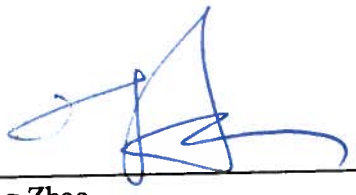
STATISTICAL ANALYSIS PLAN

LA48-0215

A Dose-Ranging Study of the Efficacy, Safety, and Pharmacokinetics of Deferiprone Delayed Release Tablets in Patients with Parkinson's Disease

Final Version 1.0

Prepared by



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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of Variance
AUCss	Area under the concentration-time curve at steady state
CI	Confidence Interval
Cmax	Maximum Concentration
COMT	Catechol O-methyltransferase
C-SSRS	Columbia Suicide Severity Rating Scale
DDFM	Denominator Degrees of Freedom Method
DFP	Deferiprone
DR	Delayed Release
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ITT	Intent-to-treat
KR	Kenward and Roger's method
LOCF	Last Observation Carried Forward
LSM	Least Square Mean
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed-Effect Model Repeated Measure
MOA	Mechanism of Action
MoCA	Montreal Cognitive Assessment
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class

1 Introduction

This document outlines the statistical analysis plan for the efficacy and safety analysis for the clinical trial LA48-0215 sponsored by ApoPharma Inc.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of four different dosages of deferiprone delayed release (deferiprone-DR) tablets in patients with Parkinson's disease

2.2 Secondary Objectives

- To evaluate the safety and tolerability of deferiprone-DR tablets in patients with Parkinson's disease
- To evaluate the pharmacokinetics of deferiprone-DR tablets in a subset of study participants
- To evaluate the relationship between the pharmacokinetics and pharmacodynamics of deferiprone-DR tablets

2.3 Exploratory Objectives

- To determine whether the efficacy responses to deferiprone differ depending on the genotype of certain enzymes that are implicated in Parkinson's disease
- To determine whether the efficacy responses to deferiprone are correlated with ceruloplasmin levels or ceruloplasmin ferroxidase activities

3 Methods

3.1 Study Design and Randomization

This is a multi-center, randomized, double-blind, placebo-controlled, dose-ranging study in 140 patients who had been diagnosed with typical Parkinson's disease within the last 3 years and were taking antiparkinsonian medication at enrollment. Screening was conducted within 30 days prior to the start of dosing. At baseline, eligible participants were randomized to one of four dosage cohorts, and within each cohort were further

randomized in a 4:1 ratio to receive either active product (n=28) or placebo (n=7). Thus, a total of 112 patients received one of the four dosages of deferiprone, and a total of 28 received placebo. The assigned study product was taken twice-daily (b.i.d.), at least 8 hours apart, for 9 months. Dosages were as follows:

- Cohort 1: 300 mg deferiprone delayed release tablets (n=28) or placebo (n=7)
- Cohort 2: 600 mg deferiprone delayed release tablets (n=28) or placebo (n=7)
- Cohort 3: 900 mg deferiprone delayed release tablets (n=28) or placebo (n=7)
- Cohort 4: 1200 mg deferiprone delayed release tablets (n=28) or placebo (n=7)

Patients returned to the site at Months 1, 2, 3, 4, 5, 6, and 9, and received a follow-up telephone call at Month 10. Safety was assessed at each site visit and at the follow-up call; efficacy measures were assessed at baseline and Months 3, 6, and 9; and sparse pharmacokinetics (PK) sampling was done on all patients at baseline and Month 3. In addition, an optional subset of 16 patients underwent extensive blood sampling for PK analysis at Month 1, and an optional subset of 18 patients each provided one sample of cerebrospinal fluid (CSF) for drug level analysis at Month 3. (No selection was done to enroll these subsets: all patients were asked if they were willing to provide either or both of these types of samples, and they were enrolled as they came until the total number of subjects was reached for each subset.) For safety reasons, all patients had their absolute neutrophil count monitored weekly after the start of dosing, at either the study site or a local laboratory. Any patient whose regimen of antiparkinsonian medication was changed, including a change in dosage, would be withdrawn from the trial.

Any patient who withdrew before completing treatment was requested to return within one month for an Early Termination visit, at which time the procedures normally scheduled for the Month 9 visit were conducted.

3.2 Determination of Sample Size and Study Power

There was no formal sample size and power calculation for this Phase II dose-finding study.

3.3 Analysis Populations

Four study populations for analysis are defined: Intent-to-Treat (ITT), Per-Protocol (PP), Safety, and Pharmacokinetics/Pharmacodynamics (PK/PD). For efficacy, all endpoints will be analyzed for the ITT population, which represents the primary analysis population, and the primary efficacy endpoint will additionally be analyzed for the PP population, which represents the secondary analysis population.

ITT Population

The ITT population is defined as all randomized patients who received at least one dose of study drug and havea baseline and at least one post-baseline efficacy assessment for the primary endpoint. All efficacy endpoints will be analyzed for the ITT population.

PP Population

The PP population is defined as all randomized patients who completed the study, have no major protocol violations, and have an efficacy assessment for the primary endpoint at the end of the study. Prior to database lock, protocol violations will be reviewed for their seriousness, and patients with major violations will be excluded from the PP population. The only endpoint that will be analyzed for the PP population is the the primary efficacy endpoint.

Safety Population

The Safety population will include all randomized patients who received at least one dose of study drug.

PK/PD Population

The Pharmacokinetics/Pharmacodynamics (PK/PD) population will include all patients who provided sufficient PK data to derive at least one PK parameter. Detailed analyses on PK assessments will be included in separate statistical analysis plan.

3.4 Interim Analysis

No interim analysis is planned or conducted.

3.5 Missing Data Handling and Derivation Rules

For safety data and PD data, all analyses will be based on observed cases (OC). No imputation will be performed on missing data.

