STATISTICAL ANALYSIS PLAN
TOZ-CL06

A Multicenter, Open-Label Study To Evaluate The Safety And Tolerability Of Tozadenant As Adjunctive Therapy In Levodopa-Treated Patients With Parkinson's Disease Experiencing End Of Dose "Wearing-Off"

Development Phase: 3

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[redacted]

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1. INTRODUCTION

TOZ-CL06 is a 52-week open-label study in levodopa-treated patients with PD experiencing end-of-dose "wearing-off". This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected in TOZ-CL06.

This SAP should be read in conjunction with the study protocol. This plan is developed using the protocol version 2.0 dated 03-FEB-2017.

2. STUDY OBJECTIVES

2.1. Primary Objectives

To evaluate the safety and tolerability of tozadenant in levodopa-treated PD patients experiencing motor fluctuations, based on assessment of treatment-emergent adverse events (TEAEs), vital signs, electrocardiograms (ECGs), and clinical laboratory tests.

2.2. Secondary Objectives

To evaluate the effects of tozadenant on the occurrence of daytime drowsiness, impulsive behavior, and suicidality.

3. STUDY DESIGN

This is a Phase 3, international, multicenter, open-label study in levodopa-treated patients with PD experiencing end-of-dose "wearing-off". This study includes a Screening Period of up to 6 weeks that starts with a Screening Visit, followed by a 52-week Open-Label Treatment Period and a Safety Follow-Up Visit 4 weeks after completion of investigational treatment. After providing written informed consent, patients will undergo screening evaluations. Patients must meet all inclusion criteria and none of the exclusion criteria and they must successfully complete the diary training and achieve 80% overall diary concordance with the PD diary trainer/rater including at least 1 OFF interval to be considered for enrollment. If preliminary eligibility is confirmed by the investigator, patients will then be scheduled for a Baseline Visit and will be required to return a valid set of Baseline diaries. Final eligibility will be determined at the Baseline Visit.

Patients will return to the study site for evaluation at scheduled visits at Weeks 2, 6, 12, 24, 36, and 52. Patients will be contacted by telephone before the start of each 3-day PD diary completion period to be reminded to complete the diary. A final Safety Follow-Up Visit (Week 56) will occur 28 ± 3 days after the patient's last open-label dose of tozadenant. Upon starting study treatment, patients will receive open-label tozadenant at a dose of 120 mg BID. Adjustments to the open-label tozadenant dose are allowed to be made by the investigator starting at Week 2 and at any of the subsequent visits. Doses of 60 or 120 mg BID are permitted; the investigator may adjust a patient's dose to either level as clinically indicated. The Interactive Response System (IXRS) will be used to assign, track and manage the tozadenant inventory at each study site.

The Schedule of Events/Evaluations for is shown below in Table 1.

Table 1: Schedule of Events/Evaluations

Study Period	Screening [a]	Baseline Predose	Open-Label Treatment (52 weeks)						Safety Follow-Up	Early Termination [w]	Unscheduled
Study Week [b]	−6 to −1	BL	2 (± 3 d)	6 (± 3 d)	12 (± 3 d)	24 (± 7 d)	36 (± 7 d)	52 (± 14 d) [16 weeks]	56 (28 ± 3 d after last dose of IMP)		
Assessments / Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9		
Written Informed Consent	X										
Demographics and Medical History, including neurological and PD history	X										
Recording of concomitant and anti-PD medications	X	X	X	X	X	X	X	X	X	X	X
BP [c], pulse [c]	X [d]	X [d]	X	X	X	X	X	X	X	X	X [e]
12-lead ECG [f]	X	X [g]	X	X	X	X	X	X	X	X	X [e]
Weight (include height at Screening)	X				X	X		X	X	X	X [e]
Physical and neurological examination	X				X	X	X	X	X	X	X [e]
PD diary training and diary concordance session	X										
Modified Hoehn and Yahr staging (observed ON; OFF estimated per history) [h]	X										
UPDRS Parts I, II, III and IV [i]	X	X	X	X	X	X	X	X		X	
MMSE-II (in ON state)	X										
mMIDI [j]	X		X	X	X	X	X	X	X	X	X [e]
ESS [h]		X	X	X	X	X	X	X	X	X	
PD diary collection (phone call prior to start of 3 consecutive 24 hour diary completion periods)	X [k]	X [k]			X [l]	X [l]		X [l]		X [m]	
PD diary review	X	X			X	X		X [m]		X [m]	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X [e]
CGI-C [h]			X	X	X	X	X	X		X	
PGI-C [h]			X	X	X	X	X	X		X	
PDQ-39 [h]		X				X		X		X	
Sudden onset of sleep	X	X	X	X	X	X	X	X	X	X	
Fall questionnaire		X				X		X		X	
Healthcare Resource Utilization			X	X	X	X	X	X		X	
Nonmotor Symptom Questionnaire		X				X		X		X	
EQ-5D-5L [h]		X				X		X		X	
Recording of AEs	X [n]	X [n]	X	X	X	X	X	X	X	X	X

Study Period	Screening [a]	Baseline Predose	Open-Label Treatment (52 weeks)						Safety Follow-Up	Early Termination [w]	Unscheduled
Study Week [b]	−6 to −1	BL	2 (± 3 d)	6 (± 3 d)	12 (± 3 d)	24 (± 7 d)	36 (± 7 d)	52 (± 14 d) [16 weeks]	56 (28 ± 3 d after last dose of IMP)		
Assessments / Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9		
Laboratory tests: hematology [o], chemistry [p] (including thyroid function q)	X	X	X	X	X	X	X	X	X	X	X [e]
FSH test, females who are postmenopausal for < 2 years	X										
Method of contraception [r]	X	X	X	X	X	X	X	X	X	X	X [e]
Urine pregnancy test, females of childbearing potential [s]	X	X	X	X	X	X	X	X	X	X	X [e]
Urinalysis [t]	X	X	X	X	X	X	X	X	X	X	X [e]
Review of inclusion/exclusion criteria	X										
Final verification of eligibility		X									
Tozadenant blood sampling			X [u]								
IMP dispensing and/or return [v]		X	X	X	X	X	X	X		X	X [e]
eCRF completion	X	X	X	X	X	X	X	X	X	X	X

