Statistical Analysis Plan

A Phase 3, Long-term, Open-label Study of Istradefylline in Subjects with Moderate to Severe Parkinson's Disease

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Statistical Analysis Plan Signature Page

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Contents

List of Abbreviations

Abbreviations

AE	adverse event
ATC	anatomical therapeutic chemical
BP	blood pressure
CS	clinically significant
ECG	electrocardiogram
eCRF	electronic case report form
HR	heart rate
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
PGI-I	Patient Global Impression-Improvement
PD	Parkinson's Disease
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TLFs	tables, data listings, figures
US	United States
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) has been developed after review of Kyowa Kirin Pharmaceutical Development Inc. Protocol 6002-018(final version dated 28 SEP 2015).

This is a Phase 3, 52-week, open-label, flexible-dose, multinational, multicenter study to evaluate the safety and tolerability of istradefylline 20 to 40 mg/d in subjects with moderate to severe Parkinson's Disease (PD) with motor fluctuations and dyskinesia on levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy plus at least one adjunctive PD medication. For subjects who completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014, the final study evaluations at Week 12 will serve as the screening evaluations for eligibility for the study. Eligible subjects will initially be treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at Week 12 based on the Investigator's judgment of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment visit between Week 2 to Week 12 is allowed in accordance with clinical judgment of the Investigator. Subjects who had a dose adjustment to 40 mg/d can have their dose decreased to 20 mg/d by the Investigator at a second unscheduled dose adjustment visit if there are tolerability issues. The istradefylline dose should remain fixed between Week 26 to Week 52.

This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" (ICH Harmonised Tripartite Guideline E9 5FEB1998) and the most recent ICH E3 Guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" (ICH Harmonised Tripartite Guideline E3 30NOV1995).

2 STUDY OBJECTIVES

The objectives of this study are as follows:

2.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of oral istradefylline (20 to 40 mg/d) as treatment for subjects with moderate to severe PD.

3 STATISTICAL CONSIDERATIONS OF PROTOCOL

3.1 General Statistical Consideration

Descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency distributions and percentages for discrete (or any categorical) variables will be utilized. The mean and median values will be displayed to one decimal place greater than the original value and the measure of variability (i.e., SD) will be displayed to two decimal places greater than the original value. All summaries and analyses conducted will be by assigned therapy and/or combined total subjects. The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.4 or higher.

3.2 Overall Study Design and Plan

This is a Phase III, 52-week, open-label, flexible-dose, multinational, multicenter study to evaluate the safety and tolerability of istradefylline 20 or 40 mg/d in subjects with moderate to severe PD with motor fluctuations and dyskinesia. Evaluations will occur on levodopa combination (levodopa/carbidopa or levodopa/benserazide) therapy plus at least one adjunctive PD medication.

Safety outcomes will be assessed by summary of Adverse Events (AEs) and clinical laboratory tests. Vital signs including blood pressure, heart rate, temperature, respiration, weight, and height will be assessed at Screening. Concomitant medications and adverse events, Patient Global Impression-Improvement (PGI-I), will be assessed at every visit throughout the study. Decrease in the dosages of levodopa combinations (levodopa/carbidopa or benserazide/levodopa) due to levodopa-related events will be permitted at the Investigator's discretion and the extent of levodopa/carbidopa or benserazide/levodopa dose reduction will be captured.

The scheduled study visits and procedures are shown in Table 3.2-1

Table 3.2-1 Schedule of Visits

Procedure	Screening[a] Week -1 (Day –1 to 7)	Baseline Day 1	Open-Label Treatment			Follow-up 30 days following Week 52/ET (± 7 days)
			Week 12 (Day 85 ± 4 days)	Week 26 (Day 183 ± 4 days)	Week 52 or ET (Day 365 ± 4 days)	
Written informed consent	X					
Inclusion/Exclusion criteria	X					
Medical history/Demographics	X					
Physical examination	X					
Weight	X					
Height	X					
Vital signs[b]	X					
Clinical laboratory tests	X			X	X	
Serum pregnancy test[c]	X	X[d]	X[d]	X	X	
Serum FSH[e]	X					
12-lead ECG	X					
Concomitant medications	X	X	X	X	X	X[f]
Adverse Events[g]	X	X	X	X	X	X[f]
PGI-I	X	X[h]	X	X	X	
Treatment compliance			X	X	X	
Dispense study drug		X	X	X		

Note: Visits should occur in the ON state**.** If possible, subjects should have each visit scheduled for approximately the same time of day from Baseline and onwards.
a: For subjects who have completed 12 weeks of double-blind treatment and the 30-day follow-up period in Study No. 6002-014 immediately prior to entering this study, the Screening Visit for those subjects will correspond to the Follow-up visit of Study No. 6002-014.
b: Vital signs to be measured are blood pressure, heart rate, temperature, and respiration rate; all measurements are to be taken in the ON state.
c: For women of childbearing potential.
d: A urine dipstick pregnancy test will be conducted at Baseline and Week 12.
e: For post-menopausal women only.
f: Subjects will be contacted by telephone for a follow-up visit 30 days (± 7 days) after their last dose of istradefylline.
g: If there are tolerability issues, subjects can be seen at an unscheduled visit in accordance with clinical judgment of the Investigator. At these visits, assessments will include concomitant medications, adverse events, and treatment compliance.
h: Identification only the "key symptom" on the PGI-I for subjects.
ECG=electrocardiogra m; ET=Early Termination; FSH=follicle stimulating hormone; PGI-I=Patient Global Impression - Improvement Scale

3.3 Treatment Plan

All subjects will be treated with istradefylline at a starting dose of 20 mg/d with an option for a dose adjustment to 40 mg/d at Week 12 based on the Investigator's judgment of each subject's response and tolerability. If deemed necessary, one unscheduled dose adjustment visit between Week 2 to Week 12 is allowed in accordance with clinical judgment of the Investigator. Subjects who had a dose adjustment to 40 mg/d can have their dose decreased to

20 mg/d by the Investigator at a second unscheduled dose adjustment visit if there are tolerability issues. The istradefylline dose should remain fixed between Week 26 to Week 52.

In general, summary tables will display one total column. Subjects with dose adjustments will not be displayed separately except where specified.

3.4 Determination of Sample Size

Approximately 300 subjects are anticipated to participate in this study. The sample size was estimated based on the number of subjects anticipated to complete 12 weeks of treatment in Study No. 6002-014 and, of these, the estimated proportion meeting the inclusion/exclusion of this study protocol and the estimated number of eligible subjects who agree to participate.

3.5 Disposition of Subjects

Subject disposition will be based on all subjects who are eligible for this study. The number entered, completed, and number discontinuing at each visit will be presented. A summary of reasons for early discontinuation will be provided. Reasons for early discontinuation include AEs, lack of efficacy, protocol violation, or non-compliance with study drug, subject's withdrawal of consent, or other (to be specified by the Investigator).

3.6 Analysis Populations

The following analysis populations will be used in the study:

- **Intent-to-Treat Set (ITT)**: Includes all subjects with both a valid screening and at least one valid post-screening efficacy assessment.
- **Safety Analysis Set:** Includes all subjects who received at least one dose of assigned study drug (even a partial dose).

The number of subjects in each of the ITT and Safety Analysis sets will be presented.

