Statistical Analysis Plan

Sponsor Name: Sunovion Pharmaceuticals Inc.

Protocol Number: CTH-301
Protocol Title: An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Protocol Version and Date:

Original/Version 1.0 - All Sites (30 December 2014)

Amendment/Version 2.0 - All Sites (18 July 2015)

Amendment/Version 3.0 - US Specific (27 October 2015)

Amendment/Version 3.1 - UK Specific (13 May 2016)

Amendment/Version 4.0 - US Specific (30 May 2017)

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Amendment/Version 4.00B - Europe Specific (22 September 2017)

Amendment/Version 5.0 - US Specific (25 February 2019)

Amendment/Version 5.00A - UK Specific (25 February 2019)

Amendment/Version 5.00B - Europe Specific (25 February 2019)

Syneos Health Project Code: 1005892

Authors:

Revision History

Version #	**Date** (DD-Mmm-YYYY)	**Document Owner**	**Revision Summary**
1.0	30-Sep-2021		Final version 1.0

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AAP	All Available Population
AE	Adverse Event
AUC_{last}	Area Under the Concentration-Time Curve from Time Zero to the Last Measurable Plasma Concentration-Time Curve Using the Linear Up Log Down Trapezoidal Rule.
AUC_{∞}	Area Under the Concentration-Time Curve from Time Zero Extrapolated to Infinity Using the Linear Up Log Down Trapezoidal Rule.
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Limit of Quantification
BMI	Body Mass index
BP	Blood Pressure
CGI-I	Clinical Global Impression of Improvement
C_{max}	Maximum Observed Plasma Concentration
C-SSRS	Columbia Suicide Severity Rating Scale
CTH-301 Completer Subjects	Subjects Who Have Previously Completed the CTH-301 Study
CV%	Coefficient of Variation
De Novo Subjects	Subjects Who Have Not Previously Participated in a Study with APL-130277
ECG	Electrocardiogram
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
HLGT	High Level Group Term
HLT	High Level Term
HR	Heart Rate
ICH	International Conference on Harmonization
L-Dopa	L-3,4-Dihydroxyphenylalanine or Levodopa
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry

Abbreviation	Description
LTS	Long-Term Safety
λz	Terminal-Phase Rate Constant
MAA	Marketing Authorization Application
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
M/P	Ratios Metabolite to Parent Ratio Of AUC and Cmax
MRT	Mean Residence Time
MMSE	Mini-Mental State Examination
OH	Orthostatic Hypotension
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire
PGI-I	Patient Global Impression of Improvement
PK	Pharmacokinetic
PT	Preferred Term
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
Rollover Subjects	Subjects Who Have Previously Completed Any of the Following Studies: CTH-201, CTH-203, CTH-300, or CTH-302
RR	Respiratory Rate
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEM	Standard Error of the Mean
SI	International System of Units
SMQ	Standardized MedDRA Query
SOC	System Organ Class
$t_{½}$	Terminal-Phase Half-Life
TEAEs	Treatment-Emergent Adverse Events
TFL	Tables, Figures, Listings
t_{max}	Observed Time Of The Maximum Concentration
WHO-DD	World Health Organization Drug Dictionary

Abbreviation	Description
ZBI	Zarit Burden Interview

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. A detailed PK analysis plan will be developed as a separate document prior to conducting PK analysis.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings, except PK.

2.2. Timings of Analyses

The primary analysis of safety, efficacy and pharmacokinetics is planned after all subjects complete the study or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

3. Study Objectives

3.1. Primary Objective

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

3.2. Brief Description

This is a multi-center, non-randomized, open-label, Phase 3 study in levodopa (L-Dopa) responsive PD subjects with motor fluctuations, designed to evaluate the long-term safety, tolerability and efficacy of APL-130277 for the treatment of up to 5 "OFF" episodes per day. Subjects return to the clinic at regular intervals for assessments as defined in the schedule of assessments.

The current version of the protocol amendments in use are version 5.00 for US specific amendment, version 5.00A for UK specific amendment, and version 5.00B for Europe specific amendment.

De Novo subjects are defined as subjects who have not previously participated in a study with APL 130277. Rollover subjects are defined as subjects who have previously completed any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302. CTH-301. Re-enroller subjects are defined as subjects who have previously completed the CTH 301 study (LTS V4) under protocol version 3.00 or earlier and re-enrolled. Beginning with protocol version 5.00, Dose Titration Phase is required for De Novo subjects only. In previous protocol versions, Rollover subjects were also required to complete the Dose Titration Phase. Eligible De novo and Rollover subjects will be asked to return to the clinic in the morning of LTS V1. Eligible CTH-301 Re-enroller subjects at re-enrollment will be asked to return to the clinic 5 to 28 days later and follow study procedures beginning at LTS V7. European subjects are enrolled for 6 months and have End of Study visits while the rest only have Early Termination visits. For details of the study design, please refer to protocol amendment section 10.

3.3. Subject Selection

For details of study population selection including inclusion/exclusion criteria, please refer to protocol amendment section 11.1.

3.4. Determination of Sample Size

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

3.5. Treatment Assignment & Blinding

Randomization was not planned for this uncontrolled, open-label study, and blinding is not applicable.

3.6. Administration of Study Medication

During Dose Titration (when required) and at designated visits in the long-term safety (LTS) phase, dosing will occur in the clinic administered by clinic staff. Time of dosing (t=0) will be the time when the sublingual film is placed underneath the tongue.

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

At each outpatient visit, subjects will be provided sufficient study medication in order to self-administer for up to 5 "OFF" episodes per day until their next scheduled visit. Subjects will be instructed to wait a minimum

of 2 hours between doses taken at home. Unused study medication will be collected by each site and inventoried.

3.7. Study Procedures and Flowchart

This study will consist of the following:

1. Screening Visits (SV1 and SV2; *De Novo* subjects only); OR

   Screening Visit (SV; Rollover subjects only)

   Screening Visit (SVP2; CTH-301 Completer subjects only)

2. Dose Titration Phase (Beginning with Protocol version 5.00 *De Novo* Subjects only. In earlier versions, Rollover subjects completed the Dose Titration Phase)

   a. Titration Visit 1 (TV1)

   b. Titration Visit 2 (TV2)

   c. Titration Visit 3 (TV3)

   d. Titration Visit 4 (TV4)

   e. Titration Visit 5 (TV5)

   f. Titration Visit 6 (TV6)

3. Long-Term Safety (LTS) Phase Year 1 (*De Novo* and Rollover Subjects only)

   a. Long-Term Safety Visit 1 (LTS V1)

   b. Long-Term Safety Visit 2 (LTS V2)

   c. Long-Term Safety Visit 3 (LTS V3)

   d. Long-Term Safety Visit 4 (LTS V4)

   e. Long-Term Safety Visit 5 (LTS V5)

   f. Long-Term Safety Visit 6 (LTS V6)

   g. Telephone Call (T1 to T5)

   h. Unscheduled Dose Adjustment Visits

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

   a. Long-Term Safety Visit 7 (LTS V7)

   b. Long-Term Safety Visit 8 (LTS V8)

c. Long-Term Safety Visit 9 (LTS V9)

d. Telephone Call (T6 to T8)

e. Unscheduled Dose Adjustment Visits

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

   a. Long-Term Safety Visit 10 (LTS V10)

   b. Long-Term Safety Visit 11 (LTS V11)

   c. Long-Term Safety Visit 12 (LTS V12)

   d. Telephone Call (T9 to T11)

   e. Unscheduled Dose Adjustment Visits

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

   a. Long-Term Safety Visit 13 (LTS V13)

   b. Long-Term Safety Visit 14 (LTS V14)

   c. Long-Term Safety Visit 15 (LTS V15)

   d. Telephone Call (T12 to T14)

   e. Unscheduled Dose Adjustment Visits

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

   a. Long-Term Safety Visit 16 (LTS V16)

   b. Long-Term Safety Visit 17 (LTS V17)

   c. Long-Term Safety Visit 18 (LTS V18)