AE, adverse event; BP, blood pressure; CGI-C, Clinical Global Impression of Change; C-SSRS, Columbia-Suicide Severity Rating Scale; d, day; ECG, electrocardiogram; eCRF, electronic case report form; ESS, Epworth Sleepiness Scale; ET, Early Termination; FSH, follicle stimulating hormone; IMP, investigational medicinal product; mMIDI, Modified Minnesota Impulse Disorders Interview; MMSE-II, Mini-Mental State Exam – Second Edition (MMSE-II); PD, Parkinson's disease; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; PGI-C, Patient's Global Impression of Change; UPDRS, Unified Parkinson's Disease Rating Scale; V, Visit.

Footnotes

[a] Screening period may not exceed 6 weeks.

[b] Visit windows for scheduled visits after Baseline (V2) are in relation to the date of the Baseline Visit (V2).

[c] Obtain and record BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 minute and 3 minutes.

[d] At Screening and Baseline (before dosing), obtain and record serial BP and pulse measurements after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes, on 3 occasions approximately 10 minutes apart.

[e] Optional activities (e.g., additional assessments for evaluation of AEs) that may be performed at the investigator's discretion.

[f] A resting supine 12-lead ECG will be collected after the patient has been in a supine position for a minimum of 5 minutes. Ensure the ECG is collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

[g] At Baseline, obtain three 12-lead ECGs (i.e., 3 serial readings, performed several minutes apart). Ensure the ECGs are collected when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

[h] To be collected during patient's ON state.

[i] UPDRS to be measured in ON state. UPDRS Part III should be measured approximately 1 to 3 hours after patients have taken a scheduled dose of levodopa (preferably their morning dose of levodopa). Patients will be instructed to have already taken their normally scheduled dose of levodopa and their IMP before arriving at the study site in order to have their UPDRS Part III evaluated in the ON state. UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in the patient's "best" ON.

Table 1: Schedule of Events/Evaluations (continued)

[j] At Screening, send patient for structured clinical interview if one or more positive mMIDI modules. If the structured clinical interview confirms that the subject does not have an ICD, he/she will not be considered ineligible on that basis. After Baseline, if patient has one or more positive modules on the mMIDI, their continued participation in the study should be discussed with the Medical Monitor.

[k] The 3-day practice diary during the Screening Period and the 3-day Baseline diary must both be valid in order to randomize a patient. The trainer/rater will call the patient before the scheduled start of the diary completion periods to remind him or her to keep the PD diary and to review completion instructions. The patient will also be reminded to send the completed practice diary to the trainer/rater and to bring their Baseline diary to the Baseline Visit. If the practice or Baseline diary is invalid, the patient may be retrained and complete another practice or Baseline diary within the 6-week window of the Screening Period, if the patient is otherwise eligible for the study.

[l] PD diary collected over the 3 consecutive 24-hour periods before the day of the scheduled study visits on Week 2, 6, 12, 18, 24, 36, and 52. The PD diary trainer/rater will call the patient before the scheduled start of the 3-day PD diary completion period (at the latest, on the last working day before the scheduled start of the PD diary completion) and review completion instructions. The patient will also be reminded to bring their PD diary to the visit. The trainer/rater will instruct the patient if the PD diary contains missing and/or invalid entries to reinforce instructions for appropriate completion.

[m] Done only if the ET date coincides with the scheduled diary collection return date.

[n] Pretreatment AEs.

[o] Hematology tests: Hemoglobin concentration, hematocrit, red blood cell count, total and differential white blood cell, thrombocyte (platelet) count.

[p] Blood chemistry (including liver function) tests: Aspartate amino transferase (AST), alanine amino transferase, (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (conjugated and unconjugated), albumin, creatinine, urea/BUN, bicarbonate, uric acid, total protein, sodium, chloride, potassium, calcium, phosphate, glucose, cholesterol, creatine phosphokinase (CK).

[q] TSH, free T_3, and free T_4.

[r] For applicable patients: At Screening, document method of contraception used by patient. At subsequent visits, verify continuation of (or any change to) contraceptive method.

[s] For females of childbearing potential: urine pregnancy test.

[t] Urinalysis: Specific gravity, pH, ketones, blood, protein, glucose. If urine dipstick is positive for leukocytes, protein, or erythrocytes, a microscopic evaluation and culture will be performed.

[u] A PK blood sample should be collected at the most convenient time during the Week 2 visit. Record the patient-reported date and approximate time when the patient took the most recent dose of IMP. Record the date and time of the PK sample collection. See **Section 8.0** of the protocol. (Note: sites participating in Expanded PK Sampling should refer to **Appendix 15.9**).

[v] Patients will be instructed to take the assigned dose of open-label tozadenant by mouth BID, in the morning and in the evening preferably at the same time each day. The evening dose should be approximately 12 hours after the morning dose. Patients will be instructed to take their morning and evening doses at least 1 hour before or 2 hours after a meal and to refrain from eating for at least 1 hour after dosing.

[w] If patient has discontinued IMP, perform Early Termination Visit as soon as possible after the last dose of IMP. If patient took the last dose of IMP 28 or more days prior to the Early Termination Visit, a Safety Follow-Up Visit (**Section 6.2.16**) is not required.

3.1. Analysis sets

3.1.1. Full Analysis Set (FAS)

The FAS will consist of all patients who are enrolled in the open-label phase 3 study.

3.1.2. Safety Set (SS)

The SS will consist of all enrolled patients who received at least one dose of IMP.