3.7 Demographic and Other Baseline Characteristics

Demographic and Baseline characteristics will be summarized descriptively for the ITT and Safety Analysis Sets for each treatment arm and in total. These summaries will include demographics (including age, race, sex, height, weight, daily caffeine intake, smoking status, and body mass index (BMI), medical history, and physical examination results of note. Baseline will be defined as the last observation obtained prior to the first dose of study drug in this study.

All demographic data and Baseline disease characteristics data will be listed by subject.

3.7.1 Medical History

Medical history for those subjects reporting any past or present conditions at screening will be summarized by body system for the Safety Analysis Set for each treatment arm and in total. Medical history data will be listed by subject.

3.8 Prior/Concomitant Medications

All prior and concomitant medications will be coded to preferred drug names and therapeutic drug class using the World Health Organization (WHO) Drug Dictionary. Prior medications refer to medications taken within 30 days prior to the first dose of study medication (i.e. the duration when taken overlaps the time interval between first dose date minus 30 to first dose date minus 1 at any single time). Concomitant medications are those with start date on or after the date of the first dose or that started prior to the date of the first dose but are indicated as continuing into the treatment period. Any medications with partial start and/or stop dates will be considered concomitant if the assignment is uncertain.

The number and percentage of subjects taking concomitant medications during the treatment period will be summarized by anatomical therapeutic chemical (ATC) and preferred term (PT) for the Safety Analysis Set. If a subject took a coded medication more than once, the subject will be counted once for that coded medication total. If a subject had more than one coded medication in a therapeutic class, the subject will be counted only once in that therapeutic class total.

All prior and concomitant medications will be listed by subject.

3.9 Duration of Therapy and Drug Compliance

Duration of therapy will be summarized as the number of weeks [defined as (days from first dosing to last dosing)/7, with precision to one decimal place] receiving treatment from the first day of dosing until the last day of dosing.

The percent compliance for taking study drug as prescribed will be calculated at Weeks 12, 26, and 52 using the formula (with precision to one decimal place):

$$\text{Compliance} = \frac{\text{(Number of tablets dispensed – Number of tablets returned)}}{\text{(Number of tablets expected to be taken)}} \times 100$$

Compliance over the entire open-label treatment period will be similarly computed using the total number of tablets dispensed from Screening to Week 52 and the total number of tablets returned and the total number of tablets expected to be taken for this period. The number of tablets expected to be taken will be derived as follows: end of study/treatment date minus

first treatment date, plus one. If subjects are escalated to 40 mg per day, and are dispensed 20 mg tablets, two tablets per day will be expected and the number of expected tablets for this time period will be derived as follows: end of treatment period date minus first treatment period date, plus one, multiplied by two. Summary statistics for compliance will be presented for the Safety Analysis Set.

Treatment adjustments will be summarized by time period, Baseline to Week 12, >Week 12 to Week 26, and >Week 26 to Week 52. The number of subjects who remained on Istradefylline 20 mg, the number for whom dose was escalated to Istradefylline 40 mg and remained at 40 mg, and the number for whom dose was escalated to Istradefylline 40 mg and later de-escalated to Istradefylline 20 mg will be displayed for each time period.

3.10 Efficacy Analysis

All efficacy data collected from the PGI-I scale used in this study will be summarized using descriptive statistics for the ITT population. Summaries will be performed overall and by treatment in 6002-014, Istradefylline versus placebo. The PGI-I scale will be summarized categorically, displaying the number and percentage of subjects in each category outlined below at weeks 12, 26, and 52. PGI-I overall condition score and subscores will be reported (fatigue, sleep, motivated to get tasks done, key symptom).

1=Moderate improvement (or greater)

2=Mild improvement

3=No change from Baseline

4=Mild deterioration

5=Moderate deterioration (or greater)

No statistical tests (i.e. p-values) will be performed.

3.11 Safety Analysis

All safety analyses will be based on the Safety Analysis Set. All continuous safety data collected in this study will be summarized using descriptive statistics at each assessment time based on actual values and change from Baseline values. Baseline is defined as the last non-missing value obtained prior to first treatment. Continuous variables will be summarized using n, mean, SD, median, minimum, and maximum values. Categorical variables will be summarized using the number and percentage of subjects in each category. All out-of-normal-range results and clinically significant changes in any safety variable will be flagged in the subject data listings.

3.11.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs reported during the study by system organ class (SOC) and PT. All summary tables will include counts of subjects with treatment-emergent adverse events (TEAEs), defined as those AEs that have a start date after the start of study drug. AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be considered TEAEs, taking the worst-case approach. All other AEs will be classified as non-TEAEs and identified in listings only. An overall summary table of TEAEs will be presented with the number and percentage of subjects having a TEAE, a serious TEAE, a TEAE leading to study discontinuation, a TEAE with an outcome of death, a TEAE related to study drug ('possibly', 'probably', or 'definitely' related), or a severe TEAE. The overall incidence of TEAEs will be summarized by SOC and by SOC and PT using the number and percentage of subjects reporting an event and by the number of events reported. The incidence of TEAEs resulting in death, serious TEAEs, and TEAEs leading to study discontinuation will be summarized in a similar manner. TEAEs will also be summarized by maximum severity (mild, moderate, or severe), and closest relationship to study drug (related or not related) with the percentage of subjects in each category. A TEAE with missing severity or relationship will be considered severe or related, respectively. If more than one TEAE is recorded for a subject within any SOC or PT, the subject will only be counted once within that SOC or PT total. Serious TEAEs, TEAEs leading to study discontinuation, and TEAEs with an outcome of death will also be presented in separate listings.

A summary of TEAEs and drug related TEAEs will be provided by dose at the first occurrence (Istradefyline 20 mg or 40 mg) and by SOC and PT. For subjects uptitrating from 20 mg to 40 mg or down-titrating from 40 mg to 20 mg, treatment start and stop dates will be used to identify the dose level at the time of the event. Subjects receiving both dose levels will be included in the denominator of both dose levels.

3.11.2 Clinical Laboratory Evaluation

Actual values and change from Baseline values for continuous data from clinical laboratory tests will be summarized descriptively at all scheduled study. Categorical data from clinical laboratory tests will be similarly summarized for the actual values. Clinical laboratory tests categorized as in or out of normal range will be summarized using shift tables by visit. Shift tables will be the cross tabulation of the Baseline result category (high, normal, low) with post-Baseline result category (high, normal, low) for each visit during the treatment period. All out-of-normal range results will be flagged in the subject data listings.

3.11.3 Vital Signs, Height and Weight

Vital signs measurements, including heart rate (HR), systolic and diastolic blood pressure (BP), respiratory rate, temperature, height and body weight are collected at screening and will be listed by subject.

3.11.4 12-Lead Electrocardiogram

Electrocardiogram (ECG) interpretations by the Investigator are collected at screening and at unscheduled visits based on clinical indication. All ECG overall interpretations will be listed by subject.

3.11.5 Physical and Neurological Examinations

Physical and neurological examinations are performed at screening and at unscheduled visits as clinically indicated. All examination findings, including general appearance, head (eyes, ears, nose, and throat), cardiovascular, respiratory, abdominal, musculoskeletal, extremities, lymph nodes, skin, and neurological examination results (cranial nerves, sensory, motor, stance/gait, reflexes, mental status), will be listed by subject.

4 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

5 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® Version 9.4. Generated outputs will adhere to the following specifications.