For all efficacy measures but one (time elapsed until rescue medication), when there are missing total scores, missing data will be assumed to be missing at random (MAR). A Mixed-Effect Model Repeated Measure (MMRM) model will be used as the primary analysis method, and the analyses will be based on observed cases. A sensitivity analysis will be conducted for the primary efficacy endpoint, with missing data being imputed as follows. In cases where early termination was due to either worsening of disease conditions or inadequate efficacy of the drug (as documented in the case report form), the "worst score" method will be used to fill in missing data. With this method, for the placebo group, the average change score of the placebo group at a particular visit will be used to impute any missing data at that visit, while for the active group, the worst change score of all patients at that visit will be used. In cases where early termination was due to some other reason, such as a missed visit, the last observation carried forward (LOCF)

method will be used to fill in the missing data. For Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) score, a score will be obtained for each part and a total score will be calculated by adding the score of each part. For each part, one would simply add the score obtained for all questions. If there is a missing answer, the score for this part will be handled as below:

- (A x B) / C = D
- Where:
  - A = sum of all item score recorded in a specific part
  - B = number of total items in a specific part
  - C = number of item with actual score in specific part
  - D = final calculated valid Part score

For example, if a part has 13 items and only 12 items have been rated, one will get the sum of these 12 items, multiply it by 13 and dividing this by 12.

However, for an imputed score to be valid for a specific part, the below maximum of item missed per part cannot be exceeded:

- Part I: max of 2 missing items
- Part II: max of 3 missing items
- Part III: max of 9 missing items
- Part IV: max of 1 missing items

If there are more than the maximum number of item missed in a part, the total score for that part will not be imputed and will be left as missing.

For Montreal Cognitive Assessment (MoCA) test score, the missing component score will be assigned a score of zero by the rater so it is expected the number of missing component score will be minimal. If there is a missing component score, it will be imputed by the LOCF method before the total score is calculated.

Date of exposure will be defined as Day 1 for all duration calculations. For example, age at entry will be calculated as the integer value of the expression:

Floor(date of exposure – date of birth) / 365.25

Time in months will be derived by dividing the time in days by 30.4.

3.6 Statistical Software and Level of Significance

All statistical analyses will be performed using SAS (version 9.3 or higher) on the Windows operating system. The null hypotheses tested are that there is no difference in true parameter between comparison groups, unless otherwise stated. A two-sided p-value of 0.05 will be used as the significance level for the determination of statistical significance in all statistical tests.

4 Statistical Analyses

Data from all patients who were randomized to receive placebo will be combined into one group for the efficacy and safety analyses. Thus, there will be a total of 5 treatment groups: the placebo group and the 300 mg, 600 mg, 900 mg, and 1200 mg deferiprone groups. Descriptive statistics will be used to summarize continuous variables, while frequency and percentage will be presented for each discrete variable. Where applicable, analysis of variance (ANOVA) will be used to compare means, and Fisher's exact test will be used to compare proportions.

As patients may not attend each study visit within the specified time window, efficacy data will be classified into scheduled visits according to the time elapsed from the first dose of medication (date of exposure) to the date of assessment, as follows:

Month 3 visit: 0 to < 4.5 months

Month 6 visit: 4.5 to < 7.5 months

Month 9 visit: 7.5 to < 10.5 months

The calculation of time elapsed from the date of exposure to the date of assessment is done as follows:

Time elapsed = (date of sample assessment) – (date of exposure) +1

The resulting time elapsed will be expressed in months. If this results in overlap in visits, the average value of the same visits will be used in the analysis.

For all continuous efficacy outcomes except for time elapsed until rescue medication (addressed below), a Mixed-Effect Model Repeated Measure (MMRM) model will be used as the primary analysis method to assess the effect of deferiprone on change from baseline to Month 9. The MMRM model will include the baseline value of the outcome as a covariate and treatment group and visit as the main factors. Baseline value is the value collected the closest prior to baseline visit.

The MIXED procedure in SAS will be used for the MMRM model analysis. Data from each patient at different visits will be considered repeated measures. A first-order

autoregressive (AR) covariance structure will be used to model the correlation between repeated measures within the same patient, and Kenward and Roger's method will be used to estimate the denominator degrees of freedom (DDFM). The Least Square Mean (LSM) and 95% confidence interval (CI) of the LSM difference will be calculated by the LSMEANS statement.

A sample SAS code for the MMRM model is shown in the box below:

```
proc mixed;
  class TREAT USUBJID VISIT;
  model CHG=TREAT VISIT TREAT*VISIT BASE/solution ddfm=kr;
  repeated VISIT/ subject=USUBJID type=ar(1);
  lsmeans TREAT*VISIT / diff cl;
run;
```

where TREAT is the discrete variable for treatment group, USUBJID represents the patient ID, VISIT is the discrete variable representing the scheduled study visit after the baseline visit, CHG is the change in value of efficacy outcome from baseline to the scheduled visit, and BASE is the baseline value of efficacy outcome.

If the treatment effect is found to be statistically significant, each deferiprone group will be compared to the placebo group to assess the treatment effect at each deferiprone dose level using the SAS code for MMRM model as presented above. Linear regression analysis will be employed to assess the dose-response relationship through a linear regression model, with the change at the study end as the dependent variable and the treatment dose as the continuous variable. If a statistically significant relationship exists between deferiprone dose and an efficacy outcome, the dose-response relationship will be further assessed and reported through pairwise comparison of each dose level to the next lower dose level: 1200 mg vs. 900 mg, 900 mg vs. 600 mg, and 600 mg vs. 300 mg, using the MMRM model SAS code as presented above.

For the analysis of time elapsed until the need for rescue medication, a time to event analysis using the Kaplan-Meier survival curve will be performed and the log-rank test will be used to compare the treatment groups. The LIFETEST procedure in SAS will be used to perform this analysis.

4.1 Patient Disposition and Drug Exposure

Patient disposition, based on the Safety population, will be summarized descriptively. Data will include the numbers and percentages of patients who were screened, enrolled, completed the study, and withdrawn (including reasons for withdrawals).

For each patient, the number of doses taken will be computed from the study drug dispensing and accountability eCRFs obtained at each visit. The extent of exposure to study medication, as well as compliance during the study, will be summarized with descriptive statistics.

The number of exposed patients at each study site will be presented by treatment group, and the number of subjects included in each population will be tabulated by treatment group.