3.1.3. modified Full Analysis Set (mFAS)

The mFAS will consist of all enrolled patients who received at least one dose of IMP and who had at least one post-baseline visit.

3.1.4. Expanded PK Population (xPK)

The xPK Population will consist of all subjects with expanded PK and for whom there are adequate samples collected to provide analyzable PK data.

3.2. Sample Size Considerations

No formal sample size determination was performed for TOZ-CL06. With an anticipated 30% screen failure rate, approximately 645 patients will be screened to enroll 450 patients.

3.3. Randomization

Not applicable since this is an open-label study where all patients start with 120mg.

4. STUDY VARIABLES AND COVARIATES

4.1. Safety Variables

Safety variables include the following:

- Treatment-emergent adverse events (TEAE).
- Physical and neurological examination.
- Supine and standing pulse and blood pressure.
- Standard 12-lead electrocardiogram (ECG): RR, PR, QRS, QT and QTcF.
- Laboratory parameters: hematology, chemistry, thyroid function (thyroid stimulating hormone [TSH], free T3, and free T4), and urinalysis.
- Columbia-Suicide Severity Rating Scale (C-SSRS).
- Daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS)
- Assessment of sudden episodes of sleep.
- Modified Minnesota Impulsive Disorders Interview (mMIDI).

4.2. Other variables

Other variables include the following:

- Unified Parkinson's Disease Rating Scale (UPDRS) Part II (Activity of Daily Living (ADL) subscale) + Part III (motor subscale) total score.
- UPDRS Part II (ADL subscale) score.
- UPDRS Part III (motor subscale) score in the ON state.
- UPDRS Part I total score.
- UPDRS Part IV total score.
- Dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV.
- Motor fluctuations as measured by question 39 of UPDRS Part IV.
- Clinical Global Impression of Improvement (CGI-I).
- Patient's Global Impression of Improvement (PGI-I).
- Parkinson's Disease Quality of Life Questionnaire (PDQ-39; total score and individual domain scores).
- Non-motor Symptom Questionnaire.
- EuroQol 5D-5L Health Questionnaire (EQ-5D-5L).
- Patient-completed diaries (number of hours per day spent as follows: OFF, ON time without troublesome dyskinesia, total ON time, ON time with troublesome dyskinesia and asleep time).
- Healthcare Resource Utilization
- Fall Questionnaire

4.3. Pharmacokinetic Variables

- Tozadenant PK concentrations at Week 2 and PK concentration and PK parameters c_{max}, t_{max}, and $AUC_{0\text{-}last}$ for expanded PK.

4.4. Predetermined Covariates and Prognostic Factors

Not applicable as exploratory analyses will be documented by descriptive statistics.

5. DEFINITIONS

5.1. Treatment Group Labels

The following treatment group label will be used in the TFLs:

- Tozadenant

5.2. Age

The following SAS® code is used to calculate subject age (years):

Age = floor((intck('month', birth date, IC date) - (day(IC date) < day(birth date))) / 12),

Where intck is a SAS® function counting integer days between birth date and informed consent date.

5.3. Valid Diary

A valid diary record will not have more than 4 invalid entries (double or missed entries) over one 24-hour period. An invalid diary entry is defined as more than 1 entry recorded in a given half-hour interval, an unreadable entry, or the absence of an entry in a given half-hour interval.

5.4. Baseline for Diary Data

Baseline is defined as the average of the 3-day Baseline diary preceding the first dose.

5.5. Baseline Complete UPDRS Assessment

A valid UPDRS assessment is one in which UPDRS Part III has been completed in the ON state. The UPDRS assessment utilized as the baseline will be the later of the Screening or

Baseline visit assessment that is valid.

The selected assessment will be used to determine the Baseline UPDRS Parts I – IV subscores and the UPDRS I-IV total score. If a valid UPDRS is not available at Screening or Baseline visit, then the subject will be excluded from "change from baseline" UPDRS summary statistics.

5.6. Baseline for Blood Pressure and Pulse Rate and ECG

Baseline is defined as the average of the 3 pre-dose measurements for the respective supine or standing measurements that are taken following 5 minutes supine rest and following 3 minutes standing, respectively and approximately 10 minutes apart prior to the first dose of IMP. Should one of the 3 measurements be missing, the baseline will be the average of the remaining two pre-dose measurements and if two or more of the 3 measurements are missing, the average of the three measurements from the screening visit will be used as baseline. Should one of the 3 measurements be missing, the baseline will be the average of the remaining two screening measurements and if two or more of the 3 measurements are missing, baseline will be missing.

Baseline for ECG will be calculated similarly.

5.7. Baseline for Variables excluding Diary Data, UPDRS, Blood Pressure, and Pulse Rate

Baseline is defined as the last measurement prior to the first dose of IMP. If for any parameter the study Day 1 pre-dose value is not done or missing, then the last value obtained at a Screening visit is used as Baseline.

5.8. Change from Baseline

Change from baseline will be the calculated as the data value measured post-baseline visits minus baseline.

5.9. Concomitant and Prior Medication other than Anti-PD Medications

Concomitant medications other than anti-PD medications are defined as any medications ongoing at the start of treatment or with a start date and time on or after the date of first dose of IMP. Prior medications are defined as a medication with a stop date prior to first dose of IMP.

For the classification of medications as prior or concomitant, medications with missing or partial stop dates will be considered as follows:

- If the stop date is completely missing, the medication will be regarded as concomitant.
- If the day and month are missing but the year is given and the year is prior to the year of first dose, the medication will be classified as prior medication. Otherwise such medications will be considered as concomitant.
- If the day is missing but the month and year are given and the month and year are prior to the day of first dose, the medication will be classified as prior medication. Otherwise such medications will be considered as concomitant.