5.1 Table, Listing, and Figure Format

5.1.1 General

1) All TLFs will be produced in landscape format.
2) All TLFs will be produced using the Courier New font, size 10.
3) The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
4) Headers and footers for figures will be in Courier New font, size 8.
5) Legends will be used for all figures with more than 1 variable, group, or item displayed.
6) TLFs will be in black and white (no color).
7) Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs. On some occasions, superscripts 1, 2, or 3 may be used (see below).
8) Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain superscripts (e.g., cm^2) will be employed on a case-by-case basis.
9) Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats.

5.1.2 Headers

1) All output should have the following header at the top of the page:

Kyowa Kirin Pharmaceutical Development, Inc. DDMMMYYYY
Istradefylline: Protocol 6002-018 Page n of N

All output should have page numbers. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

5.1.3 Display Titles

1) Each TLF should be identified by a numeral, and the designation (i.e., Table 1) should be centered above the title. A decimal system (14.x.y.z and 16.2.x.y) should be

used to identify TLFs with related contents. The title is centered in initial capital characters. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table 14.x.y.z
First Line of Title
Second Line of Title if Needed
Analysis Set

5.1.4 Column Headers

1) Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
2) For numeric variables, include "unit" in column or row heading when appropriate.
3) Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
4) The majority of the tables will be summarized using a "Total" column. For those tables displaying "by treatment", the order of treatments will be: Istradefylline 20 mg/day, Istradefylline 40 mg/day, and Total.

5.1.5 Body of the Data Display

1) Listings will be sorted for presentation in order of treatment groups as above, subject identification, collection day, and collection time (as applicable).
2) If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8
mild	3

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

3) If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included. Exception, if 'other' category is present with at least 1 subject, all pre-specified categories will be included.
4) An Unknown or Missing category for categorical summarization should be added to any parameter for which information is not available for 1 or more subjects.

5) Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic BP:

N	XX
Mean	XXX.X
SD	X.XX
Median	XXX.X
Range	(XXX, XXX)

6) Data in columns of a table should be formatted as follows:
   - alpha-numeric values are left-justified;
   - whole numbers (e.g., counts) are right-justified; and
   - numbers containing fractional portions are decimal aligned.

8) Percentage values should be printed with 1 digit to the right of the decimal point in parentheses 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)). Less-than-signs "<0.1%" should be printed when values are >0.0% and <0.1% (not 0.0%). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator.

9) Tabular display of data for 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 the active treatment group in decreasing order. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and adverse events (by PT) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically.

10) Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate. Missing descriptive statistics or p-values due to non-estimability should be reported as "-".

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

12) All observed time values must be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45, or 11:26). Time will only be reported if it was measured as part of the study.

5.1.6 Footnotes

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

2) All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
3) Footnotes should always begin with "Note:" if an informational footnote, or asterisks and other non-numeric symbols if an annotated footnote. Each new footnote starts on a new line.
4) Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
5) Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than 4 footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page. Footnotes should not repeat definitions already provided in the SAP.
6) The last line of the footnote section will be a standard source line that indicates the data source called in by the program, the name of the program used to produce the data display, and the listing source (i.e., 'Data source: xyzabc.sas7bdat Program source: myprogram.sas Listing source: 16.x.y.z').

5.2 Data-Handling Rules

This section describes naming conventions and rules for calculations that would be common to all applicable tables. Some rules specific to a table can be found in the relevant mock-ups.

5.2.1 Visits

1) Relative Study Day: The first day of treatment is Day 1. A minus (-) sign indicates days prior to the start of treatment (e.g., Day -5 represents 5 days before start of therapy. There is no Day 0.). The relative study day for a specific visit is calculated as (Visit Date - Date of First Dose +1).
2) Baseline: Evaluation taken on Day 1 or the last available evaluation prior to the first dose of study drug if the former is missing.

5.2.2 Demographics and Baseline Characteristics

- Age (if derived) = (Date of informed consent - Date of birth + 1) / 365.25 and truncated to complete years.
- Conversion factors and calculations for height, weight, and BMI (with precision to one decimal place):
    - Height (in cm) = height (in inches) * 2.54
    - Weight (in kg) = weight (in lbs) * 0.4536
    - BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

5.2.3 Prior and Concomitant Medications

1) Prior and concomitant medications will be coded and classified using the WHODRUG dictionary. The specific dictionary version will be provided in the actual tables/listings. Prior medications refer to medications taken within 30 days prior to the first dose of study medication (i.e. the duration when taken overlaps the time interval between first dose date minus 30 to first dose date minus 1 at any single time). Concomitant medications are those with start date/time on or after the date/time of dosing or that started prior to the date/time of dosing but are indicated as continuing into the treatment period. Any medications with partial start and/or stop dates will be considered concomitant if the assignment is uncertain.
2) Medications missing both start and stop dates, or having a start date prior to the last dose of study drug and missing the stop date, or having a stop date after the start of study drug and missing the start date, will be counted as concomitant. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the medication either ended prior to the start of study drug or started after the end of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the medication will be counted as concomitant.

5.2.4 Change from Baseline

Change from Baseline is defined as X-baseline for each X value at Weeks 12, 26, and 52.

5.2.5 Safety

1) If multiple results (e.g., laboratory test results) are reported at a study visit, then the first available result reported for that visit will be used in that visit summary.
2) Adverse events will be coded and classified using MedDRA dictionary. The specific dictionary version will be provided in the actual tables/listings.
3) Counting rules for TEAEs: Adverse event tables will include all recorded adverse signs and symptoms, except those with onset or stop dates prior to the first day of study drug. Adverse events with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. Special care will be taken regarding partial dates with similar logic to that of the prior/concomitant medications applied.
4) For purposes of flagging individual subject data, laboratory abnormalities are defined as values above or below the normal range.
5) Conversion factor for body temperature:

Temperature (in °C) = 5/9 * (Temperature [in °F]-32), with precision to one decimal place.

6 LIST OF TABLES, LISTINGS, AND FIGURES

Disposition and Demography Tables

Table 14.1.1	Subject Enrollment by Center
Table 14.1.2	Subject Disposition
Table 14.1.3	Demographic and Baseline Characteristics – Safety Analysis Set
Table 14.1.4	Parkinson's Disease History – Safety Analysis Set
Table 14.1.5.1	Prior Medications (Excluding Antiparkinsonian Medications) – Safety Analysis Set
Table 14.1.5.2	Concomitant Medications (Excluding Antiparkinsonian Medications) – Safety Analysis Set
Table 14.1.6.1	Prior Antiparkinsonian Medications – Safety Analysis Set
Table 14.1.6.2	Concomitant Antiparkinsonian Medications – Safety Analysis Set
Table 14.1.7.1	Duration of Therapy (weeks) – Safety Analysis Set
Table 14.1.7.2	Compliance Rate – Safety Analysis Set
Table 14.1.7.3	Treatment Adjustments – Safety Analysis Set

Efficacy Tables

Table 14.2.1.1	Patient Global Impression - Improvement by Study Visit – Overall Condition – ITT Analysis Set
Table 14.2.1.2	Patient Global Impression - Improvement by Study Visit – Fatigue – ITT Analysis Set
Table 14.2.1.3	Patient Global Impression - Improvement by Study Visit – Sleep – ITT Analysis Set
Table 14.2.1.4	Patient Global Impression - Improvement by Study Visit –Motivated to Get Things Done – ITT Analysis Set
Table 14.2.1.5	Patient Global Impression - Improvement by Study Visit – Key Symptom – ITT Analysis Set