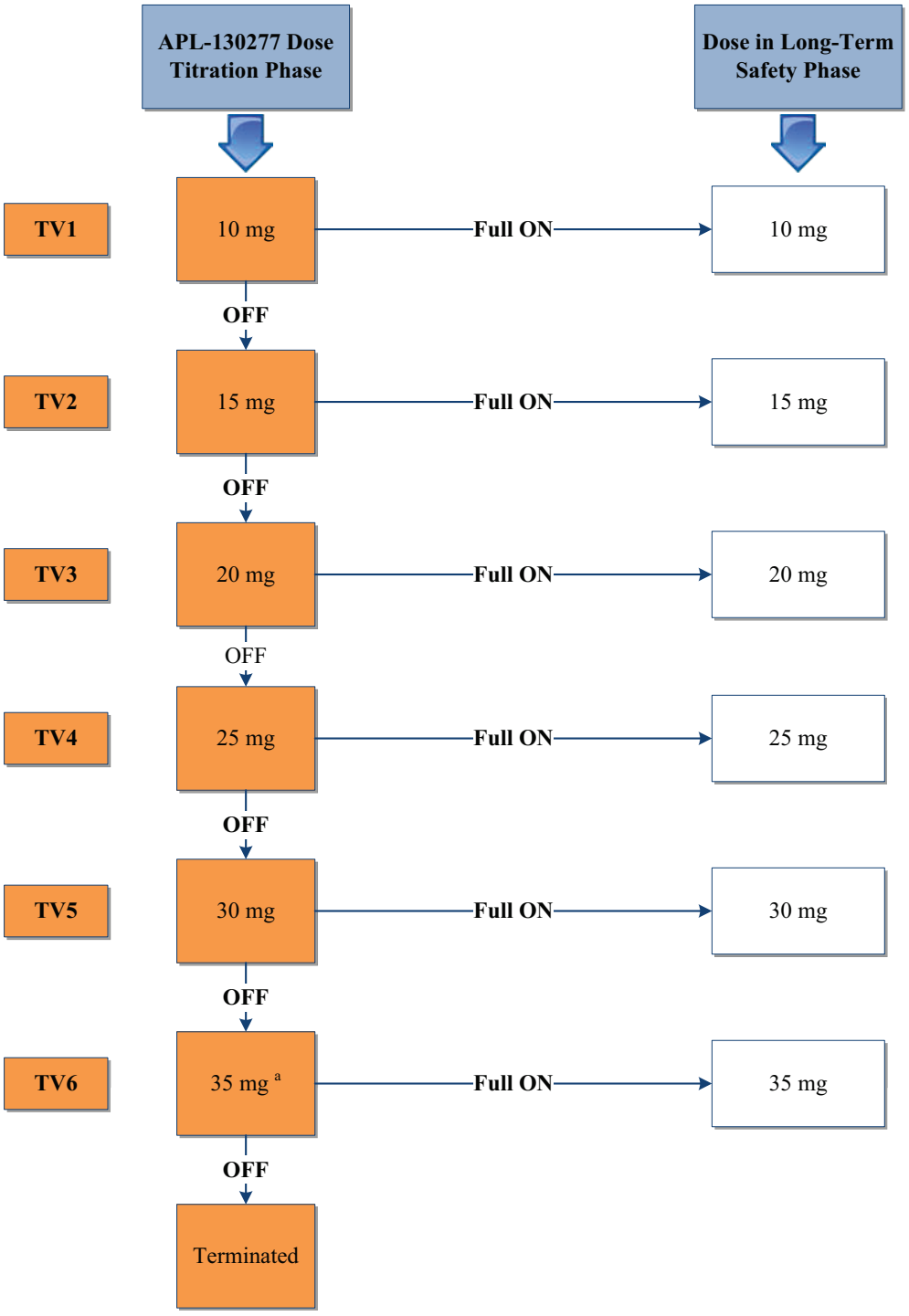
   d. Telephone Call (T15 to T17)

   e. Unscheduled Dose Adjustment Visits

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

8. Early Termination Visit (All subjects)

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



NOTE: Beginning with protocol version 5.00, dose titration is for *De novo* subjects only. In earlier protocol versions, Rollover subjects also completed the dose titration phase.

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

For *De novo* subjects, at all titration visits, at the discretion of the subject and/or Investigator, the next highest dose may be evaluated at a subsequent titration visit following a full "ON" response in order to assess the potential for the next highest dose in inducing an improved full "ON" response. If this dose produces an improved "ON" response relative to the lower dose without impacting subject safety and tolerability, the higher dose will be used during the LTS Phase of the study. If the "ON" response is the same or worse, or this higher dose is not well-tolerated, the previous dose will be used during the LTS Phase of the study.

The study procedures and flow chart differ slightly for each protocol amendment. Also, they are slightly different among region specific versions. Below is a summary of study procedures and flow chart differences comparing with protocol amendment v5.00.

US Specific	UK Specific	Europe Specific
v5.00 (25 February 2019)	v5.00A (25 February 2019)	v5.00B (25 February 2019)
v4.0 (30 May 2017)	v4.10A (22 September 2017)	v4.00B (22 September 2017)
v3.0 (27 October 2015)	v3.1 (13 May 2016)	
v2.0 (18 July 2015)		
v1.0 (30 December 2014)		

V5.00 US Specific

De Novo subjects will be required to attend 2 screening visits with informed consent obtained at the initial screening visit. All eligible subjects will be asked to return to the clinic in the morning of Titration Visit 1 (TV1) for the Dose Titration Phase of the study. After the dose is selected, subjects will continue with LTS visits.

Rollover subjects directly enter the LTS phase starting with LTS V1 after completing screening.

CTH-301 completers directly enter the LTS phase starting with LTS V7 after completing screening.

V5.00A UK Specific

All subjects are rollover subjects who will come into the study after completing study CTH-302. After completing screening, subjects will go directly to the LTS phase.

V5.00B Europe Specific

All subjects are rollover subjects who will come into the study after completing study CTH-302. After completing screening, subjects will go directly to the LTS phase.

V4.0 for US Specific

Same as V5.00

V4.10A UK Specific

Same as V5.00. Study flow based on general design for all subjects (De Novo, rollover, and CTH-301 completers)

V4.00B Europe Specific

Same as V5.00. Study flow based on general design for all subjects (De Novo, rollover, and CTH-301 completers)

V3.0 US

Rollover subject specifically refers to CTH-300 rollover.

Rollover subject required to begin with Titration phase and then proceed to LTS phase.

V3.1 UK Specific

Same as V3.10 UK specific.

Rollover subject specifically refers to CTH-300 rollover.

Rollover subject required to begin with Titration phase and then proceed to LTS phase.

V2.0
Same as V3.10 UK specific.

V1.0

Only has 1 screening visit for all subjects.

4. Endpoints

4.1. Primary Endpoint

Incidence of adverse events in the LTS phase.

4.2. Secondary Efficacy Endpoints

1. Mean change from pre-dose in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Motor Examination (MDS-UPDRS MOTOR) score at 15, 30, 60, and 90 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

2. Percentage of subjects with a patient-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

3. The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.

4.3. Other Efficacy Endpoints

1. Clinical Global Impression of Improvement (CGI-I) post dosing.

2. Patient Global Impression of Improvement (PGI-I) post dosing.

3. Change from baseline in the Parkinson's Disease Questionnaire (PDQ-39).

4. Change from baseline in the MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living.

5. Percentage of subjects with Investigator-rated full "ON" response within 30 minutes during the titration period.

4.4. Safety Endpoints

1. Observed Values and Change in 12 lead electrocardiograms (ECGs)

2. Incidence of oropharyngeal and dopaminergic adverse events (AEs)

3. Columba Suicide Severity Rating Scale (C-SSRS), and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS)

4. Change from Baseline in the MDS-UPDRS Part I and Part IV

5. Analysis Sets

5.1. All Available Population

The All Available Population (AAP) will include all subjects who have consented for the study, including screening failures. The AAP will be used for the subject disposition listing and for the summary of subject disposition.

5.2. Enrolled Population

The enrolled population consists of all subjects who have consented for the study and successfully screened and enrolled into the study. Subjects are considered enrolled into the study if the informed consent is signed and the subject is not a screen failure.

5.3. Titration Full Analysis Set

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

5.4. LTS Full Analysis Set

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

5.5. Safety Population

The safety population includes all subjects who enrolled and received at least one dose of study medication. The safety population will be used for pooled data from the dose titration phase and LTS phase and for all subject listings other than the subject disposition listing.

6. General Aspects for Statistical Analysis

6.1. General Methods

All data from all subjects entered into the database will be included in subject data listings. The listings will be generally sorted by enrollment group (*De Novo* or Rollover), center and subject number (and by visit and by time point, if applicable), unless specified otherwise.

All applicable data will be summarized descriptively. No statistical testing will be performed given the design. Data will be summarized for the total study population and additionally broken down by enrollment group (*De Novo* or Rollover) in tables, unless specified otherwise. Selected analyses will be broken down by dose level. Where appropriate, data will be summarized by visit and/or time point in addition to the grouping defined above. Early termination visits will be summarized separately. The visit will appear as early termination in the listings. Unscheduled or repeat assessments will not be included in summary tables, but will be included in listings.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Standard error of the mean (SEM) will also be provided for summaries of efficacy data, if relevant.

Descriptive statistics for categorical data will include frequency counts and percentages. The total number of subjects in the group (N) will be used as the denominator for percent calculations, unless stated otherwise.

All statistical analyses and summaries will be produced using SAS version 9.4 or higher. Deviations from the statistical plan will be reported in the clinical study report, including the rationale.

6.2. Key Definitions

Treatment Phase

De Novo subjects will be treated in dose titration phase to select a dose, and then followed to the completion of the LTS phase. The same will be generally true for Rollover subjects, but under a recent protocol amendment, a rollover subject may be treated in LTS phase only.

Study Day

Study day will be calculated separately for titration phase and LTS phase based on the first dose date in the relevant study phase. For completer subjects, study day will be computed based on the first dose date in the relevant phase, regardless of any gap in treatment.

Baseline

Baseline value is defined as the last observed value prior to the first dose of study treatment administration, unless specified otherwise. This value could be the pre-dose assessment on the first dose date or the assessment at the screening visit. If multiple values are present for the same date, the values from the last assessment will be used as the baseline unless specified otherwise. Whenever available, the time of the assessment will be utilized to make this determination.

For the MDS-UPDRS MOTOR score, the pre-dose MDS-UPDRS MOTOR score at the LTS visit predose is used for change calculations.