5.10. Concomitant Anti-PD Medications

During the study, patients' concomitant anti-PD medications may be adjusted as needed under the investigator's supervision.

Concomitant anti-PD medications are defined as any medications ongoing at the start of treatment or with a start date and time on or after the date of first dose of IMP. Prior anti-PD medications are defined as a medication with a stop date prior to first dose of IMP.

For the classification of anti-PD medications as prior or concomitant, medications with missing or partial stop dates will be considered as follows:

- If the stop date is completely missing, the medication will be regarded as concomitant.
- If the day and month are missing but the year is given and the year is prior to the year of first dose, the medication will be classified as prior medication. Otherwise such medications will be considered as concomitant.
- If the day is missing but the month and year are given and the month and year are prior to the day of first dose, the medication will be classified as prior medication. Otherwise such medications will be considered as concomitant.

5.10.1. Baseline Total Daily Levodopa

The total daily levodopa dose at baseline will be calculated as dose x # of tablets x frequency per day for levodopa medications taken at baseline.

5.10.2. Baseline Total Daily Levodopa Equivalents

The Levodopa Equivalents (LED) of each concomitant anti-PD drug being taken at baseline will be calculated as the total daily dose of the medication multiplied by a conversion factor to obtain the LED for the medication. The total daily LED will be the sum of each LED medication taken at baseline. Conversion factors for each medication will be based on Tomlinson et al, 2010 (see Section 12). Algorithm based on the Tomlinson paper is included in Appendix 2.

5.11. Missing Adverse Event Relationship or Severity

AEs with missing relationship will be considered as having a relationship of possibly related to study drug. AEs with missing or unknown severity will be considered severe. A subject with missing relationship or severity for an AE will be footnoted as having missing data in the corresponding tables and listings for the AE with missing data.

5.12. Treatment-Emergent Adverse Events (TEAEs)

TEAEs are AEs which first occur or increase in severity or relationship to study drug after the first dose of IMP through the Safety Follow-up. Should the day of the AE be "unknown" and the AE in question occurs in the same month or a following month as the date of first dose, the AE will be considered treatment emergent. Should the month of the AE be "unknown" and the AE in question occurs in the same year or a following year as the date of first dose, the AE will be considered treatment emergent. Should the start date be missing then the AE will be considered treatment emergent.

6. INTERIM ANALYSES

There is no planned interim analysis for this study.

7. DATA REVIEW

7.1. Data Handling and Transfer

Data are entered electronically into a clinical database built by Prometrica and exported as SAS® datasets. Data analyses including summary tables, figures, and data listings are produced using SAS®.

Medical conditions and AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or higher, to assign a system organ class (SOC) and preferred term (PT) to each AE. Prior and concomitant medications are coded to preferred drug names using the World Health Organization Drug Dictionary (WHODRUG) version 2015:03 or higher.

Clinical laboratory results and normal ranges will be provided as SAS datasets from the central clinical laboratory vendor. Protocol deviations and violations (PDVs) will be identified by the Sponsor prior to database lock and will be presented as data listings.

8. UNBLINDING

Not applicable since this is an open-label study.

9. STATISTICAL METHODS

The software used for all summary statistics and statistical analyses will be SAS® (SAS Institute, Inc.)[1] Version 9.2 or later.

Most continuous data will be summarized with the following descriptive statistics: number of observations, mean, SD, median, minimum, and maximum; interquartile ranges will be provided as appropriate. Categorical data will be summarized with frequencies and percentages.

Missing data will not be imputed.

Formal statistical tests will be not be conducted and thus no p-values will be reported.

For presentation of data, the mean and median will be presented to 1 decimal place greater than the original data, SD will be to 2 decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data. The format for range will be "Min, Max". Standard deviation will be abbreviated as "SD".

Data that is collected in an early termination visit may be included in the calculation of summary statistics for the week the early termination visit falls into, as long as the visit falls within the time-frame of a scheduled visit as displayed in Table 1. For example, if a subject has early termination visit 3 days prior to a previously scheduled week 12 visit, the data collected will be included in the calculation of summary statistics for week 12. If the diary data is collected from the site at this visit, the diary data would also be included in the calculation of summary statistics for week 12. If data is included for a study week as in this example above, it would not be included as part of the 'early termination column's' summary statistics, i.e., data would only be used and included once in a summary statistic calculation, i.e., used only in calculation of summary statistics for week 12 in this example.

For certain variables (i.e., ESS, UPDRS III), subjects should complete these at the site during an "ON" state, per the protocol. The site should have only collected this data if the subject was in fact in the "ON" state. However, in cases where the site collected the data anyway (i.e., in "OFF" or "fluctuating"), we will treat all data that shows up in the database as if they followed the protocol, i.e., we will not check for the subject being in the "ON" state before including in summary statistics.

9.1. Subject Disposition

Subject disposition data will be summarized for all patients who entered into TOZ-CL06. A table will include:

- Number of patients screened
- Number of patients enrolled
- Number (%) of patients who completed the study
- Number (%) of patients in the FAS

- Number (%) of patients in the SS
- Number (%) of patients in the mFAS
- Number (%) of patients in the xPK
- Number (%) of patients out of those who enrolled who early discontinued along with reasons for withdrawal
- Number (%) of patients out of those who enrolled who terminated early because of program termination

The percentages (%) will be calculated using 'Number of patients enrolled' in the denominator.

A listing of all patients who enrolled along with data on their disposition will be provided.

A table will be presented to summarize the number and percent of patients enrolled at each site by region, country and all patients.

A table will be presented to summarize the number and percent of patients who attended each study visit.

9.2. Protocol Deviations and Violations

Protocol deviations and violations (PDVs) will be identified and categorized as major or minor by the Sponsor prior to database lock.

If there is a significant number of major protocol deviations and violations, they will be summarized by deviation/violation category. Otherwise, all PDVs will be documented in a data listing only.

