STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2 Study to Examine the Safety, Tolerability and Efficacy of APL-130277 in Patients with Parkinson's Disease
Phase:	2
Protocol No.:	CTH-105
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Prepared By:	[redacted] PharPoint Research, Inc. 5003 S. Miami Blvd., Suite 100 Durham, North Carolina 27703
Prepared For:	Cynapsus Therapeutics, Inc. 828 Richmond Street West Toronto, Ontario Canada

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

[redacted] Date
Senior Biostatistician
PharPoint Research, Inc.

Review:

[redacted] Date
Chief Scientific Officer
PharPoint Research, Inc.

[redacted] Date
Chief Medical Officer
Cynapsus Therapeutics Inc.

[redacted] Date
VP, Clinical Development
Cynapsus Therapeutics Inc.

[redacted] Date
VP, Medical Affairs
Cynapsus Therapeutics Inc.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and planned analysis of data from Protocol CTH-105. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection and to the pharmacokinetic (PK) analysis plan and report for details on the PK analyses.

1.1. STUDY OVERVIEW

This multicenter Phase 2 open-label study is designed to determine the safety, tolerability and efficacy of a dose of APL-130277 needed to induce an ON response in patients with Parkinson's disease (PD). After a screening visit (Visit 1), patients will be supplied with Tigan® (300 mg tid orally) which is to be started on Day -3 and they will be asked to return to clinic at Day -1 (Visit 2) to have pre-dosing assessments of safety completed. Patients will be asked to take their last dose of Levodopa no later than 10 PM on the evening of Day -1 and prepare to return to clinic the morning of Day 1. Alternatively, patients may be monitored in the clinic overnight if such facilities exist and the patient consents. On Dosing Day 1 (Visit 3), patients who are in an OFF state will be administered a starting dose of 10mg APL-130277. Safety assessments, PK samples (at select sites), and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from initial dosing and does not experience protocol defined orthostatic hypotension, they will receive the 15mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive Levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state, the patient will receive Levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

The patient will be asked to take their last dose of Levodopa no later than 10 PM on the evening before Dosing Day 2 (Visit 4), and prepare to return the morning of Dosing Day 2 for dosing. At clinical sites where this is a possibility, patients, at their request, may stay overnight in the clinic.

Patients will be seen on the morning of Dosing Day 2 (Visit 4), perform pre-dosing safety assessments and clinical assessments to determine their OFF status.

Patients who are in an OFF state will be treated as follows:

If there was no response with either dose on Dosing Day 1:

Administer: 20mg APL-130277. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience protocol defined orthostatic hypotension, they will receive the 25mg dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90

minutes, the patient will receive Levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive Levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

If there was a response with either dose on Dosing Day 1:

Administer the dose that elicited a response on Dosing Day 1. Safety assessments, PK samples (at select sites) and efficacy measures will be completed. If the patient does not move to an ON state within 3 hours from dosing, and does not experience orthostatic hypotension as defined in Section 12.6 of the protocol, they will receive the next higher dose of APL-130277. The same procedures will be repeated. If an ON state is not seen in 90 minutes, the patient will receive Levodopa at a dose considered appropriate by the investigator to achieve an ON state. At any point in the Visit, if in the opinion of the investigator, the patient can no longer tolerate the OFF state the patient will receive levodopa at their standard dosage, or at a dosage considered appropriate by the investigator to achieve an ON state.

Patients who responded to the same dose at Dosing Day 1 and Dosing Day 2 (Visits 3 and 4) will be considered complete from a dosing perspective, and proceed to Day 7 (Visit 6).

Patients who responded to a new dose at Visit 4, or who did not respond to either dose at Visit 4 will proceed to Dosing Day 3 (Visit 5). Patients will be asked to take their last dose of Levodopa no later than 10 PM on the evening before Dosing Day 3 (Visit 5), and prepare to return the morning of Dosing Day 3 for dosing. At clinical sites where this is a possibility, patients, at their request, may stay overnight in the clinic. If patients are evaluated to be in an OFF state, they will receive either the next higher dose of APL-130277, or the dose at Day 2 (Visit 4) that elicited an ON response.

