STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2027-G000-201
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Study To Evaluate the Efficacy, Safety and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies
Date:	V4.0, 14 April 2020

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Table 1 Summary of Changes (Version 4)

Changes in Version 4	Rationale
Section 5.4 Efficacy Analyses and Section 7 Changes to Planned Analyses Revised the primary and secondary analyses o utilize MMRM for the primary analysis for non-EMA registration and have separate analyses for EMA registration.	These changes have been made due to correspondence with the FDA, separate analyses will be performed for the different registrations for the non-EMA and EMA. The supplementary analyses have been reduced to allow for clearer interpretation of the co-primary analyses.

Table 2 Summary of Changes (Version 3)

Changes in Version 3	Rationale
Sections 3.1.2, 5.1.2 and 5.4.2. Revised the order of the secondary efficacy objectives, endpoints and analyses.	To enable the secondary endpoints to be part of the statistical hierarchy of testing
Section 5.2.3 Protocol Deviations. Removed restricted medications criteria. Added criteria relating to exclusion criteria 6.	Due to blinded data review, it was found the assumption that the restricted medications would improve efficacy were incorrect, this is investigated in sensitivity analyses only. As per Exclusion Criteria 6, Geriatric Depression Scale (GDS) greater than 8, may affect efficacy.
Section 5.4.1 Primary Efficacy Analysis. Co-primary Analysis of Change from Baseline in the MoCA Total Score at 12 Weeks. Further define MAR and MNAR for the MoCA analysis.	For clarification purposes.
Section 5.4.1 Primary Efficacy Analysis, Section 5.4.2 Secondary Efficacy Analysis, Section 5.4.3 Exploratory Efficacy Analysis. Changes to censoring on restricted medications, removed from all and add as a sensitivity analysis on co-primaries only.	Due to blinded data review, it was found the assumption that the restricted medications would improve efficacy were incorrect, therefore the censoring of this data is moved to sensitivity analyses only.

Table 3 Summary of Changes (Version 2)

Changes in Version 2	Rationale
Throughout the document: Editorial corrections are made to correct typos	For clarification purposes.
Throughout the document: based on Protocol Version 4, the addition of memantine	Added subgroup analyses for memantine use.
Section 4 "Sample Size" additional information on current sample size and study data	The clinical meaningful treatment difference and SD for MoCA total score assumptions have been updated based on partial blinded study data.
Section 5.2.2 "Subject Disposition"	Wording added to summarize overall and by stratification factors.
Section 5.2.4 "Demographic and Other Baseline Characteristics"	Added further variables to be summarized.
Section 5.4.1 "Co-primary Analysis of the CIBIC-Plus Scale at 12 Weeks". Edited regarding censoring of AChEI and non-AChEI restricted medications "Table 4: Primary Efficacy Analyses" added.	Co-primary Analysis of the CIBIC-Plus Scale at 12 Weeks edited to add that changes in both AChEI and non-AChEI restricted medications will be censored. This is due to what CIBIC-Plus measures and maybe affected by changes in any of these medications. Table added to describe all of the primary, sensitivity and supplementary analyses.
Section 5.4.2 and 5.4.3 "Secondary and Exploratory Efficacy Analyses" "Table 5: Secondary Efficacy Analyses" added.	Clarification and additional analyses added regarding the censoring of changes in AChEI medications and censoring of both AChEI and non-AChEI restricted medications. Table added to describe all the secondary analyses.
Section 5.6.5 "Electrocardiograms"	Further abnormal ECGs summary added.
Section 5.6.6.2 "UPDRS-III"	Added summary censoring data after changes in DLB medication.
Section 5.7 "Other Analyses"	Detail added for censoring of data based on medication changes.

Table 3 Summary of Changes (Version 2)

Changes in Version 2	Rationale
Section 6 “Interim Analysis”, deleted.	Removed to coincide with decision to not do the adhoc futility analysis as per protocol amendment 03.
Section 8.1.2 “ Treatment Duration for Efficacy Analyses”.	Clarification for windowing
Section 8.1.4 “Censoring of Efficacy Data Based on Changes in Medications” added.	Added section to describe extra analyses and descriptions of censoring
Section 8.2.2 “Treatment Duration for Safety Analyses” added wording regarding treatment emergence.	Clarification regarding the definition of treatment emergent and windowing.
Section 8.2.4 “Safety Data Collected after the ED Visit”	Clarification given that separate ED visits will not be produced for the safety data, only treatment emergent data will be windowed as appropriate.
Section 8.4 “Algorithms for Safety Parameters” added	UPDRS-III subscore derivations added.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AChEI	Acetylcholinesterase inhibitors
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
C-CASA	Columbia- classification algorithm of suicide assessment
CFI	Cognitive Fluctuation Inventory
CGIC-DLB	Clinician Global Impression of Change in Dementia with Lewy Bodies
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CIBIC-Plus	Clinician's Interview Based Impression of Change Plus Caregiver Input
CRF	Case report form
CSF	Cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbia – Suicide Severity Rating Scale
CV	Coefficient of variation
DEMQOL	Dementia Quality of Life Measure
DEMQOL-Proxy	Dementia Quality of Life Measure by Proxy
DLB	Dementia with Lewy bodies
DMC	Data monitoring committee
DSMB	Data safety monitoring board
ECG	Electrocardiography
eCRF	Electronic case report form
ED	Early Discontinuation
EEG	Electroencephalography