Safety Tables

Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events – Safety Analysis Set
Table 14.3.1.2	Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table 14.3.1.3	Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity – Safety Analysis Set
Table 14.3.1.4	Subjects with Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug – Safety Analysis Set
Table 14.3.2.1	Subjects with Treatment-Emergent Adverse Events Leading to Deathby System Organ Class and Preferred Term – Safety Analysis Set
Table 14.3.2.2	Subjects with Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set
Table 14.3.2.3	Subjects with Treatment-Emergent Adverse Events Leading to Discontinuation from the Study by System Organ Class and Preferred Term – Safety Analysis Set
Table 14.3.4.1	Summary Statistics by Laboratory Test: Hematology – Parameter (unit) — Safety Analysis Set
Table 14.3.4.2	Summary Statistics by Laboratory Test: Blood Chemistry – Parameter (unit) –Safety Analysis Set
Table 14.3.4.3	Summary Statistics by Laboratory Test: Urinalysis – Parameter (unit) –Safety Analysis Set
Table 14.3.4.4	Shift Tables by Laboratory Test: Hematology –Safety Analysis Set
Table 14.3.4.5	Shift Tables by Laboratory Test: Blood Chemistry –Safety Analysis Set
Table 14.3.4.6	Shift Tables by Laboratory Test: Urinalysis – Continuous Parameters Safety Analysis Set
Table 14.3.4.7	Shift Tables by Laboratory Test: Urinalysis – Categorical Parameters Safety Analysis Set

Listings

Listing 16.2.1.1	Subject Completion/Discontinuation
Listing 16.2.1.2	Screen Failures
Listing 16.2.2.1	Protocol Deviations
Listing 16.2.2.2	Inclusion/Exclusion Criteria
Listing 16.2.3	Subjects Excluded from Analysis Sets
Listing 16.2.4.1	Demography
Listing 16.2.4.2	Parkinson's Disease History
Listing 16.2.4.3	Medical History
Listing 16.2.4.4.1	Prior Medications (Excluding Antiparkinsonian Medications)
Listing 16.2.4.4.2	Concomitant Medications (Excluding Antiparkinsonian Medications)
Listing 16.2.4.5.1	Prior Antiparkinsonian Medications
Listing 16.2.4.5.2	Concomitant Antiparkinsonian Medications
Listing 16.2.5.1	Study Drug Dosing Record and Compliance
Listing 16.2.5.2	Study Drug Dose Adjustment
Listing 16.2.6	Patient Global Impression - Improvement
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Serious Adverse Events and Deaths
Listing 16.2.7.3	Adverse Events Leading to Discontinuation from the Study
Listing 16.2.8.1	Laboratory Assessments - Hematology
Listing 16.2.8.2	Laboratory Assessments – Blood Chemistry
Listing 16.2.8.3	Laboratory Assessments – Urinalysis
Listing 16.2.8.4	Pregnancy Test
Listing 16.2.8.5	Follicle Stimulating Hormone
Listing 16.2.8.6	Laboratory Assessments - Comments
Listing 16.2.9.1	Vital Signs and Body Weight
Listing 16.2.9.2	12-Lead Electrocardiogram Report – Qualitative Data by Subject
Listing 16.2.9.3	Physical Examination
Listing 16.2.9.4	Neurological Examination

Table 14.1.1
Subject Enrollment by Center
Enrolled Subjects

Center Number	Investigator Name	Total		
		All	Safety[1]	ITT[2]
1	Xxxxxxx	xx	xx	xx
	Yyyyyyy	xx	xx	xx
Total		xx	xx	

[1] Safety Analysis Set: Includes all subjects who received at least one dose of assigned study drug (even a partial dose).
[2] Intent-to-Treat (ITT) set includes all subjects with both a valid baseline and at least one valid post-baseline assessment.

Data source: xyzabc.sas7bdat Program source: myprogram.sas Listing source: 16.x.y.z

NOTE TO PROGRAMMER: *Add source to all tables following the same format.*

Table 14.1.2
Subject Disposition
Enrolled Subjects

Status	Total
Randomized	xx (100%)
ITT Analysis Set [1]	xx (xx.x)
Safety Analysis Set [2]	xx (xx.x)
Completed	
Week 12	xx (xx.x)
Week 26	xx (xx.x)
Week 52	xx (xx.x)
Completed Treatment Period	xx (xx.x)
Discontinued Prematurely	xx (xx.x)
Adverse Event	xx (xx.x)
Prohibited Concomintant Medication	xx (xx.x)
Subject withdrew consent	xx (xx.x)
Investigator decision	xx (xx.x)
Noncompliance	xx (xx.x)
Administrative reasons	xx (xx.x)
Pregnancy	xx (xx.x)
Subject did not meet entry criteria	xx (xx.x)
Other	xx (xx.x)

[1] Intent-to-Treat (ITT) set includes all subjects with both a valid baseline and at least one valid post-baseline assessment.

[2] All subjects who received at least one dose of assigned study drug (even a partial dose).

Table 14.1.3
Demographic and Baseline Characteristics
Safety Analysis Set

Variable	Total (N=)
Age (years)	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)
Gender n (%)	
Male	xx (xx.x)
Female	xx (xx.x)
Race n (%)	
White	xx (xx.x)
Asian	xx (xx.x)
Black	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)
Other	xx (xx.x)
Not Applicable	xx (xx.x)
Ethnicity n (%)	
Hispanic or Latino	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)

Table 14.1.3
Demographic and Baseline Characteristics
Safety Analysis Set

Variable	Total (N=)
Height (cm)	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)
Weight (kg)	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)
BMI (kg/m2)	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)

Table 14.1.3
Demographic and Baseline Characteristics
Safety Analysis Set

Variable	Total (N=)
Current Smoker n (%)	
Yes	xx (xx.x)
No	xx (xx.x)
Number of Cigarettes Smoked per Day n (%)	
<= 5 cigarettes per day	xx (xx.x)
> 5 cigarettes per day	xx (xx.x)
Number of Cups (8 Ounces) per Day of Any Caffeinated Beverage	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)

NOTE TO PROGRAMMER: Additional baseline characteristics may be added as needed.

Table 14.1.4
Parkinson's Disease History
Safety Analysis Set

Variable Statistics	Total (N=)
Time Since Diagnosis (years) n (%)	
< 1 year	xx (xx.x)
1-3 years	xx (xx.x)
4-7 years	xx (xx.x)
>= 8 years	xx (xx.x)
Time Since Initiation of Levodopa (years)	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)
Time Since Onset of Motor Complications (years)	
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)

Programming note: The data in this table will be brought forward from the Kyowa 6002-14 Study

Table 14.1.5.1
Prior Medications (Excluding Antiparkinsonian Medications)
Safety Analysis Set

Therapeutic Class/ Preferred Term [1]	Total (N=)
Subjects who took prior medications	xx (xx.x)
Therapeutic Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Etc.	xx (xx.x)
...	

Note: This table includes medications that were taken within 30 days prior to the first dose of Iistradefyline.
[1] WHODRUG Dictionary Version 2013 SEP was used for coding.

NOTE TO PROGRAMMER:
Please present medications in descending order of total frequency by therapeutic class and then by descending order of total frequency of preferred term within the therapeutic class.