Procedures at Dosing Day 3 (Visit 5) will be identical to that of Dosing Day 2 (Visit 4). If the first dose administered at the visit is 30mg of APL-130277, the patient will proceed to the follow-up visit following a 90 minute assessment of response and resolution of the OFF episode with Levodopa if required.

Dosing Days are not required to be sequential, but all dosing must be completed within 7 days. Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day.

Patients will return to clinic on Day 7 for a full safety evaluation.

1.2. SCHEDULE OF EVENTS/STUDY VISITS

Procedures	Screen[1]	Phone Call[2]	Baseline Day	Dosing Day 1	Dosing Day 2	Dosing Day 3[15]	F/U[13]
Study Visit	**Visit 1**	**T1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Day	**-21 to -2**	**-4**	**-1**	**1**	**2**	**3**	**7**
Outpatient Visit[3]	X		X[3]	X[3]	X[3]	X	X
Written and Reconfirmation of Informed Consent	X		X	X	X	X	X
Review Entry/Restriction Criteria	X		X	X	X	X	
Medical History/Demographics	X						
Complete Physical Exam[4]	X						X
Abbreviated Physical Exam[5]				X	X	X	
Anti-nausea medication (starts on day-3)	X		X	X	X	X	
BMI, weight and height[6]	X						X
Vital Signs (BP, HR, RR and Temp.) [7, 14]	X			X	X	X	X
12-Lead ECG[8]	X			X	X	X	X
Clinical Laboratory Tests[9]	X						X
Hoehn and Yahr	X						
MDS-UPDRS Motor Function[10, 14]	X		X	X	X	X	
Clinical Confirmation of OFF or ON[11, 14]				X	X	X	
Dosing of APL-130277				X	X	X	
Blood Draw for Study Drug PK[12, 14]				X	X	X	
AEs/SAEs			X	X	X	X	X
Conclusion of Participation							X

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

[2] Reminder phone call to patient to start their Tigan 300 mg tid on the morning of Day -3.

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

[4] Physical examination to include the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including mouth; musculoskeletal system; central and peripheral nervous system; and skin.

[5]Abbreviated physical exam to include head-eyes-ears-nose and throat; heart; lungs; abdomen; and skin; to be done at t = 0 (just prior to dosing) and at t = 1.5 post dosing (each dose) at Visits 3-5

[6] Both height and weight captured at Screening Visit to calculate BMI; only weight captured during Day -1, Day 1, and Final Visit.

[7] Vital signs will be assessed at Screening Visit, Visits 3-5 at t = 0 hrs (just prior to dosing) and at t =0.25, 0.5, 0.75, 1.0, 1.5, hrs post dosing and at Visit 6; Blood pressure to be measured sitting and standing (measured within 3 minutes of standing) at all time points at Visits 3-5

[8] Triplicate 12-lead ECG at screening; single ECGs at t = 0 (just prior to dosing) and at t = 0.5 post dosing (each dose) at Visits 3-5 and a single ECG at Visit 6

[9] Blood collection for clinical laboratory tests will occur at Screening Visit and on Visit 6.

[10] MDS-UPDRS Motor Function at Visits 1 and 2, and Visits 3-5 at t = 0 (just prior to dosing), and at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs post dosing

[11] Investigator confirmation of OFF or ON at Visits 1 and 2, and Visits 3-5 at t=0.25, 0.5, 0.75, 1.0, 1.5 hrs post dosing

[12] Blood collection for APL-130277 pharmacokinetic (PK) analyses will occur at select sites only at Visits 3-5 at t = 0 (just prior to dosing) and at t = 10, 20, 30, 45, 60 and 90 minutes after each dose administered

[13] The follow-up visit will be conducted for every patient dosed with APL-130277, and the timing of the Visit can be as soon as the day immediately following last dosing

[14] Suggested Sequence of Assessments Post-Dosing: PK blood draws – UPDRS – Assessment of OFF/ON– Vitals – ECGs

[15] Dosing must be completed within 7 days

Note: Investigators, at their discretion, and with patient consent, can opt to treat one dose at a time per dosing day. All dosing must be completed within 7 days.