4.2 Patient Characteristics

Baseline characteristics will be summarized by mean, standard deviation (SD), median, and minimum and maximum values, for the ITT, PP and the Safety populations. Medical history and prior medications will be summarized descriptively as number of patients and percentage.

4.2.1 Demographics

Demographic data (age, sex, ethnicity, and race) will be summarized by treatment group.

4.2.2 Medical History

Medical history on current and historical diagnoses and co-morbidities will be coded using the preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA), and will be summarized by treatment group.

4.2.3 Prior Medications

Prior medication use will be summarized by treatment group.

4.3 Efficacy Analyses

4.3.1 Primary Efficacy Endpoint

The primary endpoint is the change from baseline to Month 9 in score on the motor examination subscale (Part III) of the MDS-UPDRS. For a detailed definition, see Section 7.1.1 of the study protocol.

The primary efficacy endpoint will be analyzed based on the ITT population. The analysis will be repeated for the PP population as a sensitivity analysis.

The data on the change in Part III score of the MDS-UPDRS from baseline to Month 9 will be summarized by treatment group. The MMRM model will be used to compare the change in score among treatment groups.

4.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed below. For detailed definitions, see Section 7.1.2 of the study protocol.

- Change from baseline to Month 9 in total score on the MDS-UPDRS
- Change from baseline to Month 9 in scores on the individual subscales of the MDS-UPDRS: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), and Part IV (motor complications)
- Change from baseline to Month 9 in the combined scores from Parts II and III of the MDS-UPDRS
- Change from baseline to Month 9 in overall cognitive function, as assessed by the Montreal Cognitive Assessment (MoCA) test
- Change from baseline to Month 9 in pharmacodynamics measures of the following oxidative stress biomarkers: total antioxidant status, lipid peroxidation (malondialdehyde), protein carbonyls, 8-OHdG, glutathione, superoxide dismutase
- Change from baseline to Month 9 in pharmacodynamics measures of the following inflammatory factor biomarkers: TNF alpha and IL-6
- Time elapsed until the need for rescue medication

The secondary efficacy endpoints will be analyzed based on the ITT population only.

The data on the changes from baseline to Month 9 in the MDS-UPDRS total score, the Parts I, II, and IV subscale scores, the combined Part II and Part III score, and the MoCA score will be summarized by treatment group. The MMRM model will be used to compare the change in each score between treatment groups.

The data on the changes from baseline to Month 9 in oxidative stress biomarkers and inflammatory factor biomarkers will be summarized by treatment group.

The time elapsed until the need for rescue medication will be presented using the Kaplan-Meier survival curve, and will be compared among the treatment groups using the log-rank test.

4.3.3 Exploratory Efficacy Endpoints

The exploratory objectives of this study are to evaluate whether the potential disease-modifying action of deferiprone is correlated with 1) specific genotypes of enzymes that play a role in Parkinson's disease, and 2) the degree of change from baseline in ceruloplasmin levels and ceruloplasmin ferroxidase activity. The Mechanism of Action (MOA) biomarkers that will be examined are listed below. For detailed definitions, see Section 7.1.3 of the study protocol.

The biomarkers are:

- D544E polymorphisms of the glycoprotein ceruloplasmin
- V158M polymorphisms of the enzyme catechol O-methyltransferase (COMT)
- Ceruloplasmin levels (to be analyzed depending on the outcomes of the primary and/or secondary efficacy endpoints)
- Ceruloplasmin ferroxidase activity (to be analyzed depending on the outcomes of the primary and/or secondary efficacy endpoints)

To evaluate the impact of the D544E and V158M genotypes on the treatment effect of deferiprone in Parkinson's disease, subgroup analyses of the data from the two genotypes will be done based on the MMRM analysis performed on the primary endpoint (change from baseline to Month 9 on the Part III score of the MDS-UPDRS), using the ITT population. If there is a treatment effect on the score from other parts of MDS-UPDRS, this analysis will be repeated for those outcomes as well. For details, see Section 4.3.4.

If there is evidence of efficacy based on the primary and/or secondary efficacy endpoints, the data on the change from baseline to Month 9 in ceruloplasmin level and ceruloplasmin ferroxidase activity will be summarized by treatment group. The MMRM model will be used to compare the change in these two biomarkers between treatment groups. Correlation analysis between the change and the primary efficacy endpoint will be performed for each biomarker. These two variables will also be included in the main MMRM model for the primary endpoint, in order to study the relationship between these two MOA biomarkers and the effect of deferiprone.

Correlation analysis of the PD endpoints (change from baseline to Month 9 for biomarkers of interest) and the PK parameters ($AUC_{0-\infty}$ and Cmax) will be performed if efficacy is evidenced. This analysis will be performed for the PK/PD population.

4.3.4 Exploratory Analyses/Sensitivity Analysis

If there are unevenly distributed baseline factors among the treatment groups, the effects of those factors on the efficacy measurements will be examined by including them in the MMRM model.

Subgroup analyses will be performed for the ITT population on the following factors: D544E genotype (Aspartate/Aspartate vs. Aspartate/Glutamate) and V158M genotype (Methionine/Methionine vs. Valine/Methionine vs. Valine/Valine). For D544E genotype, Aspartate/Aspartate corresponds to the high metabolizer phenotype (AA) and Aspartate/Glutamate to the low metabolizer phenotype (AT). For the V158M genotypes, the corresponding phenotypes are High COMT Activity, Intermediate COMT Activity, and Low COMT Activity. The analysis results will be presented by the phenotypes for each factor.

Besides analysis for the ITT population, the primary efficacy endpoint will also be analyzed for the PP population as sensitivity analyses.

As a sensitivity analysis, the efficacy data will be re-analyzed with the missing data being imputed as described in section 3.5. The sensitivity analysis will be performed only on the primary efficacy endpoint using the ITT population.

If the blinded review of the efficacy data performed before the breaking of the treatment codes indicates a severe non-normality of the data, an appropriate transformation (for example, log transformation) will be applied to the data, or nonparametric statistical methods based on ranks will be employed, if warranted.