Statistical Analysis Plan
Istradefylline 6002-018

Table 14.1.5.2
Concomitant Medications (Excluding Antiparkinsonian Medications)
Safety Analysis Set

NOTE TO PROGRAMMER:

Follow the same format as Table 14.1.5.1: Change "Subjects who took prior medications" to: "Subjects who took concomitant medications." Change note to "This table includes medications having a start date on or after the date of the first dose of Istradefyline or with a start date prior to the first dose of Istradefyline and continuing beyond the first dose of Istradefyline.".

Table 14.1.6.1
Prior Antiparkinsonian Medications
Safety Analysis Set

NOTE TO PROGRAMMER:

Follow the same format as Table 14.1.5.1: Change "Subjects who took prior medications" to: "Subjects who took prior antiparkinsonian medications"

Table 14.1.6.2
Concomitant Antiparkinsonian Medications
Safety Analysis Set

NOTE TO PROGRAMMER:

Follow the same format as Table 14.1.5.2: Change "Subjects who took concomitant medications" to: "Subjects who took concomitant antiparkinsonian medications."

Table 14.1.7.1
Duration of Therapy (Weeks)
Safety Analysis Set

Statistics	Total (N=)
Duration of Therapy (weeks) [1] n (%)	
<=12	xx (xx.x)
>12 to <=26	xx (xx.x)
>26 to <=52	xx (xx.x)
>52	xx (xx.x)
n	xx
Mean	xx.x
SD	x.xx
Median	xx.x
Range	(xx,xx)
Total Duration (subject weeks)	xx

[1] Duration of therapy = ([Last dose date – First dose date] + 1)/7

Table 14.1.7.2
Compliance Rate
Safety Analysis Set

Statistics	Total (N=)
Compliance Rate Category	
Treatment Period n (%)	
<60%	xx (xx.x%)
60 to 69%	xx (xx.x%)
70 to 79%	xx (xx.x%)
80 to 89%	xx (xx.x%)
90 to 99%	xx (xx.x%)
100 to 109%	xx (xx.x%)
>110%	xx (xx.x%)
n	xx
Mean Rate	xx.x
Median Rate	xx.x
Week 12 n (%)	
<60%	xx (xx.x%)
60 to 69%	xx (xx.x%)
...	xx (xx.x%)
n	xx
Mean Rate	xx.x
Median Rate	xx.x

NOTE TO PROGRAMMER: please also summarize compliance rate at each study visit (weeks 12, 26, & 52)

Table 14.1.7.3
Treatment Adjustments
Safety Analysis Set

Time Period Exposure Adjustment	Total (N=)
Baseline to <Week 12	
Remained on Istradefyline 20 mg	xx (xx.x%)
Escalated to Istradefyline 40 mg	xx (xx.x%)
Escalated to Istradefyline 40 mg and de-escalated to Istradefyline 20 mg	xx (xx.x%)
Week 12 to <Week 26	
Remained on Istradefyline 20 mg	xx (xx.x%)
Remained on Istradefyline 40 mg	xx (xx.x%)
Escalated to Istradefyline 40 mg	xx (xx.x%)
Escalated to Istradefyline 40 mg and de-escalated to Istradefyline 20 mg	xx (xx.x%)
≥ Week 26	
Remained on Istradefyline 20 mg	xx (xx.x%)
Remained on Istradefyline 40 mg	xx (xx.x%)
Total	
Remained on Istradefyline 20 mg (without escalation to 40 mg)	xx (xx.x%)
Escalated and Remained on Istradefyline 40 mg	xx (xx.x%)
Escalated to Istradefyline 40 mg and De-escalated to Istradefyline 20 mg	xx (xx.x%)

Note: time period: Baseline to < Week 12, 1 to 84 study days; Week 12 to < Week 26, 85 to 183 study days; ≥ Week 26, ≥ 184 study days

Table 14.2.1.1
Patient Global Impression – Improvement by Study Visit – Overall Condition
ITT Analysis Set

Visit/ Score	Treatment in 6002-014 Placebo (N=)	Istradefylline (N=)	Total (N=)
Week 12 [n(%)]	xx (100%)	xx (100%)	xx (100%)
1=Moderate improvement (or greater)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2=Mild improvement	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3=No change from Baseline	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
4=Mild deterioration	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
5=Moderate deterioration (or greater)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Week 26 [n(%)]			
...			

(Note to Programmer: Repeat for week 52)

Table 14.2.1.2
Patient Global Impression – Improvement by Study Visit – Fatigue
ITT Analysis Set

Note to Programmer: *Repeat Table 14.2.1.1*

Table 14.2.1.3
Patient Global Impression – Improvement by Study Visit – Sleep
ITT Analysis Set

Note to Programmer: *Repeat Table 14.2.1.1*

Table 14.2.1.4
Patient Global Impression – Improvement by Study Visit – Motivated to Get Things Done
ITT Analysis Set

Note to Programmer: *Repeat Table 14.2.1.1*

Table 14.2.1.5
Patient Global Impression – Improvement by Study Visit – Key Symptoms
ITT Analysis Set

Note to Programmer: *Repeat Table 14.1.5.1*

Table 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events (TEAE)
Safety Analysis Set

	Total (N=)
Subjects with any TEAE n (%)	xx (xx.x)
Subjects with any serious TEAE n (%)	xx (xx.x)
Subjects with any TEAE leading to discontinuation n (%)	xx (xx.x)
Subjects with any Related [1] TEAE n (%)	xx (xx.x)
Subjects with any Severe TEAE n (%)	xx (xx.x)
Subjects who died n (%)	xx (xx.x)

[1] Related = includes probably, possibly, and definitely study drug related.

Table 14.3.1.2
Subjects with Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class/ Preferred Term	Total (N=)
Subjects with any TEAE n (%)	xx (xx.x)
System Organ Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
...	
System Organ Class 2	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
...	

Note: If a subject experienced more than 1 TEAE within a system organ class, the subject is counted once under that SOC. If a subject has more than 1 count of a particular preferred term, the subject was counted once for that preferred term. MedDRA dictionary Version 16.1 was used for coding.

Programming Notes: For all TEAE tables (where applicable), present the data within an SOC by frequency of occurrence in decreasing order (NOT alphabetically)then by PT within SOC by frequency of occurance.

Same format will be followed for Tables 14.3.1-3, 14.3.1-4.

Table 14.3.1.3
Subjects with Treatment-Emergent Adverse Events (TEAE)
by System Organ Class, Preferred Term, and Maximum Severity
Safety Analysis Set

System Organ Class/ Preferred Term	Severity	Total (N=)
Subjects with any TEAE n (%)	Mild	xx (xx.x)
	Moderate	xx (xx.x)
	Severe	xx (xx.x)
System Organ Class 1	Mild	xx (xx.x)
	Moderate	xx (xx.x)
	Severe	xx (xx.x)
Preferred Term 1	Mild	xx (xx.x)
	Moderate	xx (xx.x)
...	Severe	xx (xx.x)

Note: If a subject experienced more than 1 TEAE within a system organ class, the subject is counted once under that SOC. If a subject has more than 1 count of a particular preferred term, the subject was counted once for that preferred term. If a subject experienced more than 1 severity within a TEAE, the subject is counted once under maximum severity. MedDRA dictionary Version 16.1 was used for coding.

NOTE TO PROGRAMMER: Please present in descending order by total count in SOC, and then in descending order by total count for PT within SOC.