9.3. Treatments

9.3.1. Extent of Study Drug Exposure

The number of days of exposure to study drug and average daily dose (mg/day) will be summarized by study visit in the SS. Average daily dose will be calculated as (number of tablets dispensed minus the number of tablets returned minus the number of tablets lost) divided by number of days from visit i-1 to visit i and multiplied by the mg of the tablets. The proportion of subjects who took 60mg, 120mg will be summarized by study visit in the SS. Subjects who took only 60mg doses from visit i-1 to visit i will be included in the numerator for the 60mg category for visit i; subjects who took only 120mg doses from visit i-1 to visit i will be included in the numerator for the 120mg category for visit i. Descriptive statistics for the total number of tablets dispensed, number of tablets returned and number of tablets lost will be displayed by study visit and overall. Compliance with study drug will be calculated as (number of tablets dispensed minus the number of tablets returned minus the number of tablets lost) divided by the scheduled number of doses, expressed as a percentage. If this percentage is calculated greater than 100%, then compliance will be calculated 1 minus (the calculated percentage minus 1). Compliance will be summarized overall and by scheduled weeks for the safety analysis set.

Study drug dispense and accountability with the reason for not returning tablets is captured on the CRF and will be presented in the data listings.

9.3.2. Concomitant and Prior Medications other than Anti-PD Medications

Prior and concomitant medications other than anti-PD medications will be coded to a preferred name according to the WHODRUG coding dictionary version 2015:03 or higher. The number and percent of subjects will be summarized for prior and concomitant medications for each preferred term (PT) in the FAS and should be displayed by therapeutic class and preferred term. All prior and concomitant medications taken during the study will be listed for each subject including dosage and indication.

9.3.3. Concomitant and Prior Anti-PD Medications

During the study, patients' concomitant anti-PD medications may be adjusted as needed under the investigator's supervision.

Prior and concomitant anti-PD medications will be coded to a preferred name according to the WHODRUG coding dictionary version 2015:03or higher. The number and percent of subjects will be summarized for prior and concomitant anti-PD medications for each preferred term (PT) and should be displayed by therapeutic class, chemical/therapeutic/pharmacological subgroup, and preferred term in the FAS. All prior and concomitant anti-PD medications will be listed separately for each subject.

The last dose of anti-PD medication taken the evening before the day when UPDRS part III test are done in defined "ON" state at Screening, Baseline (Pre-dose Day 1), Weeks 2, 6, 12, 24, 36 and 52 will be documented in a subject data listing along with the date and time of UPDRS Part III performed before anti-PD medications. The subject data listing will include medication/treatment, dose, number of tablets or capsules taken, frequency, date of last dose and time of last dose.

9.3.3.1. Total Levodopa Dose

The total levodopa dose at baseline and during the study will be calculated for each subject at each visit and summarized descriptively for each visit in the FAS. A separate listing will also be created listing each subject's calculated total levodopa dose by visit.

9.3.3.2. Total Levodopa Equivalents

The total levodopa equivalent at baseline and during the study will be calculated for each subject at each visit and summarized descriptively for each visit in the FAS. A separate listing will also be created listing each subject's calculated total levodopa equivalent by visit. Appendix 2 contains the rules to calculate levodopa equivalents.

9.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively in the FAS. These variables include:

- Gender
- Race and ethnicity
- Age (years)

- Body weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Duration of PD (years)
- Hoehn and Yahr Staging of PD in ON state and OFF state (best estimate)

Age will also be classified into 3 categories (≥ 30 to 54, ≥ 55 to 68 and ≥ 69 to 80 years).

9.5. Medical History Events

Medical conditions resolved by first dose of IMP and ongoing medical conditions will be summarized by MedDRA system organ class (SOC) and PT in the FAS. All medical conditions collected on the eCRF will be included in the listings.

9.6. Exploratory Analyses

All exploratory endpoints will be summarized descriptively in the mFAS.

9.6.1. Exploratory Variables

The exploratory variables including the change from Baseline (where applicable) will be summarized using descriptive statistics by visit:

1. UPDRS Part II (ADL subscale) + Part III (motor subscale) total score
2. UPDRS Part II (ADL subscale) score
3. UPDRS Part III (motor subscale) score in the ON state
4. UPDRS Part I total score
5. UPDRS Part IV total score
6. Dyskinesia as measured by questions 32, 33 and 34 of UPDRS Part IV
7. Motor fluctuations as measured by question 39 of UPDRS Part IV
8. Clinical Global Impression of Improvement (CGI-I)
9. Patient's Global Impression of Improvement (PGI-I)
10. Parkinson's Disease Quality of Life Questionnaire (PDQ-39; total score and individual domain scores)
11. Non-motor Symptom Assessment Scale
12. Patient-completed diaries (Change from Baseline in the number of hours per day spent as follows: OFF, ON time without troublesome dyskinesia, total ON time, ON time with troublesome dyskinesia and asleep time)
13. Healthcare Resource Utilization
14. EuroQol 5D-5L Health Questionnaire (EQ-5D-5L)
15. Fall questionnaire

9.7. Pharmacokinetic Variables

9.7.1. Tozadenant Plasma Concentrations at week 2

Blood samples will be collected for determination of plasma tozadenant concentrations at Week 2.

Plasma concentration data will be presented for all subjects. In all calculations, zero (0 ng/mL) will be substituted for concentration below the quantification limit (BLQ; equivalent to <5 ng/mL) of the assay.

Elapsed time between dosing and plasma sampling will not be tightly controlled and is expected to vary considerably between patients. Summary statistics for tozadenant blood concentrations (number of sample analyzed, number of BLQ values, minimum, and maximum) will be presented on the safety set.

All data collected on the tozadenant blood concentrations will be included in the data listings.

9.7.2. Tozadenant expanded PK

9.7.2.1. Tozadenant expanded PK Plasma concentration

Plasma concentration for the expanded PK will be described using the PK population.