Other exploratory analyses may be performed after examining the planned analyses if they are considered interesting and necessary.

4.4 Safety Analyses

The safety endpoints are listed below. For detailed definitions, see Section 7.2 of the study protocol.Adverse events (AEs)

- Serious adverse events (SAEs)
- Number of discontinuations due to AEs
- Laboratory measures (hematology, blood chemistry, and urinalysis)
- ECG
- Change from baseline in vital signs

- Physical examination
- Assessment of suicidality (as per the Columbia Suicide Severity Rating Scale, C-SSRS)

All safety data collected will be presented in listings and summary tables or graphs to give an overview of the findings. All safety endpoints will be analyzed based on the Safety population.

For laboratory findings, since patients may not attend each study visit within the scheduled time window or may withdraw early, data will be classified into visits according to the time elapsed from the first dose of study medication (date of exposure) to the date of assessment. For biochemistry, the following time windows will be employed:

Month 1 visit: 0 to <1.5 months

Month 2 visit: 1.5 to <2.5 months

Month 3 visit: 2.5 to <3.5 months

Month 4 visit: 3.5 to <4.5 months

Month 5 visit: 4.5 to <5.5 months

Month 6 visit: 5.5 to <7.5 months

Month 9 visit: 7.5 to <10 months

For the weekly hematology visits, data will be classified using half-weeks:

Week 1 visit: 0 to <1.5 weeks

Week 2 visit: 1.5 to <2.5 weeks

….

For other measurements that fall on the same scheduled visits as the efficacy outcomes, such as urinalysis, the rule defined for efficacy outcomes in the beginning of Section 4 will apply.

4.4.1 Adverse Events

A summary table of adverse events by treatment group will include the following information:

- Number of patients exposed to study treatment
- Number of patients experiencing at least one AE
- Number of patients experiencing at least one severe AE
- Number of patients experiencing at least one serious AE
- Number of patients experiencing at least one drug-related AE
- Number of deaths
- Total number of patients withdrawn
- Number of withdrawals due to AEs

Untoward medical occurrences, whether new events or the worsening of severity or frequency of pre-existing conditions, will be coded using MedDRA , and summarized by treatment and by system organ class (SOC) and preferred term (PT). An event will be considered an AE if 1) its start date is on or after the date of the first dose of study medication, 2) the start date is missing and the stop date is on or after the date of the first dose of study medication, or 3) both the start and the stop dates are missing. SAEs that begin within 30 days after the last dose of study medication, and both SAEs and non-serious AEs that are still ongoing for up to 30 days after the last dose, will be included in the database.

Adverse events will be summarized using the total number of events, the total number and percent of patients who experience an AE, and the number and percent of patients who experienced an AE within each SOC (and each PT within an SOC). AEs will also be presented by intensity (mild, moderate, severe), by seriousness (serious, non-serious) and by relationship to study medication (at least possibly related, not related). The number of patients withdrawn and the reasons for withdrawal will also be presented.

To count the number of patients who experienced each AE, a patient who experienced the same AE multiple times will be counted only once for the corresponding preferred term. Similarly, a patient who experienced multiple AEs within the same SOC will be counted only once for that SOC. AEs will be tabulated by presenting the SOCs alphabetically, and within each SOC, the preferred terms will be presented in decreasing order of the total number of patients who experienced each one. In summaries presenting the incidence of AEs by severity, seriousness, and relation to study medication, patients with multiple events coded to a given PT or SOC will be counted only once for that PT or SOC according to the most severe event, the most serious event, or the event with the closest relationship to study medication.

Listing of SAEs and listing of withdrawals due to AEs will be presented. Patient deaths will be listed separately and will be described in narratives.

4.4.2 Vital Signs and Weight

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented at each visit for supine and standing heart rate, supine and standing blood pressure, and weight. Data will also be presented graphically, for examination of possible trends. Change from baseline in these measures (for orthostatic vital signs, the baseline values will be the average of the three sets collected) will be assessed.

4.4.3 12-Lead ECG

The number and percentage of patients with normal and abnormal ECG results will be provided. Descriptive statistics will be presented for HR, PR, QRS, QT, QTcF, and QTcB.

4.4.4 Biochemistry, Hematology and Urinalysis

Descriptive statistics for each clinical laboratory test will be presented for each scheduled visit. For each test, if multiple measurements are taken on the same visit for a patient, the average value will be used. Using the laboratory's normal ranges, the results will be categorized as low (< lower normal limit), normal (within normal range), or high (> upper normal limit). Shift tables comparing the distributions of these three categories at baseline versus end of treatment will be presented.

Continuous data will also be presented graphically, for examination of possible trends.

Clinically significant abnormalities in laboratory values will be included in the analyses of adverse events.

4.4.5 Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary. Medications taken during the course of the trial (on or after the first study drug dose and before or on the date of study termination will be considered to be concomitant medications. Medications started after the study termination date will not be reported in tables, but will be presented in patient data listings. Concomitant medications that were used to treat adverse events will be differentiated from others.

Concomitant medications will be summarized according to preferred names only. To count the number of patients who took each type of medication, a patient who took the same medication multiple times will be counted only once for that medication. Medications will be tabulated in decreasing order of the total number of patients who took each one. In addition, the total number of patients to ever take any concomitant medications will be presented.

Concomitant medications will be presented based on the Safety population.

4.4.6 Suicidality

The Columbia Suicide Severity Rating Scale (C-SSRS) is an instrument used to measure suicidal ideation and behavior. For each treatment group, descriptive statistics (frequency and percentage) will be presented for any suicidal ideation and behavior reported by patients at each visit.

4.4.7 Treatment Compliance

Compliance will be determined as follows: 1) patients will use the daily diary card to record the number of tablets taken, and 2) at each visit, the investigator or a delegate will inspect the medication containers, whether empty, partly used, or unopened, and will check the number of tablets remaining. Compliance will be calculated by the number of tablets taken divided by the number prescribed, as per the dosing frequency and length of treatment. Compliance at each follow-up visit will be summarized descriptively by treatment group in a table.