Last Assessment

For efficacy assessments, unless otherwise noted, the last assessment on study is defined as the last assessment up through LTS V6. If a data record cannot be found up to and including LTS V6, then the Early Termination Visit will be used as the last assessment on study. For ease of use questionnaire, the last assessment on study is the last scheduled assessment. For laboratory data, the last assessment on study is defined as the last assessment among all visits (scheduled or unscheduled). For ECG and vital signs, the last assessment on study is defined as the last assessment with both pre-dose and post-dose timepoints among all visits (scheduled or unscheduled).

Analysis Age

Analysis age will be calculated if date of birth is incomplete. 'Jan' will be used for missing month and '01' for missing day. Age is computed at date of informed consent.

6.3. Missing Data

Generally, no imputation of missing data will be made for analysis purposes.

Incomplete AE start dates will be imputed to determine whether an AE is treatment- emergent. AE end dates may also be imputed for some analyses (Detailed in Section 9.3).

Incomplete medication start/end dates will be imputed to distinguish prior versus concomitant medications (Detailed in Section 7.5).

6.4. Pooling of Centers

Data from all investigational centers will be pooled for summaries and analyses.

6.5. Subgroups

The following subgroup analyses will be performed for MDS-UPDRS MOTOR score and percentage of subjects with a patient-rated full "ON" response within 30 minutes endpoints, and for adverse events:

- Age < 65 years versus 75 > age ≥ 65 years and age >=75 years
- Region (North America (NA) vs Europe)
- Gender (male versus female)

In addition, subgroup analyses by region (NA vs Europe) will also be done for subject disposition, demographics, prior and concomitant medications, extent of exposure, clinical/patient global impression of improvement, parkinson's disease questionnaire-39, ease of use questionnaire, vital signs, ECG, oropharyngeal cavity examination, columbia suicide severity rating scale, and questionnaire for impulsive-compulsive disorders in parkinson's disease – rating scale.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

The subject disposition will be summarized as follows and presented for the total study population and additionally broken down by enrollment group (*De Novo* or Rollover). The percentages will be calculated based on the number of subjects in the safety population, 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, only the reason leading to the last exclusion will be summarized. Subjects who screen fail and later enroll will not be counted as a screen failure.
- The number (%) of subjects enrolled into the study (% calculated from the AAP)
- The number (%) of subjects who discontinued the study prematurely during the dose titration phase, presented by highest titrated dose level received (10 mg, 15 mg, 20 mg, 25 mg, 30 mg or 35 mg and total), including the distribution of reasons for discontinuations
- The number (%) of subjects in the different study populations (Titration Full Analysis Set and LTS Full Analysis Set)
- The number (%) of subjects who completed the study (% calculated from the LTS Full Analysis Set)
- The number (%) of subjects who discontinued the study prematurely during the LTS phase including the distribution of reasons for premature discontinuations (% calculated from the LTS Full Analysis Set)
- The number (%) of subjects ongoing when study terminated (% calculated from the LTS Full Analysis Set)

In addition, a summary will be provided for the highest LTS phase dose by the highest titration dose for the LTS Full Analysis Set. Summaries will also be provided by region (NA vs Europe).

Subject disposition will be listed for enrolled population.

7.2. Protocol Deviations

Protocol deviations will be collected and categorized according to the Protocol Deviation and Non-compliance Management Plan. Protocol deviations will be identified and documented during the conduct of the study. Protocol deviations will be categorized by type, and whether major or minor based on clinical review. During the data review meeting (prior to data base lock), team will further identify the “important” deviations. Important individual deviations will be presented in a data listing. The number and percentage of subjects who reported important protocol deviation will be summarized by type of deviation for the phases and safety population.

COVID-19 related protocol deviations will be listed.

7.3. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the Titration and LTS Full Analysis Sets and safety population, and additionally broken down by enrollment group (*De Novo* or

Rollover). Summaries will also be provided by region (NA vs Europe) for the Titration and LTS Full Analysis Sets and safety population. The following variables will be summarized:

- Demographics: (age (continuous), age categorized as <65 years versus ≥65 years, gender, ethnicity, race, height, weight, body mass index (BMI), country)
- Smoking history
- Cognitive status: Mini–Mental State Examination (MMSE) total score
- On State Modified Hoehn and Yahr scale
- Screening MDS-UPDRS Total: Sum of screening MDS-UPDRS Part I score (Non-Motor Aspects of Experiences of Daily Living),screening Part II score (Motor Aspects of Experiences of Daily Living) and screening MDS-UPDRS Part III score (Motor Examination) assessed in an "OFF" state prior to L-Dopa administration
- Screening MDS-UPDRS part III (Motor Examination) score prior to levodopa dose
- Screening MDS-UPDRS part III (Motor Examination) score at 15, 30, 60, and 90 minutes post-levodopa dose
- Baseline MDS-UPDRS part III (Motor Examination) score at LTS V1 predose
- Total daily levodopa (L-Dopa) dose (mg)

Total daily levodopa dose (mg) at baseline is calculated as the sum of levodopa medication doses reported by the subject as of the first APL dose date.

Age = (Informed consent date - date of birth + 1) / 365.25 and truncated to complete years. When date of birth is incomplete (day and/or month missing), fill in January for missing month and 01 for missing day.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

7.4. Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. 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.

Parkinson's disease history will be summarized including time since diagnosis of PD measured in years at time of screening visit, presence of a rest tremor at the time of diagnosis, year when motor fluctuations began, type of OFF episodes experienced, number of OFF episodes/day, typical length of OFF episodes, and PD medications previously or currently taken. Summaries will also be provided by region (NA vs Europe) for safety population.

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

7.5. Medication

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) version March 2017.

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.

Summaries of prior and concomitant PD treatment medications (medications that start with ATC code N04) will be presented in tabular form using the ATC Level 4 and preferred term. Other prior and concomitant medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and Preferred Term (PT). Frequencies and percentages of subjects receiving medications will be presented by enrollment group and overall. 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. A summary of prior medications will be provided for the safety population. Summaries of concomitant medications will be provided for the Titration, LTS Full Analysis Sets and safety population. Summaries for prior and concomitant medications will also be provided for the PD medications by region (NA vs Europe) for the Titration Full Analysis Set and safety population.

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

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

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

8. Efficacy

The primary objective is to evaluate the long-term safety and tolerability of APL-130277 in subjects with PD. The subsequent section describes the analysis of selected secondary endpoints related to efficacy.

8.1. Secondary Efficacy Endpoints and Analyses

8.1.1. MDS-UPDRS Part III MOTOR Score of the LTS Phase

Observed and change from pre-dose in MDS-UPDRS MOTOR score at 15, 30, 60, 90 and >90 minutes after dosing will be summarized at Screening, LTS V1, V3, V4, V5, V6 of the LTS Phase and last assessment on study (latest visit up to and including LTS V6) as applicable for the LTS Full Analysis Set, separately for *De Novo* subjects, Rollover subjects and Overall. Summaries will also be provided with the APL-130277 Optimized Dose Received During the Titration Phase and by region (NA vs Europe) for the LTS Full Analysis Set. The optimized dose is the dose to which the subject was enrolled in the LTS phase.

If an item in the MDS-UPDRS Part III MOTOR score is missing then the following rules will be used to impute missing values. At pre-dose if a value is missing then the value from the prior visit will be used. If post-pose, a missing item is imputed using the maximum of the 2 non-missing values at time points adjacent to the missing item. If one of the adjacent time points is pre-dose then the adjacent post-dose value will be imputed. Imputation will be used to compute the total score if 3 or fewer items are missing. If more than 3 items are missing then the score will be missing.

Mean change from pre-dose in the MDS-UPDRS MOTOR score will be graphed by visit, time point, group and region (NA vs Europe) through LTS phase visit 6 and last assessment on study.

MDS-UPDRS Part III data will be listed.

8.1.2. Subjects Achieving a Patient-rated “ON” Response within 30 minutes and at each Individual Timepoint

The response status of subjects achieving a patient-rated “ON” response within 30 minutes will be derived based on the assessment value of the patient confirmation of “OFF” and “ON” state reported at 15 and/or 30 minutes of each visit. Subjects reported “ON” state at 15 minutes and/or 30 minutes post dose were consider achieving an “ON” response within 30 minutes; otherwise subjects reported “OFF” state at available 15 minutes and 30 minutes post dose were consider achieving an “OFF” response within 30 minutes. The visits at which there is no 15 or 30 minute assessment of the “OFF”/”ON” state will be set as having a missing value. “ON” response at each individual timepoint will also be summarized. The 90 minute timepoint was added in protocol amendment 4 (version 5.0). Subjects who completed that visit before the amendment will not have an assessment at 90 minutes. No imputation will be done for missing values.

The percentage of subjects achieving a patient-rated “ON” response will be presented at LTS V1, V3, V4, V5, V6 of the LTS Phase and last assessment on study, for the LTS Full Analysis Set overall and by region (NA vs Europe), separately for *De Novo* subjects, Rollover subjects and Overall. Summaries will also be provided with the APL-130277 Optimized Dose Received During the Titration Phase overall and by region (NA vs Europe) for the LTS Full Analysis Set.

The percentage of subjects with a patient-rated full "ON" response will be graphed by visit, group and region (NA vs Europe) for the LTS Full Analysis Set.