Table 14.3.1.4
Subjects with Treatment-Emergent Adverse Events (TEAE)
by System Organ Class, Preferred Term, and Relationship to Study Drug
Safety Analysis Set

System Organ Class/ Preferred Term	Relation to Study Drug	Total (N=)
Subjects with any TEAE n (%)	Related	xx (xx.x)
	Not Related	xx (xx.x)
System Organ Class 1	Related	xx (xx.x)
	Not Related	xx (xx.x)
Preferred Term 1	Related	xx (xx.x)
	Not Related	xx (xx.x)
...		

Note: If a subject experienced more than 1 TEAE within a system organ class, the subject is counted once under that SOC. If a subject has more than 1 count of a preferred term, the subject was counted once for that preferred term. MedDRA dictionary Version 16.1 was used for coding.

Table 14.3.2.1
Subjects with any Treatment-Emergent Adverse Events Leading to Death
by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class/ Preferred Term	Total (N=)	Dose at Occurrence	
		20 mg	40 mg
Subjects with any TEAE leading to death n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)		
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			

Note: If a subject experienced more than 1 TEAE within a system organ class, the subject is counted once under that SOC. If a subject has more than 1 count of a particular preferred term, the subject was counted once for that preferred term. MedDRA dictionary Version 16.1 was used for coding.

NOTE TO PROGRAMMER: Please present in descending order by frequency in SOC, and then by frequency in descending order by PT within SOC.

Table 14.3.2.2
Subjects with Serious Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class/ Preferred Term	Total (N=)	Dose at Occurrence	
		20 mg	40 mg
Subjects with any Serious TEAE n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			

Note: If a subject experienced more than 1 TEAE within a system organ class, the subject is counted once under that SOC. If a subject has more than 1 count of a particular preferred term, the subject was counted once for that preferred term. MedDRA dictionary Version 16.1 was used for coding.

NOTE TO PROGRAMMER: Please present in descending order by frequency in SOC, and then in descending order by frequency PT within SOC.

Table 14.3.2.3
Subjects with Treatment-Emergent Adverse Events (TEAE) Leading to Discontinuation from the Study
by System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class/ Preferred Term	Total (N=)	Dose at Occurrence	
		20 mg	40 mg
Subjects with any TEAE Leading to Discontinuation n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
...			

Note: If a subject experienced more than 1 TEAE within a system organ class, the subject is counted once under that SOC. If a subject has more than 1 count of a particular preferred term, the subject was counted once for that preferred term. MedDRA dictionary Version 16.1 was used for coding.

Table 14.3.4.1
Summary Statistics by Laboratory Test: Hematology
Actual and Change from Baseline Values
Safety Analysis Set

Parameter (Unit)

Visit/ Statistics	Total (N=) Actual	Change
Screening		
n	xx	
Mean	xx.xx	
SD	x.xxx	
Median	xx.xx	
Range	xx.x-xx.x	
Week 26		
n	xx	xx
Mean	xx.xx	xx.xx
SD	x.xxx	x.xxx
Median	xx.xx	xx.xx
Range	xx.x-xx.x	xx.x-xx.x
Week 52		

Table 14.3.4.2
Summary Statistics by laboratory Test: Blood Chemistry
Actual and Change from Baseline Values
Safety Analysis Set

Note to Programmer: *Repeat Table 14.3.4.1 for Blood Chemistry*

Table 14.3.4.3
Summary Statistics by laboratory Test: Urinalysis
Actual and Change from Baseline Values
Safety Analysis Set

Note to Programmer: *Repeat Table 14.3.4.1 for Urinalysis*

Table 14.3.4.4
Shift Table by Laboratory Test: Hematology
Safety Analysis Set

Parameter: Hemoglobin (Unit)

Post-Baseline Visit		Baseline n (%)			
		High	Low	Normal	Total
Week 26	High	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Normal	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Low	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Total	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	100%
Week 52					
	High	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Normal	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Low	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)
	Total	xx.x(xx.x)	xx.x(xx.x)	xx.x(xx.x)	100%

Note: High = above upper limit of normal reference range; Normal = within limit of normal reference range; Low = below low limit of normal reference range.
Reference range: see Preface A.

Table 14.3.4.5
Shift Table by Laboratory Test: Blood Chemistry
Safety Analysis Set

Note to Programmer: *Repeat Table 14.3.4.4 for Blood Chemistry*

Table 14.3.4.6
Shift Table by Laboratory Test: Urinalysis – Continuous Parameters
Safety Analysis Set

Note to Programmer: *Repeat Table 14.3.4.4 for Urinalysis – Continuous Parameters*

Table 14.3.4.7
Shift Table by Laboratory Test: Urinalysis – Categorical Parameters
Safety Analysis Set

Note to Programmer: *Repeat Table 14.3.4.4 for Urinalysis – Categorical Parameters*

Listing 16.2.1.1
Subject Completion/Discontinuation

Clinical Site Subject No.	Date of First Dose/ Date of Last Dose/ Day of Last Dose [1]	Date/Day of Final Visit	Dose at Final Visit (mg)	Completed Study	Reason for Discontinuation	Analysis Population
xxxx-xxx	DDMMMYYYY/ DDMMMYYYY/XX	DDMMMYYYY/XX		Yes		ITT, Safety
xxxx-xxx	DDMMMYYYY/ DDMMMYYYY/XX	DDMMMYYYY/XX		No	Adverse Event	ITT, Safety

[1] Relative to first dose of study drug.
Source: Data source: xyzabc.sas7bdat Program source: myprogram.sas

Note to Programmer: *Add source to all listings*

Listing 16.2.1.2
Screen Failures

Clinical Site Subject No.	Reason for Screen Failure
xxxx-xxx	
xxxx-xxx	

Source: Data source: xyzabc.sas7bdat Program source: myprogram.sas

Note to Programmer: *Add source to all listings*

Listing 16.2.2.1
Major Protocol Deviations

Clinical Site Subject No.	Protocol Deviation	Visit Impacted by Deviation	Description
xxxx-xxx		Screening	xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxx
xxxx-xx		Screening	

NOTE TO PROGRAMMER: *This will be programmed based on data provided by clinical.*

Listing 16.2.2.2
Inclusion/Exclusion Criteria Violations

Clinical Site Subject No	Date of Informed Consent	Satisfy All Eligibility Criteria?	Criteria Not Met	Protocol Subject Initially Consented
xxxx-xxx	DDMMMYYYY	No	xx	Amendment 2
xxxx-xxx	DDMMMYYYY	No	I01 E01	Amendment 3
xxxx-xxx	DDMMMYYYY	No	I02 E05	Amendment 4

Listing 16.2.3
Subjects Excluded from Analysis Sets

Clinical Site Subject No.	Analysis Set	Exclusion Yes/No	Reason for Exclusion
xxxx-xxx	ITT	No	
	Safety	Yes	xxxxxxxxxxxxxxxxxxx
xxxx-xxx	ITT	No	
	Safety	No	

Listing 16.2.4.1
Demography

Clinical Site Subject No.	Age (yrs)	Gender	Race	Ethnicity	Height (cm)/ Weight (kg)/ BMI (kg/m^2)	Smoker/ Cigar-ettes per Day	Caffeine Intake per Day	Number of Years of Education	Of Child-Bearing Potential?
xxxx-xxx	xx	Female	xxxxx	xxxxxxxxxx	xxx.x/ xx.x/ xx.x	Yes/<=5 / >5	2	12 Years	Yes/No
	xx	Male	xxxxx	xxxxxxxxxx	xxx.x	No	1	>12Years	
xxxx-xxx	xx	Female	xxxxx	xxxxxxxxxx	xxx.x	No	3	>12Years	Yes/No
xxxx-xxx	xx	Male	xxxxx	xxxxxxxxxx	xxx.x	Yes/xx	4	12Years	
	xx	Male	xxxxx	xxxxxxxxxx	xxx.x	Yes/xx			