1.3. GLOSSARY OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APL-130277	study drug, apomorphine hydrochloride
AST	aspartate transaminase
BMI	body mass index
BP	blood pressure
CRF	case report form
ECG	electrocardiogram
EDC	electronic data collection
F/U	follow-up
HR	heart rate
LOCF	last observation carried forward
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mITT	modified Intent-to-Treat
PD	Parkinson's disease
PK	pharmacokinetic
PP	per-protocol
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAEs	treatment-emergent adverse events

Temp.	temperature
WBC	white blood cell
WHO	World Health Organization

2. OBJECTIVES

The primary objective of this study is to evaluate the efficacy, safety and tolerability of treatment with APL-130277 in 16 patients with PD.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE

The sample size for this study was not based on statistical considerations. Up to 24 patients will be screened to yield 16 patients who are enrolled into the study and proceed to the dosing day.

3.2. RANDOMIZATION AND BLINDING

This is an open-label trial, therefore no blinding is necessary. All patients enrolled will follow the same treatment regimen, therefore randomization is not necessary.

3.3. HANDLING OF DATA

3.3.1. Missing Data and Outliers

In general, missing or invalid data of efficacy assessments will be handled by individual scales or subscales on the basis of each individual assessment. Missing data for individual items will be assessed for each assessment of each scale and imputed with the mean score of the corresponding assessment and rounded up to the nearest integer if the number of items with missing data or invalid is less than or equal to 20% of total item number. Otherwise, the assessment score will be set to missing.

For MDS-UPDRS assessments, missing data will be imputed using Last Observation Carried Forward (LOCF).

For statistical analyses, missing data that result from either early study termination or unavailability will remain as missing for efficacy measures and safety measures, unless specified otherwise.

3.3.2. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all 3 fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a patient. For many of the analyses, a complete date is necessary in order

to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation of dates for AEs and concomitant medications, all events with an incomplete end date are assumed to have ended on or before the day the form was completed. In an effort to minimize bias, the project statistician will impute dates in a systematic, reasonable manner. If the month/year is the same as the Visit 3 month/year then the date will be set to the date of Visit 3. In other cases, missing days will be imputed as the day component of Visit 3; missing months/years will be imputed as the month/year of Visit 3. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

3.3.3. By-Study Visit Displays

When data are collected serially over time, individual data presentations may include by-study visit displays for all scheduled study visits. Visits will be presented according to the nominal visit as obtained from the electronic data collection (EDC) system or laboratory data unless the visit is an unscheduled visit. All unscheduled visit values will be excluded from summary tables but will be included on data listings. If a patient has multiple non-missing values on the same date, then the last one is used, as determined by the time collected, if available.

3.3.4. Definitions and Terminology

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of APL-130277.

Pre-Dose Value
For purposes of analysis, the pre-dose value is defined as the value from the pre-dose (0 hour) time point for each dosing period (Visits 3 - 5).

Post-Dose Values
For purposes of analysis, the post-dose values are defined as the values from the post-dose (.25, .5, .75, 1, and 1.5 hour) time points for each dosing period (Visits 3 - 5).

Study Day
Study Day is defined relative to Dosing Day 1 (Visit 3). Thus, the study day of an event is calculated as:

$$\text{Study Day} = (\text{event date} - \text{date of Visit 3}) + 1$$

Study Visit
Study Visit is the nominal visit as recorded on the CRF.

Last Dose of Study Drug
Last Dose of Study Drug is defined at the last date that the patient received APL-130277 as determined by last date of dosing as recorded on the APL-130277 Dosing CRF.

Duration of Study Drug
Duration of Study Drug is defined as the number of days from Visit 3 (Dosing Day 1) to the date of Last Dose of APL-130277.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Change from Pre-Dose
Change from pre-dose for a given endpoint is defined as the Dosing Time Point X value minus the Pre-Dose Value.