Patient confirmation of OFF and ON data will be listed.

8.1.3. Instances of a Full "ON" Response within 30 Minutes of the LTS Phase Based on Home Dosing Diaries

The percentage of instances a patient-rated "ON" response was achieved within 30 minutes after self-administration of study medication at LTS V2, V3, V4, V5, V6 and last assessment on study of the LTS Phase based on home dosing diary entries will be provided.

For each subject, the percentage of instances in which the full "ON" response was achieved within 30 minutes out of all recorded doses will be calculated. Subjects can have up to 10 treated episodes for each visit (2 DAYS x 5 EPISODES). The percentage will be calculated as the number of "ON" responses within 30 minutes after each dose for 2 days prior to each visit divided by the number of treated "Off" episodes for 2 days prior to each visit multiplied by 100.

The percentage of instances a patient-rated "ON" response was achieved within 30 minutes after self-administration of study medication at LTS V2, V3, V4, V5, V6 and last assessment on study of the LTS Phase will be summarized descriptively as a continuous variable by visit for the LTS Full Analysis Set, separately for *De Novo* subjects, Rollover subjects and Overall. Summaries will also be provided by region (NA vs Europe) for the LTS Full Analysis Set.

The percentage of instances with a patient-rated full "ON" response will be graphed by visit, group and region (NA vs Europe) for the LTS Full Analysis Set.

8.2. Other Efficacy Endpoints and Analyses

8.2.1. Clinical Global Impression of Improvement (CGI-I) Post Dosing

The non-missing values will be categorized as improvements (very much improved, much improved, minimally improved) or non-improvements (no change, minimally worse, much worse, very much worse).

The proportions of subjects who improved (defined as very much improved, much improved or minimally improved) will be tabulated by enrollment group and visit (LTS V4, V5, V6 and last assessment on study) . This summary will be complemented by the distribution of each response category (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse) tabulated by the enrollment group and visit based on the observed results. This summary will be done separately for *De Novo* subjects, Rollover subjects and Overall. Summaries will also be provided by region (NA vs Europe) for the LTS Full Analysis Set.

8.2.2. Patient Global Impression of Improvement (PGI-I) Post Dosing

The non-missing values will be categorized as improvements (very much improved, much improved, minimally improved) or non-improvements (no change, minimally worse, much worse, very much worse).

The proportions of subjects who improved (defined as very much improved, much improved or minimally improved) will be tabulated by enrollment group and visit (LTS V4, V5, V6 and last assessment on study).

This summary will be complemented by the distribution of each response category (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse) tabulated by the enrollment group and visit based on the observed results. This summary will be done separately for *De Novo* subjects ,Rollover subjects and Overall. Summaries will also be provided by region (NA vs Europe) for the LTS Full Analysis Set.

8.2.3. Change from Baseline in Parkinson's Disease Questionnaire-39 (PDQ-39)

Change from baseline (SV2 for *De Novo* and SV for Rollover) to LTS V1, Week 24, Week 36, Week 48 visits (LTS V4, V5, and V6 of the LTS Phase), and last assessment on study in PDQ-39 sub-scores (mobility score, activities of daily living, bodily discomfort score, emotional well being score, social support score, communication score, cognitive impairment score, and stigma score) and summary index score will be calculated. The questionnaire provides scores on eight dimensions as outlined below:

- mobility (10 items, #1 to 10)
- activities of daily living (6 items, #11 to 16)
- emotional well-being (6 items, #17 to 22)
- stigma (4 items, #23 to 26)
- social support (3 items, #27 to 29)
- cognitions (4 items, #30 to 33)
- communication (3 items, #34 to 36)
- bodily discomfort (3 items, #37 to 39).

Items are scored from 0 (never) to 4 (always). Dimension scores are obtained by dividing the sum of the item scores by the maximum possible score for any given dimension and expressing this as a percentage. For example:

- mobility = (sum of scores of #1 to 10)/(4 x 10) x 100
- activities of daily living = (sum of scores of #11 to 16)/(4 x 6) x 100.

For social support, if the response indicates that a subject does not have a spouse or partner for #28, social support can be calculated as [(sum of scores of #27 and 29)/(4 x 2) x 100].

A summary index is then calculated as the sum of the total score of the dimensions divided by the number of dimensions, i.e. (sum of dimension scores / 8). If any item score is missing, the relevant dimension score and the summary index will be missing.

The PDQ-39 summary index and the sub-scores will be summarized with descriptive statistics. This summary will be provided for *De Novo* subjects, Rollover subjects and Overall. Summaries will also be provided by region (NA vs Europe) for the LTS Full Analysis Set.

8.2.4. Change from Baseline in MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living

The change from baseline (SV2 for *De Novo* and SV for Rollover) to Week 12, Week 24, Week 36, and Week 48 visits (LTS V3, V4, V5, and V6) of the LTS Phase and last assessment on study in MDS-UPDRS Part II score will be summarized descriptively and separately for *De Novo* subjects , Rollover subjects and Overall. Summaries will also be provided by region (NA vs Europe) for the LTS Full Analysis Set. The MDS-UPDRS Part II score will be calculated as the sum of the individual items of the MDS-UPDRS Part II questionnaire (items 2.1 – 2.13). Missing individual items will not be imputed. If there is at least 1 missing item, the corresponding MDS-UPDRS Part II score will be set as missing.

8.2.5. Percentage of Subjects with Investigator-Rated Full “ON” Response within 30 minutes and at each Individual Timepoint

The response status of subjects achieving an investigator-rated “ON” response within 30 minutes will be derived based on the assessment value of the clinical confirmation of “OFF” and ”ON” state reported at 15 and/or 30 minutes of each visit. A reported “ON” state at 15 minutes and/or 30 minutes post dose is considered achieving an “ON” response within 30 minutes; otherwise an “OFF” state at available 15 minutes and 30 minutes post dose is considered achieving an “OFF” response within 30 minutes. The visits at which there is no 15 or 30 minute assessment of the “OFF”/”ON” state will be set as having a missing value. “ON” response at each individual timepoint will also be summarized.The 90 minute timepoint was added in protocol amendment 4 (version 5.0). Subjects who completed that visit before the amendment will not have an assessment at 90 minutes. No imputation will be done for missing values.

The percentage of subjects achieving an investigator-rated “ON” response will be presented at LTS V1, V3, V4, V5, V6 of the LTS Phase and last assessment on study, for the LTS Full Analysis Set overall and by region (NA vs Europe), separately for *De Novo* subjects, Rollover subjects and Overall. Summaries will also be provided with the APL-130277 Optimized Dose Received During the Titration Phase overall and by region (NA vs Europe) for the LTS Full Analysis Set.

The percentage of subjects with an Investigator-rated Full “ON” response by time point will be graphed by visit, group and region (NA vs Europe) for the LTS Full Analysis Set.

Clinical confirmation of OFF and ON data will be listed.

8.2.6. Change from Baseline in the Epworth Sleepiness Scale (ESS)

The ESS is used to determine the level of daytime sleepiness. There are 8 situations (sitting and reading, watching TV, sitting, inactive in public place, passenger for an hour without a break, lying down to rest in the afternoon, sitting and talking, sitting quietly after a lunch without alcohol, in a car or bus, while stopping for few minutes in traffic) listed for which subjects rate their likelihood of dozing or sleeping (0=would never doze or sleep, 1=slight chance of dozing or sleeping, 2=moderate chance of dozing or sleeping, and 3=high chance of dozing or sleeping). The total score is the sum of 8 item scores and can range between 0 and 24. In case of missing item scores, the total score will be set as missing. A higher total score indicates a higher level of daytime sleepiness. A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy.

The changes from baseline (SV2 for *De Novo* and SV for Rollover) to LTS V1, Week 24, Week 36, Week 48 visits (LTS V4, V5, and V6 of the LTS Phase), and last assessment on study in the total ESS score will be

summarized with descriptive statistics. In addition, the proportion of subjects who are sleepy (score of 10 or more) or very sleepy (score of 18 or more) will be tabulated. This analysis will be done separately for *De Novo* subjects, Rollover subjects and Overall.

8.2.7. Additional Summaries

Ease of Use Questionnaire and European Quality of Life – 5 Dimensions (EQ-5D) will be summarized. Ease of Use Questionnaire summary will also be provided by region (NA vs Europe) for the LTS Full Analysis Set.

The EQ-5D is a utility scale consisting of three components: health state dimensions, health state thermometer scale and health state index. The health state dimensions will be described by the 5 dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 response choices, listed in order of increasing severity. The health state dimensions will be evaluated by presenting the distribution of responses separately for each of the 5 dimensions. The health state thermometer scale asks respondents to rate their present health status on a 0 to 100 visual analog scale (VAS). The change from SV to week 4 on the VAS scores will be evaluated. The health state index score will be calculated based on EQ-5D-5L Crosswalk Index Value Calculator - EuroQol, using the dimension scores from the 5 dimensions, ranging between 1.0 (best imaginable health) and -0.594 (worst imaginable health). The health state dimensions will be evaluated by presenting the distribution of responses separately for each of the 5 dimensions by treatment and visit.