Listing 16.2.4.2
Parkinson's Disease History

Clinical Site Subject No.	Screening Visit Date/Day [1]	PD Diagnosis Duration	Levodopa Initiated		Onset of Motor Complications	
			Date	Duration (Yrs)	Date	Duration (Yrs)
xxxx-xxx	DDMMMYYYY/XXX	< 1 year	DDMMMYYYY	XX	DDMMMYYYY	XX
xxxx-xxx	DDMMMYYYY/XXX	1-3 years	DDMMMYYYY	XX	DDMMMYYYY	XX
xxxx-xxx	DDMMMYYYY/XXX	4-7 years	DDMMMYYYY	XX	DDMMMYYYY	XX

Note: data from Study 6002-014.
[1] Relative to first dose of study drug.

Listing 16.2.4.3
Medical History

Clinical Site Subject No.	Reported Term	Start Date	Ongoing?
xxxx-xxx	XXXXXXXXXXXXXXX	DDMMMYYYY	No
xxxx-xxx	XXXXXXXXXXXXXXX	DDMMMYYYY	Yes
xxxx-xxx	XXXXXXXXXXXXXXX	DDMMMYYYY	No

Listing 16.2.4.4.1
Prior Medications (Excluding AntiParkinsonian Medications)

Clinical Site Subject No.	Preferred Term [1]	Medication	Total Daily Dose (Unit)	Start Date/Day[2]	Stop Date/Day[2]	Indication
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	Ongoing	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx

[1] XXX dictionary Version YYY was used for coding.
[2] Relative to first dose of study drug.

Listing 16.2.4.4.2
Concomitant Medications (Excluding AntiParkinsonian Medications)

Clinical Site Subject No.	Preferred Term [1]	Medication	Total Daily Dose (Unit)	Start Date/Day[2]	Stop Date/Day[2]	Indication
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	Ongoing	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx

[1] XXX dictionary Version YYY was used for coding.
[2] Relative to first dose of study drug.

Listing 16.2.4.5.1
Prior Antiparkinsonian Medications

Clinical Site Subject No.	Preferred Term [1]	Medication	Total Daily Dose (Unit)	Start Date/Day[2]	Stop Date/Day[2]	Indication
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	Ongoing	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx

[1] XXX dictionary Version YYY was used for coding.
[2] Relative to first dose of study drug.

Listing 16.2.4.5.2
Concomitant Antiparkinsonian Medications

Clinical Site Subject No.	Preferred Term [1]	Medication	Total Daily Dose (Unit)	Start Date/Day[2]	Stop Date/Day[2]	Indication
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	Ongoing	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx
xxxx-xxx	xxxxx	xxxxx	10 mg	DDMMMYYYY/xx	DDMMMYYYY/xx	xxxxxxxxxx

[1] XXX dictionary Version YYY was used for coding.
[2] Relative to first dose of study drug.

Listing 16.2.5.1
Study Drug Dosing Record and Compliance

Clinical Site Subject No.	Visit	Date Dispensed-day/ Returned-day [1]	Bottle Number	Dose Level	Number of Tablets Dispensed 40 mg/20mg	Number of Tablets Returned 40mg/20mg	Compliance Rate [2]	70% or Greater Compl-iant?	Reason for Non-compliance
		DDMMMYYYY-xx/							
xxxx-xxx	xxx	DDMMMYYYY-xx	xxx	20 mg/d	xxx/xxx	xxx/xxx	xx.x%	No	AE
		DDMMMYYYY-xx/							
xxxx-xxx	xxx	DDMMMYYYY-xx	xxx	40 mg/d	xxx/xxx	xxx/xxx	xx.x%	No	Other:XXXX
		DDMMMYYYY-xx/							
xxxx-xxx	xxx	DDMMMYYYY-xx	xxx	20 mg/d	xxx/xxx	xxx/xxx	xx.x%	Yes	

Note:
[1] Relative to first dose of study drug.
[2] Compliance rate = [(Number of tablets dispensed – Number of tablets returned) / (Number of tablets expected to be taken)] * 100.

Listing 16.2.5.2
Study Drug Dose Adjustment

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	Was the Dose Level Adjusted?	Reason for Dose Adjustment	If AE, Specify	If Other, specify
xxxx-xxx	xxx	DDMMMYYYY/XX	Yes	xxxxxxxxxxx	xxxxxxxxxxx	xxxxxxxxxxx
xxxx-xxx	xxx	DDMMMYYYY/XX	No			
xxxx-xxx	xxx	DDMMMYYYY/XX	No			

Note:
[1] Relative to first dose of study drug.

Listing 16.2.6
Patient Global Impression - Improvement

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	Overall Condition [2]	Fatigue [2]	Sleep [2]	Motivated to Get Tasks Done [2]	Key Symptom
xxxx-xxx	End of 6002-014	DDMMMYYYY/XX					XXXXXXX/4
	Baseline	DDMMMYYYY/XX					XXXXXXX/5
	Week 12	DDMMMYYYY/XX	1	2	3	4	XXXXXXX/5
	Week 26	DDMMMYYYY/XX	1	2	3	4	XXXXXXX/5
	Week 52	DDMMMYYYY/XX	1	2	3	4	XXXXXXX/5
xxxx-xxx	End of 6002-014	DDMMMYYYY/XX					XXXXXXX/4
	Baseline	DDMMMYYYY/XX					XXXXXXX/3
	Week 12	DDMMMYYYY/XX	1	2	3	4	XXXXXXX/3
	...						

[1] Relative to first dose of study drug.
[2] PGI-I Scale: 1=Moderate improvement (or greater), 2=Mild improvement, 3=No change from Baseline, 4=Mild deterioration, 5=Moderate deterioration (or greater).

Listing 16.2.7.1
Adverse Events

Clinical Site Subject No.	SOC/PT/Verbatim	AE Start Date/ Day [1]	AE Stop Date/ Day [1]	Istra-defylline dose at AE onset	SAE	Severity [2]	Relation [3]	Action taken [4]	Outcome [5]
							Def/ Prob/ Poss/ Unlike/ Not R/ N/A	Drug W/D/ Dose Int/ No Chg; N/A	Res/ Res'ing/ Not Res/ Res Seq/ Fatal/ Unk
	xxxxxxxxx /xxxxxxxxxx	DDMMMYYYY/ XX	DDMMMYYYY/ XX			Mild/ Mod/ Severe			
xxxx	/xxxxxxxxxxxxx				Yes				

Note: XXX dictionary Version YYY was used for coding. AE=Adverse Event; SOC=System Organ Class; PT=Preferred Term; SAE=Serious Adverse Event.
[1] Relative to first dose of study drug. Negative days at AE Start indicate the AE occured prior to first dose.
[2] Severity: Mod=Moderate.
[3] Relationship to Study Drug: Def=Definitely; Prob=Probably; Poss=Possibly; Unlike=Unlikely; Not R=Not Related; N/A=Not Applicable.
[4] Action taken: Drug W/D=Drug Withdrawn; Dose Int=Dose Interrupted; No Chg=Dose Not Changed; N/A=Not Applicable.
[5] Outcome: Res=Recovered/Resolved; Res'ing=Recovering/Resolving; Not Res=Not Recovered/Not Resolved; Res Seq= Recovered/Resolved with Sequelae; Unk=Unknown.