For expanded PK blood samples for plasma concentration, one pre-dose/trough PK sample will be collected prior to the administration of tozadenant. After the administration of tozadenant, four additional samples will be collected at 3, 5, 6 and 8 hours.

Trough concentration will be summarized in terms of n, arithmetic mean, SD, arithmetic CV%, median, minimum, maximum, geometric mean and geometric CV%. The plasma concentration at 3 hours, 5 hours, 6 hours, and 8 hours will be described similarly. Values that are BLQ will be set to zero when calculating the aforementioned descriptive statistics. If one or more of the concentration values in a data series is zero, the geometric mean and geometric CV% will not be calculated and will be denoted as NC.

Concentrations will be listed to the same degree of accuracy as supplied by the bioanalytical laboratory. As well, units of concentration will be presented as they are received from the bioanalytical laboratory.

Individual plasma concentration-time profiles and individual concentration listings will be presented using actual sampling times. Arithmetic mean plasma concentration-time profiles will be plotted on linear and semi-logarithmic scales.

9.7.2.2. Tozadenant expanded PK Pharmacokinetic parameters

Pharmacokinetic parameters for the expanded PK will be described using the PK population.

The following pharmacokinetic parameters for tozadenant will be calculated using non-compartmental analysis using Phoenix WinNonlin Version 6.4 or higher:

Parameter	Definition
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the last measurable concentration, as calculated by the trapezoidal method.

C_{max} Maximum plasma concentration
t_{max} Time of maximum measured plasma concentration (C_{max})

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles. If C_{max} occurs at multiple timepoints, the earliest time will be used for t_{max}.

C_{max} and $AUC_{0\text{-last}}$ will be summarized in terms of n, arithmetic mean, SD, arithmetic CV%, median, minimum, maximum, geometric mean and geometric CV%. For the parameter t_{max}, the descriptive statistics will include n, arithmetic mean, SD, minimum, median, and maximum.

9.7.2.2.1. Criteria for handling concentrations below the limit of quantification in Pharmacokinetic analysis

Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, these values will be set to zero.

9.8. Safety Analyses

All safety analyses will be performed on the SS.

9.8.1. Adverse Events

A summary of TEAEs that occur including the number of events reported, the number and percentage of subjects reporting at least 1 AE, the number and percentage of subjects discontinuing due to an AE, the number and percentage of subjects with at least 1 serious adverse event, and the number and percentage of deaths will be presented.

A breakdown of the number and percentage of subjects reporting each TEAE will be presented, categorized by SOC and PT coded according to the MedDRA dictionary. Note that counting will be by subject, not event, and subjects are only counted once within each SOC or PT.

A further tabulation of these data will be presented for TEAEs that are related to study drug, as defined by those AEs with relationship to study drug recorded on the eCRF as Possible or Probable. Events that are unrelated or remotely/Unlikely related will not be considered “related” for the Causality assessment. An AE with a missing relationship will be considered as having a relationship to study drug of possible. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most drug-related event within that SOC or PT.

A summary of events reported, categorized by severity (mild, moderate, severe) will also be provided. AEs with missing or unknown severity will be considered severe. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

A summary of adverse events leading to discontinuation will be provided, grouped by system organ class and preferred term.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed along with other information such as duration, severity, action taken, and perceived relationship to study drug.

9.8.2. Deaths and Serious Adverse Events

Serious TEAEs will be summarized by the number and percentage of subjects reporting each AE, categorized by SOC and PT coded according to the MedDRA dictionary. Note that counting will be by subject, not event, and subjects are only counted once within each SOC or PT.

9.8.3. Laboratory Data

Clinical laboratory values will be evaluated by subject for each laboratory parameter at Weeks 2, 6, 12, 24, 36, 52, early termination and safety follow-up. Laboratory test results will be reported and they will be assigned a LNH classification by each laboratory according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Reference (normal) ranges for laboratory parameters provided by the central lab will be included in the clinical study report for this study and will be used for shift tables. Summary tabulations of the continuous clinical laboratory (hematology, chemistry, thyroid function (TSH, free T3 and free T4), and urinalysis) data (n, mean, standard deviation, median, minimum, and maximum) for baseline, each scheduled visit (defined in Table 1), and change from baseline for laboratory data will be provided. Quantitative urinalysis data will only be listed. Shifts from baseline to each scheduled visit will be summarized for hematology, chemistry, thyroid, and urinalysis variables that are assigned a LNH classification. In addition, shifts from baseline to worst post-baseline for the same laboratory variables will be presented based on the LNH classification.

Prespecified continuous laboratory hematology (WBC, Neutrophils, Lymphocytes) and chemistry (AST, ALT, GGT, Glucose, CK) parameters will have the worst post-baseline value plotted versus the baseline visit. The minimum lower limit of the normal range and the maximum upper limit of the normal range amongst laboratories will be drawn on the x and y axis as vertical lines.

All laboratory data collected will be included in the data listings.

9.8.4. Systolic and Diastolic Blood Pressure and Pulse Rate

Systolic and diastolic blood pressure and pulse rate will be measured in both the supine and standing positions. The scheduled visits that will be summarized are Weeks 2, 6, 12, 24, 36, 52, early termination and safety follow-up.

Summary tabulations of the systolic and diastolic blood pressure and pulse rate in both standing and supine positions as well as the orthostatic change (n, mean, standard deviation, median, minimum, and maximum) for each scheduled visit, and change from baseline will be provided.

At each scheduled visit and time point (Weeks 2, 6, 12, 24, 36, 52, early termination and safety follow-up), the number and percent of subjects meeting each abnormal criteria displayed below will be summarized.