The MDS-UPDRS Part I represents non-motor aspecs of experiences of daily living, and Part IV represents motor complications. Descriptive statistics will be provided overall and by enrollment group and visit (both actual values and changes from baseline) and region (NA vs Europe) for the LTS Full Analysis Set. Additional summaries will be added for Part IV Time Spent with Dyskinesias, Functional Impact of Dyskinesias, Time Spent in the OFF State, Functional Impact of Fluctuations, Complexity of Motor Fluctuations, Painful OFF State Dystonia, % of Dyskinesia Time, % of Motor Flucturations Time, and % of Dystonia Time. Shift in category of Improved, No Change and Worsened will also be provided for Time Spent with Dyskinesias, Functional Impact of Dyskinesias, Time Spent in the OFF State, Functional Impact of Fluctuations, Complexity of Motor Fluctuations, and Painful OFF State Dystonia. The additional summaries will also be provided by region.

9. Safety

The safety data will be summarized overall and by enrollment group (*De Novo* or Rollover), separately for dose titration phase and LTS phase. The dose titration phase summary is based on Titration full analysis set. The LTS phase summary is based on LTS phase full analysis set.

In addition, all safety data will be listed based on the safety population. Listings will also identify subjects as Rollover or *De Novo*. Beginning with protocol version 5.00, Dose Titration Phase is required for De Novo subjects only.

9.1. Extent of Exposure

The number of subjects exposed to study treatment in the titration phase will be summarized at each dose level (10 mg, 15 mg, 20 mg, 25 mg, 30 mg, or 35 mg) and subjects' final dose received during the titration phase will be summarized by enrollment group and overall. The Final dose (i.e. the optimal dose to which the subject was titrated) is the dose dispensed at LTS V1.

A summary of subject exposure during the LTS phase will be provided by enrollment group and overall, by highest dose received during the LTS phase (10 mg, 15 mg, 20 mg, 25 mg, 30 mg or 35 mg), by exposure category (0 to 3 months, >3 to 6 months, >6 to 12 months, >12 months as well as >6 months and >12 months), and by region (NA vs Europe), including the following:

- Duration of exposure (days), defined as date of last dose received in LTS phase – date of first dose received in LTS phase + 1, classified by enrollment group. For subjects who re-enrolled, the duration of exposure is calculated as the total number of days over all LTS phase participation, i.e. any gap time in study participation is excluded from the calculations.
- Total exposure to study treatment, expressed as person years (sum of duration of exposure to study treatment over all subjects in days divided by 365.25, classified by enrollment group).
- Average Total Daily Dose is based on the diary. The total dose (mg) will be computed for each day in the LTS phase. The average of the total daily dose values will be computed for each subject.

The following information is based on data collected in dosing diary:

- The average number of doses taken, classified by enrollment group.
- Proportion of doses taken at days with 5, 4, 3, 2, 1 doses taken and average daily dose along with total daily dose (during the days when the information was collected).
- Proportion of subjects using >5, 5, 4, 3, 2, 1 or 0 doses/day at least once (during the days when the information was collected), classified by enrollment group.

9.2. Treatment Compliance

The number and percentage of subjects taking more than 5 doses of study medication per day at least once during the study will be provided during the titration phase and during the LTS phase.

9.3. 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. Dose titration phase TEAEs are defined as all AEs that start on or after the date of the first dose of APL-130277 during the dose titration phase but before the date of the first dose of study medication during the LTS phase. The LTS phase TEAEs are defined as all AEs that start on or after the first dose of study medication during the LTS phase. Relationship, as indicated by the Investigator, is classified as "not related", "unlikely", "possible", "probable", or "certain". A "related" AE is defined as an AE with a relationship to study treatment as "possible", "probable", or "certain" related to study treatment. AEs with a missing relationship to study treatment will be regarded as "related" to study treatment. Severity is classified as mild/ moderate/ severe (increasing severity). AEs starting after the first dose of study treatment with a missing severity will be classified as severe. Separate summaries will be generated for AEs of special interest (oropharyngeal AEs, nausea, vomiting and orthostatic hypotension).

TEAEs will be summarized by SOC and PT and by enrollment group when applicable. 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.

All TEAEs will be summarized by enrollment group separately for "dose titration phase" and "dose titration + LTS phase" based on the Titration Full Analysis Set and safety population, respectively.

In addition, LTS phase TEAEs will be summarized by enrollment group based on LTS Full Analysis Set.

The following summaries will be provided:

- An overall and by region (NA vs Europe) summary of the number and percentage of subjects reporting any TEAEs and the number of TEAE events, drug-related TEAEs, severe TEAEs, serious TEAEs, non-serious TEAEs, TEAEs leading to drug withdrawal, TEAEs leading to drug interruption, TEAEs leading to dose reduction, and TEAEs leading to death
- TEAEs by SOC, PT by overall and region (NA vs Europe), both as event and subject counts
- TEAE by SOC, HLT, and PT, both as event and subject counts
- TEAEs by PT, both as event and subject counts
- Drug-Related TEAEs by SOC, PT by overall and region (NA vs Europe) as both event and subject counts.
- Severe TEAEs by SOC, PT by overall and region (NA vs Europe) as both event and subject counts
- TEAEs by SOC, PT, actual dose received (dose prior to onset of AE) during the study phase by overall and region (NA vs Europe), 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 maximum severity; percentages will be calculated for the subject count out of total number of subjects
- 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 SOC, PT by overall and region (NA vs Europe), both as event and subject counts
- TEAEs leading to drug withdrawal by SOC, PT by overall and region (NA vs Europe), both as event and subject counts
- TEAEs leading to drug interruption by SOC and PT, both as event and subject counts
- TEAEs leading to dose reduction by SOC, PT by overall and region (NA vs Europe), both as event and subject counts
- TEAEs leading to death by SOC, PT by overall and region (NA vs Europe), both as event and subject counts

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

An exposure adjusted incidence rate table will be provided for TEAEs by SOC and PT. The exposure years censored will be computed as the time in years to first event for a subject or total exposure if no event for each SOC and PT. The exposure adjusted incidence rate is calculated as the number of subjects with the event / exposure years censored. The exposure adjusted incidence rate will also be provided for TEAEs of special interest.

Separate summaries will be generated for TEAEs of special interest, tabulated by category and PT using the categories as specified below:

- Hypotension, orthostatic hypotension: defined as all TEAEs with HLGT “decreased and non-specific blood pressure disorders and shock”
- Syncope: defined as all TEAEs with any of the following PTs
  - “Hypotonic-hyporesponsive episode” (MedDRA code 10021121)
  - “Altered state of consciousness” (MedDRA code 10001854)
  - “Depressed level of consciousness” (MedDRA code 10012373)
  - “Hypokinesia” (MedDRA code 10021021)
  - “Hypokinesia neonatal” (MedDRA code 10021022)
  - “Hyporesponsive to stimuli” (MedDRA code 10071552)
  - “Loss of consciousness” (MedDRA code 10024855)

- "Neurogenic shock" (MedDRA code 10058119)
- "Presyncope" (MedDRA code 10036653)
- "Shock" (MedDRA code 10040560)
- "Shock symptom" (MedDRA code 10040581)
- "Syncope" (MedDRA code 10042772)
- "Unresponsive to stimuli" (MedDRA code 10045555)

Or HLGT of "Seizures (incl subtypes)"

– Falls & injuries: defined as all TEAEs meeting the criteria for the standardized MedDRA Query (SMQ) "Accidents and injuries" (narrow terms)

– Dyskinesias: defined as all TEAEs meeting the criteria for the SMQ "Dyskinesia" (narrow terms)

– Hallucinations and psychotic behaviors: defined as all TEAEs meeting the criteria for the SMQ "Psychosis & psychotic disorders" (narrow terms)

– Impulse control disorders: defined as all TEAEs meeting the following criteria.

  - HLT "Impulse Control Disorders"
  - HLT "Paraphilia and paraphilic disorders" or "Sexual desire disorders"
  - Binge eating: PT "Binge Eating" (MedDRA code 10004716)
  - Gambling: PT "Gambling" (MedDRA code 10017655) or Gambling Disorder (MedDRA code 10078070)
  - Compulsive shopping: PT "Compulsive shopping" (MedDRA code 10067948) or any TEAE with verbatim term including the text "spending"

– Daytime sudden onset of sleep: defined as all TEAEs with HLGT "Sleep disorders and disturbances" or the PT "Sudden onset of sleep"

– QT prolongation and ventricular arrhythmias: defined as all TEAEs meeting the criteria for the SMQ "Torsade de pointes /QT prolongation" (broad terms)

– Acute Coronary Syndrome, Myocardial infarction, Angina: defined as all TEAEs meeting the criteria for the SMQ "Myocardial infarction" (broad terms)

– Suicidal ideation & attempts: defined as all TEAEs meeting the criteria for the SMQ "Suicide/self-injury" (narrow terms)

– Melanoma: defined as all TEAEs meeting the criteria for the SMQ "Skin malignant tumors" (narrow terms)

- Stomatitis, Oral ulcers, Oral irritation: defined as all TEAEs meeting the criteria for the SMQ "Oropharyngeal disorders" (narrow terms)
- Allergic/sensitivity response to the formulation: defined as all TEAEs meeting the broad criteria for the SMQ "Hypersensitivity" (broad terms)
- Serious TEAEs of special interest by category and PT, both as event and subject counts
- TEAEs of special interest leading to drug withdrawal by category and PT, both as event and subject counts
- TEAEs of special interest by category, PT and Actual Dose Received, both as event and subject counts

Separate summaries will be also be generated for TEAEs associated with the topics below

- Withdrawal-emergent Neuroleptic Malignant Syndrome: defined as MedDRA PTs of Hyperthermia malignant, Neuroleptic malignant syndrome, and Serotonin syndrome.
- Dopamine Agonist Withdrawal Syndrome: defined as MedDRA PTs of Drug withdrawal syndrome, Withdrawal syndrome, or Therapy cessation, plus at least one of the following: Agitation, Anxiety, Depression, Fatigue, Hyperhidrosis, Dizziness, Drug dependence, Flushing, Panic attack, Insomnia, Irritability, Nausea, Vomiting, Orthostatic hypotension, and Pain.
- Dopamine Dysregulation Syndrome: defined using the search criteria in Appendix 15.2

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 whether an AE is treatment-emergent:

- 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 same as month of first dose date of study treatment. If yes, impute to first dose date of study treatment; else impute first day of the month.
- If the start day and month are missing: Check if year is same as the year of the first dose date of study treatment. If yes, impute to first dose date of study treatment; else impute to first day of the first month (January).