Treatment-emergent Adverse Event
Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with investigational drug and prior to 7 days after the end of treatment, or AEs starting prior to the start of treatment but increasing in severity or relationship at the time of or following the start of treatment.

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of APL-130277 and prior to 7 days after the end of treatment. This definition includes medications started prior to the initiation of APL-130277, but continuing concomitantly with APL-130277.

Prior Medications
Prior medications are those medications taken prior to the initiation of APL-130277, but stopped before initiation of APL-130277.

MDS-UPDRS Scoring
The total score is defined as the sum of scores from all of the questions, excluding the dyskinesia questions (i.e. the total score from questions 3.1 – 3.18).

First Full ON Dose
The first ON dose is defined as the earliest dose in which a subject achieves a Full ON state as assessed by the Investigator.

Duration of ON Response
The duration of ON response is defined as the length of time in which a subject is confirmed ON within a dose.

Orthostatic Hypotension
Orthostatic hypotension is defined as:

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

4. ANALYSIS POPULATIONS

The populations for analysis will include Safety, mITT, PP, PK, and Responder.

4.1. SAFETY POPULATION

The safety population is defined as all patients who are enrolled into the study and have received at least 1 dose of the study drug.

4.2. MODIFIED INTENTION-TO-TREAT POPULATION

The modified intention-to-treat (mITT) population is defined as all patients who have received at least 1 dose of study drug.

4.3. PER-PROTOCOL POPULATION

The per-protocol (PP) population is defined as all patients in the mITT population who complete the study and are deemed to be protocol-compliant. To be protocol-compliant, a patient will not have any major protocol violations during the entire study period. Major protocol violations will be identified and assessed and decisions regarding the PP population will be made at the database lock meeting.

4.4. PK POPULATION

The PK population will be defined as those patients that complete the PK blood sampling procedures as outlined in the protocol.

4.5. RESPONDER POPULATION

The responder population is defined as all patients who have received at least 1 dose of study drug and have at least one investigator confirmation of Full ON.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of patients (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data, and frequencies and percentages for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted by patient number and by date within each patient number.

The statistical analyses will be conducted with the SAS® software package version 9.1.3 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient disposition will be presented for all patients. The number of patients who completed the study and discontinued from the study will be will be provided. The reasons for early discontinuation at any point also will be presented by treatment group. Additionally, the number of days on study and study drug will be summarized for all treated patients.

Demographic data and baseline characteristics including age, gender, race, ethnicity, height, weight, BMI, history of Parkinson's disease, and medical history will be summarized using descriptive statistics for the Safety population. This information will be reviewed for baseline differences, but no statistical testing will be performed.

5.2. EFFICACY ANALYSIS

The first Full ON response will be used to calculate the primary and secondary endpoints. Any Partial ON recorded prior to the first Full ON response will not be used.

5.2.1. Primary Efficacy Endpoints

The primary efficacy endpoints for the study are:

- Number of patients with resolution of an OFF episode to a Full ON state as assessed by the investigator at 15, 30, 45, 60 and 90 minutes after dosing. The investigators will use their clinical judgment to assess resolution of the OFF episode.
- Time to Full ON from time of dosing
- Duration of Full ON response
- Tolerability: Percent of patients that complete trial and experience a Full ON episode

All efficacy analyses will be conducted on the mITT, Responder, and PP populations unless stated otherwise.

5.2.2. Primary Efficacy Analysis

The number and percentage of patients with resolution of an OFF episode to a Full ON state as assessed by the investigators overall and at 15, 30, 45, 60 and 90 minutes after dosing will be summarized across study treatment doses. Event counts will also be summarized in order to account for the patients that have multiple resolutions within the same dose and time point. A Wilcoxon signed-rank test will be implemented for comparison of each time point to pre-dose. Subgroup analyses (age ≥65 versus <65 and Baseline OFF Episodes ≥ 4 versus < 4) will also be presented.