5 Listing of Tables and Figures

The summary tables and figures that will be produced based on the statistical analyses detailed in this document are listed bleow. All tables and figures will be presented by treatment group. Tables and figures are numbered following ICH structure, but the final numberings that appear in the clinical study report may be changed if more tables and/or figures are added. The standards used to compile the clinical data will be based on the Study Data Tabulation Model v1.4, SDTM implementation guide v 3.2 as well as controlled terminology v 2017-06-30 from the Clinical Data Interchange Standards Consortium (CDISC). Tables, listings and figures will be programmed using data from the SDTM datasets.

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Figure 14.2.1.3 Mean line graph for MDS-UPDRS Part I over visit – ITT population
Figure 14.2.1.4 Mean line graph for MDS-UPDRS Part II over visit – ITT population
Figure 14.2.1.5 Mean line graph for MDS-UPDRS Part IV over visit – ITT population
Figure 14.2.1.6 Mean line graph for MDS-UPDRS Part II/Part III over visit – ITT population
Figure 14.2.1.7 Mean line graph for MoCA over visit – ITT population
Figure 14.2.1.8 Mean line graph for Total Antioxidant Status over visit – ITT population
Figure 14.2.1.9 Mean line graph for Lipid Peroxidation over visit – ITT population
Figure 14.2.1.10 Mean line graph for Protein Carbonyls over visit – ITT population
Figure 14.2.1.11 Mean line graph for 8-OHdG over visit – ITT population
Figure 14.2.1.12 Mean line graph for Glutathione over visit – ITT population
Figure 14.2.1.13 Mean line graph for Superoxide Dismutase over visit – ITT population
Figure 14.2.1.14 Mean line graph for TNF Alpha over visit – ITT population
Figure 14.2.1.15 Mean line graph for IL-6 over visit – ITT population
Figure 14.2.2.1 Kaplan-Meier survival curve for the time to the need for rescue medication

14.3 Safety

14.3.1 Hematology

Figure 14.3.1.1 Mean line graph for hemoglobin over visit – safety population
Figure 14.3.1.2 Mean line graph for total white blood cell (WBC) count over visit – safety population
Figure 14.3.1.3 Mean line graph for absolute neutrophil count (ANC) over visit – safety population
Figure 14.3.1.4 Mean line graph for platelets over visit – safety population
Figure 14.3.1.5 Mean line graph for mean corpuscular volume (MCV) over visit – safety population

14.3.2 Biochemistry

Figure 14.3.2.1 Mean line graph for serum ferritin over visit – safety population

6 Data Listings

Data listings are numbered following ICH structure. The final numberings for subject data listings in the clinical study report can be changed if more subject data listings are made in the addition to those in the SAP. Collected data have been mapped to SDTM compliant terminology. Randomized subjects who received at least one dose of study drug are included in the listings.

16.2 Subject Data Listings

16.2.1 Subject Disposition

16.2.1.1 Listing of Screening Failures
16.2.1.2 Listing of Disposition

16.2.2 Protocol Deviations

16.2.2.1 Listing of Protocol Deviations

16.2.3 Subjects Excluded from the Efficacy Analysis

16.2.3.1 Listing of Randomization
16.2.3.2 Assignment of Subjects to Analysis Sets

16.2.4 Demographic Data and Medical History

16.2.4.1 Listing of Informed Consent Form
16.2.4.2 Listing of Demographics
16.2.4.3 Listing of Parkinson's Disease Diagnosis
16.2.4.4 Listing of Physical Exam
16.2.4.5 Listing of Medical History

16.2.5 Compliance and/or Drug Concentration Data

16.2.5.1 Listing of Compliance
16.2.5.2 Listing of Exposure
16.2.5.3 Listing of Changes to Exposure

16.2.6 Efficacy Data

16.2.6.1 Listing of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores
16.2.6.2 Listing of Montreal-Cognitive Assessment (MoCA)

16.2.7 Adverse Events Listing

16.2.7.1 Listing of Medical Events
16.2.7.2 Listing of Adverse Events
16.2.7.3 Listing of Adverse Drug Reactions
16.2.7.4 Listing of Serious Adverse Events
16.2.7.5 Listing of Serious Adverse Drug Reactions
16.2.7.6 Listing of Withdrawals due to AEs

16.2.8 Listing of Individual Laboratory Measurements by Subjects

16.2.8.1 Listing of Hematology
16.2.8.2 Listing of Biochemistry
16.2.8.3 Listing of Urinalysis
16.2.8.4 Listing of Pregnancy Test
16.2.8.5 Listing of Oxidative Stress Biomarkers
16.2.8.6 Listing of Inflammatory Factor Biomarkers

16.2.9 Other Listings

16.2.9.1 Listing of Vital Signs
16.2.9.2 Listing of Height and Weight
16.2.9.3 Listing of Concomitant Medications
16.2.9.4 Listing of Concomitant Medications to treat adverse events
16.2.9.5 Listing of Medications started after the study termination date
16.2.9.6 Listing of Columbia Suicide Severity Rating Scale (C-SSRS)
16.2.9.7 Listing of Telephone Contacts
16.2.9.8 Listing of Bottle Numbers
16.2.9.9 Listing of PK Assessment - Informed Consent Form
16.2.9.10 Listing of PK Assessment
16.2.9.11 Listing of 12-Lead ECGs

7 Table Shells

The table shells shown below provide a framework for the display of data in this study. The final tables may not be designed exactly as shown here, but the shells are intended to reflect the general layout of the data that will be included in the clinical study report.

- For descriptive statistics except observation number n, one more decimal place than in the raw data will be presented, and all percentages will be presented with one decimal point unless presented differently in the actual table.
- Note that 'c' in the table shells indicates an alphanumeric character, while 'x' indicates a number from 0 to 9.
- The analysis population is indicated at the end of the table title.
- For tables that are repeated for different populations, those for the PP population will have an 'a' added to the table number, those for the Safety population will have a 'b' added, and those repeated as a sensitivity analysis will have an 's' added: i.e., Table 14.x.x for the ITT population, Table 14.x.xa for the PP population, Table 14.x.xb for the Safety population, and Table 14.x.xs for the sensitivity analysis.