If the AE stop date is partial, then it will be imputed as follows:

- If the stop date is completely missing and the AE is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.

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

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

The original date and time will be shown on all listings of AEs. Listings will be provided for all AEs, serious AEs, serious TEAEs, TEAEs leading to death, TEAEs leading to drug withdrawal, and TEAEs of special interest. The listings will display study day, calculated as the AE start date – date of first dose in the relevant study phase (Dose Titration or LTS 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.

Oropharyngeal adverse event cluster analysis will be provided by enrollment group and overall. Treatment emergent adverse events will be tabulated by cluster and individual PT using the clusters specified in Appendix 15.1. TEAE cluster summaries will be presented both for the Titration Full Analysis Set and for the LTS Full Analysis Set, unless specified otherwise. TEAE cluster summaries will be presented by severity, leading to drug withdrawal, and actual dose received at AE onset. Summaries by PT and actual dose received at AE Onset during LTS Phase will also be provided by region (NA vs Europe). An exposure adjusted incidence rate table will be provided for oropharyngeal AE clusters by PT. The exposure years censored will be computed as the time in years to first event for a subject or total exposure if no event for each cluster and PT. The exposure adjusted incidence rate is calculated as the number of subjects with the event / exposure years censored.

Kaplan-Meier curves will be used to illustrate the time to first onset of each cluster event (days) with frequency > 10% and overall (any oral cluster event). For a given subject, the first onset date across the relevant individual cluster events will be used for this analysis. For censored subjects without an event at at the time of analysis, end of study date for the subjects who completed the study or data cut-off date for on-going subjects will be used as the censoring date. These plots will be presented by enrollment group and will also be provided by region (NA vs Europe) for the Titration and LTS Full Analysis Sets and safety population.

Prevalence plots display the percentage of the subjects who are experiencing a cluster event during a specific interval of time. In the plot, the time intervals (treatment weeks) are shown on the horizontal axis. Time zero corresponds to first dose of treatment received. On the vertical axis, the percentage of subjects with an adverse event cluster within each time interval is shown. The event may span multiple intervals depending on its duration. Ongoing events are counted in each time interval in which they occur to assess the prevalence of the event over time. For cluster events which are ongoing at study completion or ongoing at the time of analysis, end of study date for that subject or data cut-off date respectively was used to calculate duration of event.

Each bar displays the total percentage of subjects with an event in each weekly time interval. The number of subjects at risk at the beginning of each weekly interval is shown in the bottom row of the figure and is the denominator for the percentage calculation. Subjects who drop-out of the study prior to a given time interval are removed from the risk set (denominator) for that interval. Within each bar, the different shading

breaks the bar up into distinct segments by severity of event (mild, moderate or severe) as shown in the legend. If a subject has more than one event of the same type within an interval, the maximum severity is used for this classification. The segments in each stacked bar add to the total percentage for each interval. Changes in the total percentage, as well as the percentage within segments of the same shading, can be evaluated over time. Percentages for intervals where the number of subjects at risk was less than 10 are not shown. These plots will be presented by enrollment group and will also be provided by region (NA vs Europe) for the Titration and LTS Full Analysis Sets and safety population.

9.4. Laboratory Evaluations

Laboratory test results include hematology, serum chemistry, urinalysis and serology (at the Screening Visit Only). 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 for the LTS Full Analysis Set:

- Numeric laboratory parameters: Actual values at each visit and change from baseline (last assessment prior to first APL dose) to last available visit, if applicable, 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 each post-baseline visit will be classified by the baseline category.
- Categorical laboratory parameters: The distribution of the categories will be summarized by visit.

The abnormalities occurring at least once post-baseline during the study, either at pre-dose or post-dose assessment points, including unscheduled visits will be summarized. The criteria for analysis of outliers are provided in Table 1.

Table 1 Criteria for Potentially Clinically Significant (PCS) Values in Selected Laboratory Tests

		Criteria for PCS Values	
Laboratory Parameter	**Unit**	**Low**	**High**
Hemoglobin (Female)	g/L	≤ 95 g/L	≥ 175 g/L
Hemoglobin (Male)	g/L	≤ 115 g/L	≥ 190 g/L
Hematocrit (Female)	Fraction of 1	≤ 0.32	≥ 0.54
Hematocrit (Male)	Fraction of 1	≤ 0.37	≥ 0.60
RBC	10^12/L	≤ 3.5	≥ 6.4
Total WBC Count	10^9/L	≤ 2.8	≥ 16
Basophils/Leukocytes	%	N/A	≥ 10 %
Eosinophils/Leukocytes	%	N/A	≥ 10 %
Lymphocytes/Leukocytes	%	N/A	≥ 75 %
Monocytes/Leukocytes	%	N/A	≥ 15 %
Neutrophils/Leukocytes	%	≤ 15 %	≥ 85 %
Albumin	g\L	≤ 25 g/L	N/A
ALT		N/A	≥ 3 x ULN

Alkaline Phosphatase	mmol/L		≥ 3 x ULN
Potassium	mmol/L	≤ 3	≥ 6
AST		N/A	≥ 3 x ULN
Urea (BUN)	mmol/L	N/A	≥ 11
Creatinine	µmol/L	N/A	≥ 176.8
Glucose	µmol/L	≤ 2.22	≥ 9.71
Sodium	µmol/L	≤ 126	≥ 156
Total Bilirubin	µmol/L	N/A	≥ 34.2
Uric Acid (Female)	µmol/L	N/A	≥ 506
Uric Acid (Male)	µmol/L	N/A	≥ 625
Chloride	µmol/L	≤ 90	≥ 118
Platelet count	10^9/L	<100	>500

ULN = Upper limit of normal range, NA = Not Applicable

9.5. Vital Signs

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

During the Dose Titration Phase (*De Novo* subjects and Rollover subjects prior to protocol version 5), if the 60 minute MDS-UPDRS Part III assessment is not performed since the subject did not experience a full "ON" response within 45 minutes of dosing, the vital signs assessment will be performed at the approximate time it would have been scheduled if the MDS-UPDRS Part III assessment were performed (ie 70 minutes).

The following summaries will be done:

- Change from baseline (last assessment prior to first APL dose) to other visit pre-dose values for each parameter separately for *De Novo* subjects and Rollover subjects. The change from baseline to the last available visit values will also be presented.
- Actual values and change from pre-dose to post-dose, if applicable, at each visit for each parameter overall and by region (NA vs Europe).

Orthostatic hypotension (OH) 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 across all visits and time point overall and by region (NA vs Europe).

The outlier analysis includes the tabulation of outlier vital signs values using the criteria shown below. The data will be presented as subject counts and percentages. The abnormalities occurring at least once post-baseline during the study, including unscheduled visits will be summarized. In the summary, the largest value will be used for each subject, such that a subject is counted only once in a category.

- SBP changes (within same position)
  - SBP increase > 20 mmHg – 40 mmHg

  - SBP increase> 40 mmHg
  - SBP decrease > 20 mmHg – 40 mmHg
  - SBP decrease > 40 mmHg
- DBP changes (within same position)
  - DBP increase > 10 mmHg – 20 mmHg
  - DBP increase > 20 mmHg
  - DBP decrease> 10 mmHg – 20 mmHg
  - DBP decrease> 20 mmHg
- HR changes
  - HR increase > 15 bpm – 30 bpm
  - HR increase > 30 bpm
  - HR decrease > 15 bpm -30 bpm
  - HR decrease > 30 bpm.

9.6. ECG

A standard 12-lead ECG will be performed at all timepoints outlined in the protocol. A triplicate 12-lead ECG will be performed at the second Screening Visit (SV2) for *De Novo* subjects, at Screening Visit (SV) for Rollover subjects, and at Screening Visit Period 2 (SVP2) for CTH-301 Completer subjects. If required by the Investigator to assess *De Novo* subject eligibility, a triplicate ECG may be performed at SV1, but will not be repeated at SV2.

ECGs will be performed in a semi-recumbent position and after 5 minutes of rest.

The following summaries will be done:

- Change from baseline (last assessment prior to first APL dose) to other visit pre-dose values for each parameter. The change from baseline to the last available visit values will also be presented.
- Actual values and change from pre-dose to post-dose, if applicable, at each visit for each parameter overall and by region (NA vs Europe).