The time to Full ON state from time of dosing in minutes will be calculated from timing noted by the investigators and recorded in the eCRF, and summarized across study treatment. Values will be presented by dose and time point on a bar graph.

The number and percentage of patients that complete trial and experience a Full ON episode as assessed by the investigators will be tabulated and summarized across study treatment doses.

The duration of Full ON response in minutes will be calculated from the time noted by the investigators and recorded in the eCRF of an ON state to that of an OFF state on a per patient per dose basis and compared across study treatment doses. A repeated measures analysis of variance (ANOVA) will be implemented for this comparison with treatment as the fixed effect.

5.2.3. Secondary Efficacy Endpoint

The secondary efficacy endpoint for the study is:

- Mean and Percent change in MDS-UPDRS Motor Score from pre-dose to 15, 30, 45, 60 and 90 minutes after dosing for Full ON or last dose for those who do not convert to an ON.

5.2.4. Secondary Efficacy Analysis

The MDS-UPDRS Motor Score will be summarized across doses at pre-dose and 15, 30, 45, 60 and 90 minutes after dosing. The mean and percent change in score from pre-dose to 15, 30, 45, 60 and 90 minutes after dosing will also be summarized. The above measures will be calculated at Full ON for responders and last dose for those who do not convert to an ON state. A paired t-test will be implemented for comparison of each time point to pre-dose. The UPDRS Motor Score will also be summarized in the same fashion as a sensitivity analysis. Mean change from pre-dose will also be summarized as above for all Full ON doses and all Full ON doses excluding the first Full ON.

The number and percentage of patients with 5, 8, and 10 point score reduction and a 30% reduction from baseline and pre-dose in MDS-UPDRS Motor Score overall and across all time points at Full ON or last dose for those who do not convert to an ON will be presented. The UPDRS Motor Score will also be summarized in the same fashion as a sensitivity analysis.

Additional subgroup analyses for mean and percent change from pre-dose will be summarized by dose, age ≥65 versus <65 and ≥4 OFF episodes per day versus <4. A paired t-test will be implemented for comparison of each time point and to pre-dose.

Mean and percent change from pre-dose in MDS-UPDRS Motor Score for the first Full ON dose for responders and last dose for non-responders and all doses will be plotted over time across 15, 30, 45, 60 and 90 minutes for the mITT population.

Mean and percent change from pre-dose in MDS-UPDRS Motor Score for the first Full ON dose will be plotted over time by study population.

5.3. SAFETY

5.3.1. Safety Endpoints

The safety and tolerability endpoints for the study are as follows:

- Evaluation of clinical laboratory tests
- 12-lead ECGs
- Physical Examination
- Vital Signs (including body temperature and weight)
- Adverse Events

All safety analyses will be conducted on the Safety Population.

5.3.2. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 preferred term and system organ classification. If a patient experiences multiple events that map to a single preferred term, the greatest severity grade and strongest investigator assessment of relation to study medication will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication. The occurrence of treatment-emergent adverse events (TEAEs) will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events, TEAEs related to APL-130277, and events leading to the discontinuation of APL-130277 will be generated. TEAEs will be summarized overall and by dose. All adverse events reported will be listed for individual patients showing both verbatim and preferred terms. All

adverse events that occurred prior to the initiation of study treatment or more than 7 days post-discontinuation of treatment will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 3.3.2 as required to determine TEAEs.

5.3.3. Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) dictionary (Version: June, 2014). Concomitant medications will be summarized by frequency of ATC (Anatomical Therapeutic Chemical) classification and generic drug name. Prior and concomitant medications will be presented in a data listing.

5.3.4. Clinical Laboratory Assessments

The following clinical laboratory test samples will be collected at Visits 1 and Visit 6:

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelet count (or estimate), white blood cell (WBC) count including differential,
Serum Chemistry:	albumin, total bilirubin, total protein, alkaline phosphatase, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea, creatinine, glucose, sodium, potassium, uric acid, globulin
Urinalysis:	pH, specific gravity, blood, glucose, protein, ketones

Descriptive summaries including change from baseline of selected (quantitative) clinical laboratory results will be presented by study visit.