Disposition tables

Table 14.1.1 Number of patients in different populations

Population	Placebo	300 mg	600 mg	900 mg	1200 mg	Overall
ITT	xx	xx	xx	xx	xx	xx
PP	xx	xx	xx	xx	xx	xx
Safety	xx	xx	xx	xx	xx	xx
PK/PD	xx	xx	xx	xx	xx	xx

Table 14.1.2 Subject disposition – Safety population

	Screened= xx					
n (%)	Placebo	300 mg	600 mg	900 mg	1200 mg	Overall
Randomized	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Exposed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawn	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 14.1.3 Subject exposure to study medication – Safety population

	Group					
	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)	Overall (N=xx)
Subjects Exposed	xx	xx	xx	xx	xx	xx
Total Exposure (person-years)	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x	xxx.x
Length of Exposure (years)						
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
(Min, Max)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)

Table 14.1.4 Number of patients enrolled by study site – Safety population

Country	Site	Group					
		Placebo	300 mg	600 mg	900 mg	1200 mg	Overall
Xxx	000x	xx	xx	xx	xx	xx	xx
…	…	xx	xx	xx	xx	xx	xx
Total	x	xx	xx	xx	xx	xx	xx

Table 14.1.5 Summary of the reasons for not completing the study – Safety population

		Group				
		Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Reason	Detail	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse event	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Voluntary withdrawal	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow up	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator decision	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol deviation	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Rescue medication used	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of efficacy/ worsening of the disease	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Ccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Demographics and baseline characteristics tables

Table 14.1.6 Summary of demographics data at baseline – ITT population

	Group						
	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)	Overall (N=xx)	*p*-value§
Age (years) (Mean ± SD) (Minimum, Median, Maximum)	xx.x ± xx.x (xx, xx, xx)	xx.x ± xx.x (xx, xx, xx)	xx.x ± xx.x (xx, xx, xx)	xx.x ± xx.x (xx, xx, xx)	xx.x ± xx.x (xx, xx, xx)	xx.x ± xx.x (xx, xx, xx)	0.xxxx
Sex: n (%)							0.xxxx
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Racial Origin: n (%)							0.xxxx
White	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Black	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Native American	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Multi-Racial	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Ethnic Origin: n (%)							0.xxxx
Hispanic/Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	

§ ANOVA for means and Fisher's exact test for percentages
Similar Table 14.1.6a will be based on PP population
Similar Table 14.1.6b will be based on Safety population

Table 14.1.7 Summary of baseline characteristics – ITT population

				Group			
	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)	Overall (N=xx)	*p*-value[§]
MDS-UPDRS Part III							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
MDS-UPDRS Total Score							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
MDS-UPDRS Part I							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
MDS-UPDRS Part II							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
MDS-UPDRS Part IV							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	

MDS-UPDRS Part II/Part III							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
MoCA							0.xxxx
n	xx	xx	xx	xx	xx	xx	
(Mean ± SD)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	
(Minimum, Maximum)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	

§ ANOVA

Similar Table 14.1.7a will be based on PP population

Table 14.1.8 Medical History – Safety population

	Group					
	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)	Overall (N=xx)
Illness/Event by MedDRA Primary System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
cccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
cccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 14.1.9 Prior Medication – Safety population

	Group					
	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)	Overall (N=xx)
Drug Name	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)
Preferred Name	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cccccc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Efficacy outcomes tables

Table 14.2.1.1 Change in MDS-UPDRS Part III score at each follow-up visit – ITT population

	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
MDS-UPDRS Part III score n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 3	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 6	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)

Similar Table 14.2.1.1a will be based on PP population

Table 14.2.1.2 Primary outcome least square mean (LSM) change from baseline to month 9 from MMRM model – ITT population

Outcome	Placebo (N=xx)	300 mg (N=xx)	300 mg - Placebo LSM (95% CI) p-value	600 mg (N=xx)	600 mg - Placebo LSM (95% CI) p-value	900 mg (N=xx)	900 mg - Placebo LSM (95% CI) p-value	1200 mg (N=xx)	1200 mg - Placebo LSM (95% CI) p-value
MDS-UPDRS Part III score LSM (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx

Similar Table 14.2.1.2a will be based on PP population
Similar Table 14.2.1.2s will be based on sensitivity analysis population (ITT with missing data imputation)

Similar Tables 14.2.1.2.1 and 14.2.1.2.2 will be based on ITT population and D544E polymorphisms (AA vs. AT)
Similar Tables 14.2.1.2.3, 14.2.1.2.4 and 14.2.1.2.5 will be based on ITT population and V158M polymorphisms (High vs. Intermediate vs. Low COMT Activity)

Table 14.2.1.3 Dose-response assessment for all efficacy outcomes by linear regression model – ITT population

Dependent variable	Regression Slope	P - value
MDS-UPDRS Part III score	x.xx	0.xxxxx
Repeat for other secondary and exploratory efficacy endpoints	....	....

Table 14.2.1.4 Primary outcome least square mean (LSM) change from baseline to month 9 from MMRM model 2 – ITT population

Outcome	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	600 mg – 300 mg LSM (95% CI) p-value	900 mg (N=xx)	900 mg – 600 mg LSM (95% CI) p-value	1200 mg (N=xx)	1200 mg – 900 mg LSM (95% CI) p-value
MDS-UPDRS Part III score LSM (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx

Note: only produced when there is a significant dose-response relationship in treatment effect

Table 14.2.2.1 Change in other MDS-UPDRS scores and MoCA at each follow-up visit – ITT population

	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
MDS-UPDRS Total score n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 3	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 6	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
Repeat for MDS-UPDRS Part I, II, IV and sum of Part II/III score and MoCA	…	…	…	…	…	…

Table 14.2.2.2 Change in oxidative stress biomarkers at each follow-up visit – ITT population

	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Total Antioxidant Status n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 3	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 6	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
Repeat for Lipid Peroxidation, Protein Carbonyls, 8-OHdG, Glutathione, and Superoxide Dismutase	…	…	…	…	…	…