The ECGs will be assessed by the investigator and deemed “Normal”, “Abnormal, not clinically significant” and “Abnormal, clinically significant” and tabulated across all visits and time point.

In addition, QTc Intervals meeting the following criteria at least one post-dose value across all visits will be reported for Bazett’s correction and for Fridericia’s correction:

- Values > 500 msec
- Values increasing > 15% from baseline if baseline value is ≥ 440 msec
- Values increasing > 30% from baseline if baseline value is < 440 msec
- Increase from baseline > 30 msec
- Increase from baseline > 60 msec

The outlier analysis includes the tabulation of outlier ECG values using the criteria shown below. The outliers occurring at least once post-baseline during the study, including unscheduled visits will be summarized. In the summary, the highest post-baseline ECG value for a subject within treatment will be used.

- QTcF normal (≤ 450 ms), >450 – 480 ms, >480 – 500 ms, and >500 ms
- QTcB normal (≤ 450 ms), >450 – 480 ms, >480 – 500 ms, and >500 ms

The outlier analysis for the changes from baseline includes the tabulation of the criteria shown below. The data will be presented as subject counts and percentages. All the comparisons will be against baseline pre-dose assessment. The abnormalities occurring at least once during the study/studies will be summarized. In the summary, the largest value will be used for each subject.

- QTcF change from baseline >30 - <60 ms, and ≥60 ms
- QTcB change from baseline >30 -<60 ms, and ≥60 ms

9.7. Physical Examination

The frequency and percentage of subjects with each type of oropharyngeal cavity examination finding will be summarized by visit, time point (when applicable), and location, overall and by region (NA vs Europe).

The oropharyngeal cavity examination data will be listed.

9.8. Other Safety

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 enrollment group and visit, overall and by region (NA vs Europe).

The QUIP-RS is an instrument used to measure the extent of impulsive and compulsive behaviors in PD subjects. The QUIP-RS consists of four questions which have to be answered for each disorder (gambling, sex, buying, eating, hobbyism, punding and PD medication use) on a 5-point Likert scale. Scoring range for each scale (i.e. disorder) is 0–16. The frequency and percentage of subjects with positive response ("rarely" or higher) for each disorder will be summarized by enrollment group and visit. Furthermore, the total Impulsive Control Disorder (ICD) score and the total QUIP-RS score will be summarized with descriptive statistics by enrollment group and visit (both absolute actual values and changes from baseline), overall and by region (NA vs Europe).

The Zarit Burden Interview (ZBI) is used to assess caregiver burden, when a caregiver is present. This data will be listed.

10. Changes from Analysis Planned in Protocol

This SAP is based on protocol amendment Version 5.00 (US specific) finalized on 25 February 2019. There are no changes from the analyses planned in the protocol.

11. Reference List

Protocol: An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes). CTH-301, Version 5.00.

Interim Analysis Statistical Analysis Plan: An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes). CTH-301, Version 1.0.

12. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

12.1. General Considerations

- One SAS program can create several outputs
- Each output will be stored in a separate file
- Output files will be delivered in Word format (Note: final outputs will also be delivered in portable document format pdf.)
- Numbering of TFLs will follow International Conference on Harmonization (ICH) E3 guidance

12.2. Table, Listing, and Figure Format

12.2.1. General

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

12.2.2. Headers

- All output should have the following header at the top left of each page:

  Sunovion Pharmaceuticals, Inc.
  CTH-301

- Data Extraction: DDMMYYYY

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. Outputs are numbered as 1, 2, 3, etc. in order. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

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

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the enrollment group columns and total column (if applicable).

- For numeric variables, include “unit” in column or row heading when appropriate.

- Analysis set sizes will be presented for each enrollment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of columns in the tables and listings will be Rollover, De Novo, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. *General Conventions*

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

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

12.2.5.2. *Table Conventions*

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

Severity Rating	N
severe	0
moderate	8
mild	3

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

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

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the enrollment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant enrollment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

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

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

12.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of enrollment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

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

- Units will be included where available

12.2.5.4. *Figure Conventions*

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

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

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

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

14. Shells

Templates of the TFLs are provided in a separate document.

15. Appendices

Appendix 15.1: Oropharyngeal Adverse Event Clusters & Associated MedDRA v 19.1 Preferred Terms

Cluster	Term
Oropharyngeal edema	Epiglottic oedema
	Gingival oedema
	Gingival swelling
	Lip oedema
	Lip swelling
	Mouth swelling
	Oedema mouth
	Oedema mucosal
	Oropharyngeal swelling
	Palatal oedema
	Palatal swelling
	Pharyngeal oedema
	Swollen tongue
	Tongue oedema
Oropharyngeal inflammation / erythema	Epiglottic erythema
	Epiglottitis
	Epiglottitis obstructive
	Gingival erythema
	Gingivitis
	Gingivitis ulcerative
	Glossitis
	Lichen planus
	Lineal gingival erythema
	Noninfective gingivitis
	Oral mucosal erythema
	Parotitis
	Periodontitis
	Pharyngeal erythema
	Pharyngeal inflammation
	Tonsillar erythema
	Tonsillar inflammation
	Behcet's syndrome
	Buccal mucosal roughening
	Oral lichen planus

Cluster	Term
	Oral pruritus
	Oral submucosal fibrosis
	Parotid gland enlargement
	PFAPA syndrome
	Pharyngeal exudate
	Sjogren's syndrome
	Tongue pruritus
Oropharyngeal discoloration	Gingival discolouration
	Gingival hyperpigmentation
	Leukoplakia oral
	Oral mucosal discolouration
	Oral pigmentation
	Oropharyngeal plaque
	Tongue discolouration
	Oral leukoedema
	Tongue pigmentation
Oropharyngeal infections	Abscess of salivary gland
	Abscess oral
	Acute postoperative sialadenitis
	Adenoiditis
	Angina gangrenous
	Aspergillosis oral
	Bacterial parotitis
	Cellulitis pharyngeal
	Chronic tonsillitis
	Foot and mouth disease
	Gingival abscess
	Hand-foot-and-mouth disease
	Herpangina
	Herpes pharyngitis
	Herpes simplex pharyngitis
	Herpes zoster pharyngitis
	Infective glossitis
	Laryngitis
	Lip infection
	Ludwig angina
	Mumps
	Necrotising ulcerative gingivostomatitis
	Necrotising ulcerative periodontitis

Cluster	Term
	Oral bacterial infection
	Oral candidiasis
	Oral fungal infection
	Oral helminthic infection
	Oral herpes
	Oral infection
	Oral pustule
	Oral tuberculosis
	Oral viral infection
	Oro-pharyngeal aspergillosis
	Oropharyngeal candidiasis
	Oropharyngeal gonococcal infection
	Oropharyngitis fungal
	Parotid abscess
	Peritonsillar abscess
	Peritonsillitis
	Pharyngeal abscess
	Pharyngeal chlamydia infection
	Pharyngitis
	Pharyngitis bacterial
	Pharyngitis mycoplasmal
	Pharyngitis streptococcal
	Pharyngoconjunctival fever of children
	Pharyngotonsillitis
	Salivary gland induration
	Staphylococcal parotitis
	Staphylococcal pharyngitis
	Strawberry tongue
	Subglottic laryngitis
	Tongue abscess
	Tongue fungal infection
	Tonsillar exudate
	Tonsillitis
	Tonsillitis bacterial
	Tonsillitis fungal
	Tonsillitis streptococcal
	Tonsillolith
	Uvulitis
	Viral parotitis

Cluster	Term
	Viral pharyngitis
	Viral tonsillitis
Oropharyngeal mass / neoplasm	Acinic cell carcinoma of salivary gland
	Adenocarcinoma of salivary gland
	Adenoid cystic carcinoma of salivary gland
	Benign salivary gland neoplasm
	Buccal polyp
	Carcinoma ex-pleomorphic adenoma
	Epiglottic carcinoma
	Epiglottic cyst
	Epiglottic mass
	Epulis
	Giant cell epulis
	Gingival cancer
	Gingival cyst
	Gingival polyp
	Leukoplakia
	Lip and/or oral cavity cancer
	Lip and/or oral cavity cancer recurrent
	Lip and/or oral cavity cancer stage 0
	Lip and/or oral cavity cancer stage I
	Lip and/or oral cavity cancer stage II
	Lip and/or oral cavity cancer stage III
	Lip and/or oral cavity cancer stage IV
	Malignant palate neoplasm
	Melanoplakia oral
	Metastases to mouth
	Metastases to pharynx
	Metastases to salivary gland
	Metastases to tonsils
	Metastatic salivary gland cancer
	Mouth cyst
	Mucoepidermoid carcinoma of salivary gland
	Oral cavity cancer metastatic
	Oral fibroma
	Oral haemangioma
	Oral hairy leukoplakia
	Oral neoplasm
	Oral neoplasm benign