Listing 16.2.7.2
Serious Adverse Events and Deaths

Clinical Site Subject No.	SOC/PT/Verbatim	AE Start Date/ Day [1]	AE Stop Date/ Day [1]	Istra-defylline dose at AE onset	Sever-ity [2]	Relation [3]	Action taken [4]	Outcome [5]
						Def/ Prob/ Poss/ Unlike/ Not R/ N/A	Drug W/D/ Dose Int/ No Chg; N/A	Res/ Res'ing/ Not Res/ Res Seq/ Fatal/ Unk
xxxx	xxxxxxxxx /xxxxxxxxxx /xxxxxxxxxxxxx	DDMMMYYYY/ XX	DDMMMYYYY/ XX		Mild/ Mod/ Severe			

Note: XXX dictionary Version YYY was used for coding. AE=Adverse Event; SOC=System Organ Class; PT=Preferred Term; SAE=Serious Adverse Event.
[1] Relative to first dose of study drug. Negative days at AE Start indicate the AE occured prior to first dose.
[2] Severity: Mod=Moderate.
[3] Relationship to Study Drug: Def=Definitely; Prob=Probably; Poss=Possibly; Unlike=Unlikely; Not R=Not Related; N/A=Not Applicable.
[4] Action taken: Drug W/D=Drug Withdrawn; Dose Int=Dose Interrupted; No Chg=Dose Not Changed; N/A=Not Applicable.
[5] Outcome: Res=Recovered/Resolved; Res'ing=Recovering/Resolving; Not Res=Not Recovered/Not Resolved; Res Seq= Recovered/Resolved with Sequelae; Unk=Unknown.

Listing 16.2.7.3
Adverse Events Leading to Discontinuation from the Study

Note to Programmer: *Repeat listing 16.2.7.1 for AE Leading to Discontinuation from the Study.*

Listing 16.2.8.1
Laboratory Assessments – Hematology

Clinical Site Subject No.	Parameter	Unit	Normal Range Low-High	Visit	Sample Date/Time/Day [1]	Lab Value	Flag*
xxx-xxx	xxxxxxxxxxxxxxx	xxx	xx.x – xx.x	xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
				xxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	H
				xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
	xxxxxxxxxxxxxx	xxx	xx.x – xx.x	xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
				xxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	H
				xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
	xxxxxxxxxxxxxxxx	xxx	xx.x – xx.x	xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
				xxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	H
				xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
xxx-xxx	xxxxxxxxxxxxxx	xxx	xx.x – xx.x	xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
				xxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	H
				xxxxxxxx			
	xxxxxxxxxxxxxx	xxx	xx.x – xx.x	xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
				xxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	H
				xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
xxx-xxx	xxxxxxxxxxxxxx	xxx	xx.x – xx.x	xxxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	
				xxxxxxx	DDMMMYYYY/HH:MM/XXX	xx.x	H
				xxxxxxxx			

Note: CS = clinically significant.
[1] Relative to first dose of study drug.
* H = above upper limit of normal reference range; L = below lower limit of normal reference range.

Listing 16.2.8.2
Laboratory Assessments – Blood Chemistry

Note to Programmer: *Repeat listing 16.2.8.1 for blood chemistry parameters*

Listing 16.2.8.3
Laboratory Assessments – Urinalysis

Note to Programmer: *Repeat listing 16.2.8.1 for urinalysis parameters*

Listing 16.2.8.4
Pregnancy Test

Clinical Site Subject No.	Visit	Assessment Date/Day []	Sample Type	Result
xxxx-xxx	Screening	DDMMMYYYY/XXX	Serum	Negative
	Day 1	DDMMMYYYY/XXX	Urine	Negative
	Week 26	DDMMMYYYY/XXX	Serum	Negative
	Week 52	DDMMMYYYY/XXX	Serum	Negative
xxxx-xxx	Screening	DDMMMYYYY/XXX	Serum	Negative
	Day 1	DDMMMYYYY/XXX	Urine	Negative

[1] Relative to first dose of study drug.

Listing 16.2.8.5
Follicle Stimulating Hormone

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	FSH > 30 IU/L
xxxx-xxx	Screening	DDMMMYYYY/XX	Yes

[1] Relative to first dose of study drug.

Listing 16.2.8.6
Laboratory Assessments - Comments

Clinical Site Subject No.	Parameter (Unit)	Normal Range Low-High	Visit	Sample Date/Day [1]/Time	Lab Value	Comment
xxx-xxxxxx	xxxxxxx (xxxxxx)	x.x-x.x	Week xx	ddMMMyyyy/xx/hh:mm	x.x	<---text---------->
	xxxxxxx (xxxxxx)	x.x-x.x	Week xx	ddMMMyyyy/xx/hh:mm	x.x	<---text---------->
			Week xx	ddMMMyyyy/xx/hh:mm	x.x	<---text---------->

(Programming Note:Only list lab data having an associated comment in SDTM dataset SUPPLB.)

Listing 16.2.9.1
Vital Signs and Body Weight

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	Height (cm)	Weight (kg)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart Rate (bpm)	Respiratory Rate (resp/min)	Temp (C)
xxxx-xxx	Screening	DDMMMYYYY/ XX	XXX	XXX	XXX	XXX	XXX	XX	XX.X
								XX	XX.X
	Unscheduled	DDMMMYYYY/XX							
xxxx-xxx	Screening	DDMMMYYYY/XX							
	Unscheduled	DDMMMYYYY/XX							

Note: Height was only collected at screening. Only screening systolic/diastolic blood pressure and heart rate are presented on this listing..
[1] Relative to first dose of study drug.

Listing 16.2.9.2
12-Lead Electrocardiogram Report – Qualitative Data by Subject

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	Assessment Time	Investigator Interpretation of ECG Result [2]
xxxx-xxx	Screening	DDMMMYYYY/XX		
. . .	Unscheduled	DDMMMYYYY/XX	XX:XX	Abnormal, CS
xxxx-xxx	Screening	DDMMMYYYY/XX		
. . .	Unscheduled	DDMMMYYYY/XX	XX:XX	Abnormal, CS

[1] Relative to first dose of study drug.
[2] CS=Clinically significant.

Listing 16.2.9.3
Physical Examination

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	Assessment Time	Physical Exam Findings [2]
xxxx-xxx	Screening	DDMMMYYYY/XX		
	Unscheduled	DDMMMYYYY/XX		
xxxx-xxx	Screening	DDMMMYYYY/XX		
	Unscheduled	DDMMMYYYY/XX		

[1] Relative to first dose of study drug.
[2] CS=Clinically significant.

Listing 16.2.9.4
Neurological Examination

Clinical Site Subject No.	Visit	Assessment Date/Day [1]	Assessment Time	Neurological Exam Findings [2]
xxxx-xxx	Screening	DDMMMYYYY/XX	XX:XX	Normal
	Unscheduled	DDMMMYYYY/XX		
xxxx-xxx	Screening	DDMMMYYYY/XX		
	Unscheduled	DDMMMYYYY/XX		

[1] Relative to first dose of study drug.
[2] CS=Clinically significant.