Table 14.2.2.3 Change in inflammatory factor biomarkers at each follow-up visit – ITT population

	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
TNF Alpha n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 3	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 6	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
Repeat for IL-6	…	…	…	…	…	…

Table 14.2.2.4 Secondary outcomes least square mean (LSM) change from baseline to month 9 from MMRM model – ITT population

Outcome	Placebo (N=xx)	300 mg (N=xx)	300 mg - Placebo LSM (95% CI) p-value	600 mg (N=xx)	600 mg - Placebo LSM (95% CI) p-value	900 mg (N=xx)	900 mg - Placebo LSM (95% CI) p-value	1200 mg (N=xx)	1200 mg - Placebo LSM (95% CI) p-value
MDS-UPDRS Total score LSM (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx
Repeat for MDS-UPDRS Part I, II, IV and sum of Part II/III score and MoCA	…	…	…	…	…	…	…	…	…

Table 14.2.2.5 Secondary outcomes least square mean (LSM) change from baseline to month 9 from MMRM model 2 – ITT population

Outcome	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	600 mg – 300 mg LSM (95% CI) p-value	900 mg (N=xx)	900 mg – 600 mg LSM (95% CI) p-value	1200 mg (N=xx)	1200 mg – 900 mg LSM (95% CI) p-value
MDS-UPDRS Total score LSM (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx
Repeat for MDS-UPDRS Part I, II, IV and sum of Part II/III score and MoCA	...	...	...	...	...	...	...	...

Note: only produced when there is a significant dose-response relationship in treatment effect

Table 14.2.3.1 Change in MOA biomarkers at each follow-up visit – ITT population

	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Ceruloplasmin n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 3	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 6	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Change at Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
Repeat for Ceruloplasmin ferroxidase activity	…	…	…	…	…	…

Note: only produced if efficacy is evidenced

Table 14.2.3.2 MOA biomarkers least square mean (LSM) change from baseline to month 9 from MMRM model – ITT population

Outcome	Placebo (N=xx)	300 mg (N=xx)	300 mg - Placebo LSM (95% CI) p-value	600 mg (N=xx)	600 mg - Placebo LSM (95% CI) p-value	900 mg (N=xx)	900 mg - Placebo LSM (95% CI) p-value	1200 mg (N=xx)	1200 mg - Placebo LSM (95% CI) p-value
Ceruloplasmin LSM (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx
Repeat for Ceruloplasmin ferroxidase activity	…	…	…	…	…	…	…	…	…

Note: only produced if efficacy is evidenced

Table 14.2.3.3 MOA biomarkers least square mean (LSM) change from baseline to month 9 from MMRM model 2 – ITT population

Outcome	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	600 mg – 300 mg LSM (95% CI) p-value	900 mg (N=xx)	900 mg – 600 mg LSM (95% CI) p-value	1200 mg (N=xx)	1200 mg – 900 mg LSM (95% CI) p-value
Ceruloplasmin LSM (SE)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx	xx.x (xx.x)	xx.x (xx.x, xx.x) 0.xxxx
Repeat for Ceruloplasmin ferroxidase activity	…	…	…	…	…	…	…	…

Note: only produced if efficacy is evidenced and when there is a significant dose-response relationship in treatment effect

Safety outcomes tables

Table 14.3.1.1 Overall summary of adverse events – safety population

	Treatment Group				
	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Number of subjects with at least one AE	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of subjects with at least one SAE	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of subjects with at least one severe AE	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of subjects with at least one ADR	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of deaths	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of subject withdrawn	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of subject withdrawals due to AE	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Table 14.3.1.2 Summary of adverse events – safety population

	Placebo		300 mg		*Repeat for 600 mg, 900 mg, and 1200 mg*	
	Exposure (subject-years): x.xx		Exposure (subject-years): x.xx		Exposure (subject-years): x.xx	
	Total Subjects Exposed: xx		Total Subjects Exposed: xx		Total Subjects Exposed: xx	
	Total Events: xxx		Total Events: xxx		Total Events: xxx	
	Total Subjects Reporting: xx (xx%)		Total Subjects Reporting: xx (xx%)		Total Subjects Reporting: xx (xx%)	
System Organ Class Preferred Term	N Subjects (%)	N Events (Rate/100 patient years)	N Subjects (%)	N Events (Rate/100 patient years)	N Subjects (%)	N Events (Rate/100 patient years)
CCCCCC	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)
Cccccc	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)
Cccccc	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)
Cccccc	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)
……..	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)	x (x.x)	x (x.xx)

Table 14.3.1.3 All adverse events by severity – safety population

	Placebo (N = xx)			300 mg (N = xx)			*Repeat for 600 mg, 900 mg, and 1200 mg*		
	Mild	Moderate	Mild	Moderate	Severe	Severe	Mild	Moderate	Severe
Any Adverse Event	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
System Organ Class 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Continue for all SOC and PTs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
SOCs and Preferred terms sorted alphabetically	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Table 14.3.1.4 All adverse events by seriousness – safety population

	Placebo (N = xx)		300 mg (N = xx)		*Repeat for 600 mg, 900 mg, and 1200 mg*	
	Non-serious	Serious	Non-serious	Serious	Non-serious	Serious
Any Adverse Event	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
System Organ Class 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Continue for all SOC and PTs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
SOCs and Preferred terms sorted alphabetically	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Table 14.3.1.5 All adverse events by relatedness to study medication – safety population

	Placebo (N = xx)		300 mg (N = xx)		*Repeat for 600 mg, 900 mg, and 1200 mg* (N = xx)	
	Related	Unrelated	Related	Unrelated	Related	Unrelated
Any Adverse Event	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
System Organ Class 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Preferred Term 1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Continue for all SOC and PTs	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
SOCs and Preferred terms sorted alphabetically	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Table 14.3.1.6 Summary of most common (>5%) adverse drug reactions – safety population