- Supine and standing systolic blood pressure
  - ≥160 mmHg
  - < 100 mmHg
  - ≥20 mmHg increase from baseline
  - ≥20 mmHg decrease from baseline
  - ≥40 mmHg increase from baseline
  - ≥40 mmHg decrease from baseline
- Supine and standing diastolic blood pressure
  - ≥100 mmHg
  - <50 mmHg
  - ≥10 mmHg increase from baseline
  - ≥10 mmHg decrease from baseline
  - ≥20 mmHg increase from baseline
  - ≥20 mmHg decrease from baseline
- Supine and Standing Pulse rate
  - ≥120 bpm
  - <48 bpm
  - ≥30 bpm increase from baseline
  - ≥30 bpm decrease from baseline
- Orthostatic change ≥20 mmHg increase from baseline for systolic blood pressure and diastolic blood pressure
- Orthostatic change ≥20 mmHg decrease from baseline for systolic blood pressure and diastolic blood pressure

For Weeks 2, 6, 12, 24, 36, and 52 plots of the mean change from baseline at each timepoint will be displayed for blood pressure and pulse rate in supine and standing position and orthostatic change.

All vital sign data collected will be included in the data listings.

9.8.5. Body Weight

Body weight will be summarized at Weeks 12, 24, 52, early termination and safety follow-up visits.

Summary tabulations of weight (n, mean, standard deviation, median, minimum, and maximum) at each scheduled visits, and change from baseline will be provided.

All body weight data collected will be included in the data listings.

9.8.6. Columbia-Suicide Severity Rating Scale

The number and percent of subjects reporting "Yes" for each of the 5 questions to suicidal ideation and 6 questions about suicidal behavior will be summarized. In addition, for suicidal behavior, the total number of actual attempts, total number of interrupted attempts and total number of aborted attempts will be summarized (n, mean, standard deviation, median, minimum and maximum) by visit.

All C-SSRS data collected will be included in the data listings.

9.8.7. Modified Minnesota Impulsive Disorders Interview

mMIDI is reported at Weeks 2, 6, 12, 24, 36, 52, early termination and safety follow-up. For the mMIDI module scores and total score, if a question is not answered with a module, then that given module score and the total score will not be determined for the subject at the visit.

The mMIDI modules are Buying Disorder, Compulsive Gambling, Compulsive Sexual Behavior, Compulsive Eating, and Punding Behavior. The number and percent of subjects in each module with a positive/negative indication for the module will be reported. In addition, shift from baseline to each scheduled visit will be summarized.

All mMIDI data collected will be included in the data listings.

9.8.8. Epworth Sleepiness Scale and Assessment of Sudden Episodes of Sleep

Epworth Sleepiness Scale (ESS) is reported at Weeks 2, 6, 12, 24, 36, 52, early termination and safety follow-up, collected during patient's ON state. Daytime sleepiness as measured by the ESS, including assessment of episodes of sudden onset of sleep. ESS will summarized by visit. Assessment of sudden episodes of sleep will be analyzed similarly.

All ESS data collected will be included in the data listings.

9.8.9. ECG

ECG data will be summarized for the following visits: Weeks 2, 6, 12, 24, 36, 52, early termination and safety follow-up. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) of each parameter (HR, PR, RR, QRS, QT, and QTcF) will be displayed for the observed value and change from baseline at each scheduled listed above.

The number and percentage of subjects with maximum post-dose QT/QTcF interval within the following ranges will be summarized:

- ≤450 msec
- >450 msec and ≤480 msec
- >480 msec and ≤ 500 msec
- >500 msec.

In addition the number and percentage of subjects with maximum change from Baseline in QT/QTcF interval within the following ranges will be summarized:

- ≤30 msec
- >30 msec
- ≤60 msec, and >60 msec.

ECG findings will be classified as normal or abnormal, with abnormal values further classified according to clinical significance (yes/no).The percentage of subjects with clinically significant findings and clinically significant treatment-emergent findings will be summarized for each visit.

All ECG data collected will be included in the data listings.

9.8.10. Physical and Neurological Examinations

Physical and neurological examinations are performed at Weeks 12, 32, 36, 52, early termination and safety follow-up visits. The number and percentage of subjects with normal/abnormal findings will be summarized by body system/neurological area and visit.

All abnormalities reported will be included in the data listings.

10. VALIDATION

- 100% of unique tables will be independently programmed by a second programmer for numeric results. Statisticians will be involved in the process of programming and validating tables.
- Figures will be checked for consistency against the corresponding tables and listings.
- Listings will be checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TFL will be checked for completeness and consistency.

11. PROGRAMMING SPECIFICATIONS

11.1. Format of Appendix Tables/Figures/Listings

1. Unless otherwise specified, all computer-generated tables, figures and listings (TFL) should be produced (via SAS® ODS) into RTF output, which can be imported in table format via Microsoft® Word. The TFLs should be in landscape mode with required margins: at least 1.5 inches on top (the binding margin, or left for portrait output), at least 1 inch on right, left, and bottom. All output should have the following headers on each page:
   - "CONFIDENTIAL" header in the upper center:
   - Two-line header at the upper left margin:

ACORDA THERAPEUTICS, INC.

PROTOCOL No.: *TOZ-CL06*

- Header with a date (time and date output was automatically generated via SAS) and page number at the upper right margin:

  DATE: &SYSTIME &SYSDATE
  PAGE: X of N

TFLs should be internally paginated in relation to total length (i.e., page number should appear sequentially as page X of N, where N is the total number of pages within a table or listing).

2. Each TFL should be identified by in a sequential numeric order, and the TFL designation (e.g., Table 1) should be centered above the title. A decimal system within the numeric numbering (i.e., x.y and x.y.z) should be used to identify TFLs with related contents. The title is centered in initial capital characters and should include the population type analyzed (e.g. Safety Population). The title and designation are single-spaced, but are separated from the TFL by at least a double space.

Table No.