Cluster	Term
	Oral papilloma
	Oropharyngeal cancer
	Oropharyngeal cancer recurrent
	Oropharyngeal cancer stage 0
	Oropharyngeal cancer stage I
	Oropharyngeal cancer stage II
	Oropharyngeal cancer stage III
	Oropharyngeal cancer stage IV
	Oropharyngeal lymphoepithelioma
	Oropharyngeal neoplasm
	Oropharyngeal neoplasm benign
	Oropharyngeal squamous cell carcinoma
	Papillary cystadenoma lymphomatosum
	Pharyngeal cancer
	Pharyngeal cancer metastatic
	Pharyngeal cancer recurrent
	Pharyngeal cancer stage 0
	Pharyngeal cancer stage I
	Pharyngeal cancer stage II
	Pharyngeal cancer stage III
	Pharyngeal cancer stage IV
	Pharyngeal cyst
	Pharyngeal leukoplakia
	Pharyngeal mass
	Pharyngeal neoplasm
	Pharyngeal neoplasm benign
	Pharyngeal polyp
	Pleomorphic adenoma
	Salivary gland adenoma
	Salivary gland cancer
	Salivary gland cancer recurrent
	Salivary gland cancer stage 0
	Salivary gland cancer stage I
	Salivary gland cancer stage II
	Salivary gland cancer stage III
	Salivary gland cancer stage IV
	Salivary gland neoplasm
	Squamous cell carcinoma of pharynx
	Squamous cell carcinoma of the oral cavity

Cluster	Term
	Squamous cell carcinoma of the tongue
	Throat cancer
	Tongue cancer metastatic
	Tongue cancer recurrent
	Tongue carcinoma stage 0
	Tongue carcinoma stage I
	Tongue carcinoma stage II
	Tongue carcinoma stage III
	Tongue carcinoma stage IV
	Tongue cyst
	Tongue dysplasia
	Tongue neoplasm
	Tongue neoplasm benign
	Tongue neoplasm malignant stage unspecified
	Tongue polyp
	Tonsil cancer
	Tonsil cancer metastatic
	Tonsillar cyst
	Tonsillar neoplasm
	Tonsillar neoplasm benign
Oropharyngeal numbness / changes in sensation	Dysaesthesia pharynx
	Hypoaesthesia oral
	Oral dysaesthesia
	Oral hyperaesthesia
	Paraesthesia oral
	Pharyngeal hypoaesthesia
	Pharyngeal paraesthesia
Oropharyngeal pain	Burn oral cavity
	Burning mouth syndrome
	Burning sensation
	Gingival discomfort
	Gingival pain
	Glossodynia
	Lip pain
	Odynophagia
	Oropharyngeal discomfort
	Oral discomfort
	Oral pain

Cluster	Term
	Oropharyngeal pain
	Tongue discomfort
	Throat irritation
Oropharyngeal ulcerations	Angina bullosa haemorrhagica
	Angular cheilitis
	Aphthous ulcer
	Chapped lips
	Cheilitis
	Contact stomatitis
	Epiglottis ulcer
	Gingival erosion
	Gingival blister
	Gingival ulceration
	Lip blister
	Lip exfoliation
	Lip ulceration
	MAGIC syndrome
	Mouth ulceration
	Nicotinic stomatitis
	Oral mucosal blistering
	Oral mucosal eruption
	Palatal ulcer
	Pharyngeal enanthema
	Pharyngeal erosion
	Pharyngeal lesion
	Pharyngeal ulceration
	Oropharyngeal blistering
	Tongue blistering
	Tongue ulceration
	Tonsillar ulcer
	Stomatitis
	Stomatitis haemorrhagic
	Stomatitis necrotising
	Stomatitis radiation
	Oral mucosa erosion
	Oral mucosal exfoliation
	Sialometaplasia
Alterations in taste	Ageusia
	Dysgeusia

Cluster	Term
	Hypogeusia
Salivary complaints and oral	Aptyalism
	Dry mouth
	Dry throat
	Lip dry
	Noninfective sialoadenitis
	Ranula
	Saliva altered
	Saliva discolouration
	Salivary duct inflammation
	Salivary duct obstruction
	Salivary duct stenosis
	Salivary gland atrophy
	Salivary gland calculus
	Salivary gland cyst
	Salivary gland disorder
	Salivary gland enlargement
	Salivary gland fistula
	Salivary gland mass
	Salivary gland mucocoele
	Salivary gland pain
	Salivary hypersecretion
	Sialoadenitis
	Tongue dry
	Foaming at mouth
	Sordes
	Tongue coated
Dental complaints	Dental caries
	Periodontal destruction
	Periodontal disease
	Periodontal inflammation
	Pulpitis dental
	Sensitivity of teeth
	Tooth abscess
	Tooth discolouration
	Tooth fracture
	Tooth infection
	Tooth loss
Trauma	Chronic cheek biting

Cluster	Term
	Corrosive oropharyngeal injury
	Gingival bleeding
	Gingival injury
	Lip injury
	Mouth injury
	Mouth haemorrhage
	Oral contusion
	Oral mucosa haematoma
	Pharyngeal injury
	Pharynx radiation injury
	Radiation salivary gland injury
	Tongue biting
	Tongue injury
	Traumatic ulcerative granuloma with stromal eosinophilia
Other	Acquired macroglossia
	Adenoidal disorder
	Adenoidal hypertrophy
	Ankyloglossia acquired
	Atrophic glossitis
	Auriculotemporal syndrome
	Buccoglossal syndrome
	Chronic throat clearing
	Coating in mouth
	Cobble stone tongue
	Exposed bone in jaw
	Gingival atrophy
	Gingival disorder
	Gingival hypertrophy
	Gingival hypoplasia
	Gingival pruritus
	Gingival recession
	Glossoptosis
	Hypertrophy of tongue papillae
	Mikulicz's disease
	Mikulicz's syndrome
	Oral allergy syndrome
	Oral cavity fistula
	Oral disorder
	Oral mucosa atrophy

Cluster	Term
	Oral mucosal hypertrophy
	Oral papule
	Oral toxicity
	Oropharyngeal cobble stone mucosa
	Oropharyngeal scar
	Palatal disorder
	Palatal dysplasia
	Palatal palsy
	Parotid duct obstruction
	Parotid gland haemorrhage
	Parotid lipomatosis
	Pharyngeal disorder
	Pharyngeal dyskinesia
	Pharyngeal fistula
	Pharyngeal haematoma
	Pharyngeal haemorrhage
	Pharyngeal hypertrophy
	Pharyngeal mucosa atrophy
	Pharyngeal necrosis
	Pharyngeal pouch
	Pharyngeal stenosis
	Plicated tongue
	Protrusion tongue
	Pyostomatitis vegetans
	Scalloped tongue
	Sialectasia
	Sialocele
	Sialogram abnormal
	Submaxillary gland enlargement
	Swallow study abnormal
	Throat lesion
	Tongue atrophy
	Tongue disorder
	Tongue eruption
	Tongue geographic
	Tongue haematoma
	Tongue haemorrhage
	Tongue infarction
	Tongue movement disturbance

Cluster	Term
	Tongue necrosis
	Tongue paralysis
	Tongue spasm
	Tonsillar atrophy
	Tonsillar disorder
	Tonsillar haemorrhage
	Tonsillar hypertrophy
	Velopharyngeal incompetence

Appendix 15.2: Dopamine Dysregulation Syndrome Search Criteria

1. MedDRA PT: Dopamine dysregulation syndrome OR
2. Any combination of the **any selected PTs** from the SMQ drug abuse and dependence PLUS at least one of the PTs from group **a, b, or c** below.

Selected MedDRA PTs from the SMQ Drug abuse and dependence (broad):

Drug abuse

Drug abuser

Drug dependence

Drug use disorder

Intentional overdose

Intentional product misuse

Substance abuse

Substance abuser

Substance dependence

Substance use disorder

Accidental overdose

Dependence

Disturbance in social behaviour

Drug level above therapeutic

Drug level increased

Intentional product use issue

Overdose

Substance use

Substance-induced mood disorder

Substance-induced psychotic disorder

PLUS one of the below:

a. *Impulse control/compulsive behavior*: MedDRA terms: MedDRA High Level Term of "Impulse control disorders", "Paraphilias and paraphilic disorders", or "Sexual desire disorders". MedDRA Preferred Terms of Stereotypy, Binge eating, Gambling, Gambling disorder, Compulsive shopping; or any TEAE with a verbatim term that included the text "spending."
b. *Behavioral changes*: selected MedDRA PTs from SMQ Hostility/Aggression:

Aggression

Anger

Borderline personality disorder

Defiant behaviour

Intermittent explosive disorder

Psychopathic personality

Abnormal behaviour

Agitated depression

Agitation

Attention-seeking behaviour

Behaviour disorder

Disturbance in social behaviour

Hypomania

Impatience

Irritability

Mania

Manic symptom

Personality change

Personality disorder

Psychotic behaviour

Psychotic disorder

Pyromania

Substance-induced psychotic disorder

c. *Dyskinesia*: selected MedDRA PTs from MedDRA SMQ Dyskinesia

Athetosis

Ballismus

Buccoglossal syndrome

Chorea

Choreoathetosis

Dyskinesia

Dyskinesia oesophageal

Grimacing

Oculogyric crisis

Pharyngeal dyskinesia

Rabbit syndrome

Tardive dyskinesia

Abnormal involuntary movement scale

Chronic tic disorder

Complex tic

Drooling

Extrapyramidal disorder

Motor dysfunction

Movement disorder

Muscle twitching

Provisional tic disorder

Tic