	Placebo (N = xx)			300 mg (N = xx)			*Repeat for 600 mg, 900 mg, and 1200 mg* (N = xx)		
	n (%)	Time to onset (Days) Mean (SD) Median (Min, Max)	Duration (Days) Mean (SD) Median (Min, Max)	n (%)	Time to onset (Days) Mean (SD) Median (Min, Max)	Duration (Days) Mean (SD) Median (Min, Max)	n (%)	Time to onset (Days) Mean (SD) Median (Min, Max)	Duration (Days) Mean (SD) Median (Min, Max)
Any Adverse Event	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)
System Organ Class 1	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)
Preferred Term 1	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)
Continue for all SOC and PTs	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)
SOCs and Preferred terms sorted alphabetically	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx (xx%)	xx.xx (xx.x) xx.x (xx.x, xx.x)	xx.xx (xx.x) xx.x (xx.x, xx.x)

Table 14.3.2.1.1 Hematology at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Hemoglobin (g/L) n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 1	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 2	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Repeat for Month 3, 4, 5, 6 and 9 visits	…	…	…	…	…
Repeat for other hematology parameters	…	…	…	…	…	…

Table 14.3.2.1.2 Shift table comparing three laboratory value categories at baseline and end of study: Hematology – safety population

Laboratory Test	Treatment	Baseline	End of study			Total
			Low	Normal	High	
Hemoglobin	Placebo	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	300 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	600 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	900 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	1200 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
Repeat for other tests of interest						

Table 14.3.2.2.1 Blood biochemistry at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Zinc (g/L) n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 1	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 2	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Repeat for Month 3, 4, 5, 6 and 9 visits	…	…	…	…	…
Repeat for other biochemistry parameters	…	…	…	…	…	…

Table 14.3.2.2.2 Shift table comparing three laboratory value categories at baseline and end of study: Blood biochemistry – safety population

Laboratory Test	Treatment	Baseline	End of study			Total
			Low	Normal	High	
Zinc	Placebo	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	300 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	600 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	900 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
	1200 mg	Low	xx	xx	xx	xx
		Normal	xx	xx	xx	xx
		High	xx	xx	xx	xx
		Total	xx	xx	xx	xx
Repeat for other tests of interest						

Table 14.3.2.3.1 Proportions of abnormal urinalysis results in each visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Abnormal Urinalysis n Abnormal (n (%))	Baseline	xx xx (xx.x)	xx xx (xx.x)	xx xx (xx.x)	xx xx (xx.x)	xx xx (xx.x)
	Month 3	xx xx (xx.x)	xx xx (xx.x)	xx xx (xx.x)	xx xx (xx.x)	xx xx (xx.x)
	Repeat for Month 6 and 9 visits	…	…	…	…	…

Table 14.3.3.1 Summary of vital signs at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Supine Heart Rate n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 1	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 2	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Repeat for Month 3, 4, 5, 6 and 9 visits	…	…	…	…	…
Repeat for standing heart rate, supine and standing blood pressure	…	…	…	…	…	…

Table 14.3.3.2 Change of vital signs from baseline at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Change in Supine Heart Rate n Mean (SD) Median (Min, Max) *p*-value	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 1	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx
	Month 2	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx
	Repeat for Month 3, 4, 5, 6 and 9 visits	…	…	…	…	…
Repeat for standing heart rate, supine and standing blood pressure	…	…	…	…	…	…

Table 14.3.3.3 Summary of weight at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Weight n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)

Table 14.3.3.4 Change of weight from baseline at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Change in weight n Mean (SD) Median (Min, Max) *p*-value	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx	xx xx.x (xx.x) xx.x (xx.x, xx.x) 0.xxxx

Table 14.3.4.1 Summary of 12-lead ECG parameters at each follow-up visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Heart Rate (bpm) n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 9	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
Repeat for PR Interval, QRS Interval, QT Interval, QTcB Interval,and QTcF Interval	…	…	…	…	…	…

Table 14.3.4.2 Proportions of normal and abnormal ECG results in each visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
ECG n Abnormal (n (%)) Normal (n (%))	Baseline	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)
	Month 9	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)

Table 14.3.5.1 Treatment compliance (%) by visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
Compliance (%) n Mean (SD) Median (Min, Max)	Baseline	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 1	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Month 2	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)	xx xx.x (xx.x) xx.x (xx.x, xx.x)
	Repeat for Month 3, 4, 5, 6 and 9 visits	…	…	…	…	…

Table 14.3.6.1 Concomitant Medications – safety population

	Placebo	300 mg	600 mg	900 mg	1200 mg
	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx
	Total Subjects Exposed: xx	Total Subjects Exposed: xx	Total Subjects Exposed: xx	Total Subjects Exposed: xx	Total Subjects Exposed: xx
	Total Subjects Reporting: xx	Total Subjects Reporting: xx	Total Subjects Reporting: xx	Total Subjects Reporting: xx	Total Subjects Reporting: xx
Drug Name					
Preferred Name	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)
Cccccc	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Cccccc	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
……..	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)

Table 14.3.6.2 Concomitant PD Medications – safety population

	Placebo	300 mg	600 mg	900 mg	1200 mg
	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx	Exposure (subject-years): x.xx
	Total Subjects Exposed: xx	Total Subjects Exposed: xx	Total Subjects Exposed: xx	Total Subjects Exposed: xx	Total Subjects Exposed: xx
	Total Subjects Reporting: xx	Total Subjects Reporting: xx	Total Subjects Reporting: xx	Total Subjects Reporting: xx	Total Subjects Reporting: xx
Drug Name					
Preferred Name	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)	N Subjects (%)
Cccccc	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Cccccc	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
……..	x (x.x)	x (x.x)	x (x.x)	x (x.x)	x (x.x)

Table 14.3.7.1 Summary of C-SSRS in each visit – safety population

Test	Visit	Placebo (N=xx)	300 mg (N=xx)	600 mg (N=xx)	900 mg (N=xx)	1200 mg (N=xx)
C-SSRS n Any Suicidal Ideation (n (%)) Any Suicidal Behavior (n (%))	Baseline (Lifetime)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)
	Baseline (past 9 months)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)
	Month 1	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)	xx xx (xx.x) xx (xx.x)
	Repeat for Month 2, 3, 4, 5, 6 and 9 visits	…	…	…	…	…