First Line of Title
Second Line of Title (if needed)
Population Type Analyzed

3. Column headings for tables and listings should be in initial upper-case characters.
4. For variables with numeric values, include "unit" in column heading when appropriate.
5. Footnotes should be single spaced, but separated by at least a double space from the bottom line of the TFL. The notes are left justified, with each note starting on a new line. Avoid numeric references, which can be confused with data; rather use asterisks and other non-numeric symbols to refer to footnotes. Patient-specific footnotes should be avoided. The source data set name (and for tables and figures the source listing number) as well as the source SAS program names and locations (with reduced font if necessary) should be displayed as the last footnotes in each TFL. For example the set of footnotes for a table:

   *: Footnote 1
   **: Footnote 2
   Note: Footnote 3
   Source Listing: Listing *X* (*data set name*)
   SOURCE PROGRAM: path\filename

6. All data listings should be sorted by investigator site, patient within investigator site, and study visit date/time within patient where appropriate.
7. For tables that summarize categorical (discrete) data, all categories between the maximum and minimum category should be presented in the table, even if there is zero

entry for a particular category. An Unknown or Missing category should be added to any variables to indicate missing information, if appropriate

Severity Rating	n
Severe	0
Moderate	8
Mild	3
Missing	2

8. 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 patient represented in 1 or more groups should be included.
9. Unless specified otherwise, tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, drug class, or SOC with the highest occurrence in decreasing order. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Specifically, prior and concomitant medications other than Anti-Parkinson's medications should be displayed by therapeutic class and preferred term. Prior and concomitant Anti-Parkinson's medications should be displayed by therapeutic class, chemical/therapeutic/pharmacological subgroup, and preferred term.
10. Unless otherwise specified, the estimated mean and median for a set of values should be printed out to one more decimal place than the original values and rounded appropriately. Standard errors (or standard deviations) should be printed out to two additional decimal places than the original values and rounded appropriately. The range should report the same as the original values. For example, for age (with original value in whole years):

N	xx
Mean	xx.x
S.E.	xx.xx
Median	xx.x
Range	xx-yy

11. All fractional numeric values should be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3).
12. Unless otherwise specified, percentage values should be printed with one digit to the right of the decimal point (e.g., 12.8%, 5.4%). While count and percentage values are presented together, percentage values should be printed in parentheses 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)). Any counts of 0 will be presented as 0 and not as 0 (0%). Unless otherwise noted, for all percentages, the number of patients in the analysis set for the cohort who have an observation will be the denominator.
13. Missing descriptive statistics due to non-estimability in tables, as well as missing data in patient listings should be represented 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.

14. Dates printed as a result in the TFL should be printed in SAS DATE9. format ("DDMONYYYY": 01 Jul 2002). Missing portions of dates should be represented on patient listings as dashes (e.g., -- Jul 99). Dates that are missing because they are not applicable for the patient should be listed as "N/A", unless otherwise specified.
15. All observed time values should be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45, or 11:26).
16. Data in columns of a table should be formatted as follows:
    - Alphanumeric values are left-justified;
    - Whole numbers (e.g., counts) are right-justified; and
    - Numbers containing fractional portions are decimal aligned

12. REFERENCES

1) SAS® Version 9.2, SAS Institute, Cary, NC 27513.

2) Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010).Systematic review of levodopa equivalency reporting in Parkinson's disease. *MovDisord*. 25(15):2649-53.

APPENDIX 1 GLOSSARY OF ABBREVIATIONS

ADaM	Analysis Dataset Model
ADL	Activity of Daily Living
AE	Adverse Event
BMI	Body Mass Index
BID	Twice a Day
CDISC	Clinical Data Interchange Standards Consortium
CGI-S	Clinical Global Impression-Severity
CGI-I	Clinical Global Impression-Improvement
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
FAS	Full Analysis Set
LLQ	Lower Level of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mMIDI	Modified Minnesota Impulsive Disorders Interview
mFAS	Modified Full Analysis Set
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Questionnaire
PGI-I	Patient Global Impression-Improvement
PK	Pharmacokinetics
PT	Preferred Term
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figures and Listings
UPDRS	Unified Parkinson’s Disease Rating Scale
WHODRUG	World Health Organization Drug Dictionary

APPENDIX 2 LEVODOPA EQUIVALENT ALGORITHM

Rules for Levodopa Equivalent

a) Ignore carbidopa – carbidopa does not go into the calculation of LevoEq

Steps:

1. Calculate total immediate release daily Levodopa (note: there are combination drugs containing levodopa and you must separate these out and include in your calculation of daily Levodopa) by multiplying the mg per dose of levodopa by dosing frequency (BID=2, TID=3, QD=4, etc.)
2. Calculate total control release daily Levodopa. Multiply this by 0.75 (to account for loss of bioavailability)
3. Calculate total extended release Levodopa (i.e., Rytary). Multiply this by .60.
4. Add 1) and 2) and 3) to get total daily Levodopa
5. If Entacapone is taken (including combination drugs with Entacapone, i.e., Stalevo), multiply total daily Levodopa in 4) by 0.33.
6. If Tolcapone is taken, multiply total daily Levodopa in 3) by 0.5
7. If Duodopa is taken, multiply the daily mg by 1.11
8. If Pramipexole (as salt) is taken, multiply the daily mg by 100
9. If Ropinirole or RequipXL is taken, multiply the daily mg by 20
10. If Rotigotine is taken, multiply the daily mg by 30
11. If Selegiline – oral is taken, multiply the daily mg by 10
12. If Selegiline – sublingual is taken, multiply the daily mg by 80
13. If Rasagiline is taken, multiply the daily mg by 100
14. If Amantadine is taken, multiply the daily mg by 1
15. If Apomorphine is taken, multiply the daily mg by 10
16. Calculate total LevoEq = 4) + 5) + 6) + 7) + 8) + 9) + 10) + 11) + 12) + 13) + 14) + 15)