Laboratory abnormalities will be determined according to the reference ranges. The number and percentage of patients with treatment-emergent (occurred at Follow-Up) abnormal findings in each category will be produced for each treatment group. Clinically significant laboratory abnormalities will be summarized in a similar manner. For all clinical laboratory tests, a shift table will be produced summarizing changes from normal to abnormal and vice-versa.

5.3.5. 12-Lead ECG

The number and percentage of patients with normal and abnormal ECG findings will be displayed for each treatment group at each time point. Descriptive statistics including change from pre-dose of quantitative ECG variables also will be presented.

QTcB results > 500 ms and QTcF results > 60 ms over pre-dose will be flagged. The number and percentage of patients with these criteria will be summarized by time point across doses.

5.3.6. Physical Examination

The number and percentage of patients with normal and abnormal findings in the complete physical examination will be displayed for each treatment group.

5.3.7. Vital Signs

Descriptive summaries including change from pre-dose of vital signs will be presented by study visit across doses.

Also, the number and percentage of patients will be summarized based on the following criteria by time point across doses:

- Change in post-dose systolic and diastolic blood pressure from sitting to standing exceeds 25%
- Change in post-dose systolic and diastolic blood pressure from sitting to standing exceeds 25% and post-dose systolic blood pressure < 90 mmHg
- Change in post-dose systolic and diastolic blood pressure from sitting to standing exceeds 25% and post-dose diastolic blood pressure < 45 mmHg
- Change in post-dose systolic and diastolic blood pressure from sitting to standing exceeds 25%, decrease in post-dose systolic blood pressure from sitting to standing ≥ 20 mmHg and/or decrease in post-dose diastolic blood pressure from sitting to standing ≥ 10 mmHg

6. PROTOCOL VIOLATIONS

Possible protocol deviations will be identified and displayed in a data listing and sorted by patient and study day (where applicable). In addition, the following deviations may be identified from the database:

- Missing efficacy assessments
- Violations of inclusion/exclusion criteria
- Non-compliance with APL-130277

7. CHANGES IN THE PLANNED ANALYSES

Deviations from the protocol:

1. A responder population has been added to the Analysis Populations (Section 4).

2. Orthostatic hypotension is defined as a decrease in systolic pressure < 90mmHg AND a decrease of >25% from Visit 3 pre-dose reading levels and/or a diastolic pressure < 45mmHg AND a decrease of >25% from Visit 3 pre-dosing reading levels in Section 12.6 of the protocol. However, it was determined the more relevant definition to use for reporting purposes is defined in Section 3.3.4 of the SAP.
3. Sensitivity analyses for First ON Dose results have been added throughout. See Section 3.3.4 for the definition for First ON Dose.
4. See section 5.3.5. Additional analyses have been added for 12-Lead ECG that are not defined in the protocol.
5. See section 5.3.7. Additional analyses have been added for Vital Signs that are not defined in the protocol.

8. REVISION HISTORY

Date	Revision	Rationale

9. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all patients enrolled.
- Group headers: In the summary tables, the group headers will identify the summary group and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of patients actually summarized within any given summary module; some patients in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of patients actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of patients in the analysis population.
    - ♦ In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
    - ♦ For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by summary group, patient number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:

- Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
- Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
- Means will be reported to the same number of significant digits as the parameter.
- Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HHMM).

10. PROPOSED TABLES, LISTINGS, AND FIGURES FOR FINAL ANALYSIS

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Accountability and Baseline Characteristics

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14.2.5.2.1	MDS-UPDRS Motor Score Mean Change from Pre-Dose Summary - First Full ON Dose, mITT Population
14.2.5.2.2	MDS-UPDRS Motor Score Mean Change from Pre-Dose Summary - First Full ON Dose, Responder Population
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14.2.5.7.1	Subgroup Analysis: UPDRS Motor Score Mean Change from Pre-Dose Summary (>= 65 versus <65 Age) - First Full ON Dose, mITT Population
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