatment group when applicable. TEAEs with onset after the last dose of the study treatment period are attributed to the last treatment received. 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.

- An overall summary of the number and percentage of subjects reporting TEAEs and the number of TEAE events, drug-related TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study treatment discontinuation and TEAEs leading to death
- TEAEs by SOC and PT, both as event and subject counts
- TEAEs by PT, both as event and subject counts
- Drug-related TEAEs by PT, both as event and subject counts
- Severe TEAEs by PT, both as event and subject counts
- TEAEs by SOC, PT and severity, as event counts; percentages will be calculated for the event count out of total number of events
- TEAEs by SOC, PT and relationship, as event counts; percentages will be calculated for the event count out of total number of events

- Serious TEAEs by PT, both as event and subject counts
- TEAEs leading to study treatment discontinuation by PT, both as event and subject counts
- TEAEs leading to study treatment temporary withdrawal by PT, both as event and patient counts
- TEAEs leading to dose adjustment by PT, both as event and subject counts

The tables will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT based on the subject count for the APL-130277 column. If only event count is presented, the sorting will be done based on the event count.

Furthermore, the adverse events (by PT) will also be summarized by subgroups as defined in section 9.5 of this document. In addition, the following tables will be summarized by dose of APL-130277 at AE onset: Serious TEAEs and TEAEs leading to study treatment discontinuation.

Note: the AEs collected on the Case Report Form include a checkbox to indicate an AE of special interest. However, since the definition of AEs of special interest in this study may differ from other APL-130227 reports, the indicator for AEs of special interest will not be summarized or listed.

15.4 Laboratory safety variables

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

- Numeric laboratory parameters: Actual values and changes from baseline to the end or study for each parameter will be summarized with descriptive statistics.
- Laboratory parameters which have an upper or lower reference range: Number and percentage of subjects with low, normal or high (i.e., below, within or above reference range) values at each visit for each parameter will be summarized
    - These values will be presented as a shift table, i.e. the distribution of the three response categories at the end-of-study visit will be classified by the baseline category.
- Categorical laboratory parameters: The distribution of the categories will be summarized by visit.

15.5 Vital signs

Standard vital sign measurements include heart rate (HR), respiratory rate (RR), blood pressure (BP) and body temperature. Vital signs will be measured at all scheduled study visits at various time points after the subject has been in a supine position for 5 minutes. BP will also be measured within three minutes of standing at all time points. 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:

- Change from baseline (SV2) to other visit pre-dose values for each parameter (including the standing minus supine values). The change from baseline to the End of Study visit values will also be presented.
- Actual values and change from pre-dose to post-dose, if applicable, at each visit for each parameter (including the standing minus supine values).

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 and listed by visit and time point.

15.6 12-Lead ECG (resting)

A standard single resting 12-lead ECG will be performed pre-dose and 45 or 60 minutes post-dose at all treatment visits. In addition, triplicate ECGs will be taken at SV2 and at the end of the study. The following parameters will be captured: 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:

- Change from baseline (SV2) to other visit pre-dose and post-dose values for each parameter. The change from baseline to the End of Study visit values will also be presented.
- Actual values and change from pre-dose to post-dose, if applicable, at each visit for each parameter.

The ECGs will be assessed by the investigator and deemed "Normal", "Abnormal, not clinically significant" and "Abnormal, clinically significant" and tabulated by visit and time point.

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

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

15.7 Other safety variables

The 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 subjects with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized as appropriate by treatment group and visit.

The frequency and percentage of subjects with physical and oropharyngeal examination findings will be summarized by treatment group (when applicable), visit, time point (when applicable) and body system. In addition, the frequency and percentage of subjects with each type of oropharyngeal cavity examination finding will be summarized by treatment group, visit, time point (when applicable) and location.

16 Other variables

Major protocol deviations will be tabulated including the frequency and percentage of subjects with each type of deviation by treatment group. Deviations considered major will be identified as such prior to study unblinding. Summaries will be based on the Safety Population and provided for the combined Dose Titration Phase and Crossover Phase. All other data collected but not specifically mentioned will be listed.

17 Deviations from the analyses planned in the study protocol

This analysis plan presents the planned analyses in more detail and several details and analyses have been added. This SAP is based on study protocol version 5.00. The differences between the study protocol version 5.00 and this SAP are summarized below:

Topic	Protocol Version 5.00	SAP	Rationale for change
Safety analysis sets	One safety analysis set was defined.	Separate safety analysis sets were defined for all subjects who received at least one dose of APL-130277 and for all subjects who received study medication after randomization (during the Crossover Phase).	Safety data will be analyzed separately for the Dose Titration Phase and for the Crossover Phase.
PK-PD Analysis Set	PK-PD Analysis Set was defined.	PK-PD Analysis Set was not defined.	The analysis of PK-pharmacodynamics will be defined in a separate analysis plan.
ECG Analysis Set	At least one evaluable pre-dose ECG is required for inclusion.	Evaluable baseline ECG data is required for inclusion.	The analysis of the ECG (holter) data uses only baseline data (P1V1 pre-dose), not the pre-dose data from the other visits
Central tendency analysis	Should a significant treatment by gender/region interaction be observed, it will also be included in the model.	Interaction terms (other than treatment group by time point, which is required to estimate the treatment differences by time point) will not be included in the model.	Inclusion of interaction terms in the model was not considered necessary.

MDS-UPDRS part III and other efficacy endpoints	These endpoints will be evaluated as a secondary objective.	These endpoints will be evaluated as an exploratory objective.	The amended protocol allows enrolment of patients without at least one well defined "OFF" episode per day or with a total daily "OFF" time duration of < 2 hours. Due to this, the efficacy endpoints became less relevant, as all patients may not have enough pre-dose symptoms required for the efficacy evaluation.
Analysis of MDS-UPDRS part III	Dose level will be included as a fixed factor in the model.	Dose level will not be included in the model.	As the number of patients per dose level will be small, this factor was not considered feasible.
Other efficacy endpoints	The other efficacy endpoints will be analyzed with similar principles as MDS-UPDRS Part III	The other efficacy endpoints will be analyzed using time-to-event methods.	Time-to-event methods allow censoring for patients who do not turn "ON" or "OFF".

18 Execution of statistical analyses

Statistical analyses will be performed by 4Pharma Ltd supervised by CLINTREX LLC and/or Sunovion Pharmaceuticals.

19 Hardware and software

Statistical analysis, tables and subject data listings will be performed with SAS® version 9.3 or later for Windows (SAS Institute Inc., Cary, NC, USA)

20 References

Clinical Study Protocol: Version 5.00 (28 August, 2017), Company: Sunovion Pharmaceuticals Inc.

Tao J, Kiernan K, Gibbs P. Advanced Techniques for Fitting Mixed Models Using SAS/STAT® Software. Paper SAS1919-2015.

21 Appendices

21.1 Table and figure plan

21.2 Data listing plan