EQ VAS	Overall health rating of EQ-5D
EQ-5D	EuroQol-5 Dimension questionnaire
EQ-5D Proxy	EuroQol-5 Dimension questionnaire by Proxy
FAS	Full analysis set
GDS	Geriatric Depression Scale
GLMM	Generalized linear mixed models
IA	Interim Analysis
ITT	Intent to treat
LP	Lumbar puncture
LS	Least squares
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effects models for repeated measures
MMSE	Mini Mental State Examination
MNAR	Missing not at random
MoCA	Montreal Cognitive Assessment
NPI	Neuropsychiatric Inventory
PD	Pharmacodynamic
PGx	Pharmacogenomic
PK	Pharmacokinetic
PP	Per protocol
PT	Preferred term
QALYs	Quality-adjusted life years
QD	Once daily
QoL	Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system

SCOPA-Sleep	Scales for Outcome in Parkinson's disease-Sleep
SD	Standard deviation
SE	Standard error
SI	Système International
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEMAV	Treatment-emergent markedly abnormal laboratory
TLG	Tables, listings, and graphs
UPDRS-III	Unified Parkinson Disease Rating Scale - III
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results based on clinical database for the Eisai Protocol E2027-G000-201. PK/PD/PGx analysis and relevant endpoints will not be described in this SAP but will be described in separate PK/PD/PGx analysis plans.

3.1 Study Objectives

3.1.1 Primary Objectives

To determine whether E2027 is superior to placebo on the cognitive endpoint of Montreal Cognitive Assessment (MoCA) in subjects with dementia with Lewy bodies (DLB) after 12 weeks of treatment

To determine whether E2027 is superior to placebo on the global clinical endpoint of Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus) after 12 weeks of treatment

3.1.2 Secondary Objectives

1. To determine whether E2027 is superior to placebo on the following secondary endpoints after 12 weeks of treatment:

    1.1. Clinician Global Impression of Change in Dementia with Lewy Bodies (CGIC-DLB)

    1.2. Cognitive Fluctuation Inventory (CFI)

    1.3. Mini-Mental State Examination (MMSE)

    1.4. Neuropsychiatric Inventory (NPI)

2. To evaluate the safety and tolerability of E2027 in subjects with DLB

3. To characterize the population pharmacokinetics (PPK) of E2027 in subjects with DLB, including evaluation of the effects of intrinsic and extrinsic factors on E2027 PK

3.1.3 Exploratory Objectives

1. To explore the efficacy of E2027 compared to placebo on the following endpoints after 12 weeks of treatment:

    1.1. Scales for Outcome in Parkinson's disease-Sleep (SCOPA-Sleep)

1.2. Dementia-related quality of life as assessed by the Dementia Quality of Life Measure (DEMQOL; interview of subject) and Dementia Quality of Life Measure by Proxy (DEMQOL-Proxy; interview of caregiver or informant about subject)

1.3. General health status as assessed by the EuroQol-5 Dimension questionnaire (EQ-5D; completed by subject) and EuroQol-5 Dimensions questionnaire by Proxy Version 1 (EQ 5D Proxy; caregiver or informant completion of report about subject)

To evaluate the relationship between PK exposure of E2027 and its effects on various efficacy and safety endpoints

To explore the PK/pharmacodynamic (PD) relationship between the exposure of E2027 in cerebrospinal fluid (CSF)/plasma and its effects on CSF PD biomarker endpoints, including CSF cyclic guanosine monophosphate (cGMP), if data permit

To explore the relationship between the E2027 PD effects (including CSF cGMP) with E2027 effects on various efficacy endpoints, if data permit

To explore collected pharmacogenomic (PGx) samples by investigating heterogeneity in clinical features of disease, including differences in baseline characteristics as well as response to compound (efficacy, safety and/or absorption, distribution, metabolism, and excretion [ADME]). These exploratory analyses are not limited to this protocol or project. These findings may be used for identification and validation of new drug targets

3.2 Overall Study Design and Plan

This is a multicentre, randomized, double-blind, placebo-controlled, parallel-group study in subjects with DLB who will be treated with placebo or E2027 (50 mg once daily [QD]) for 12 weeks.

In some of the countries selected for this study, donepezil is approved for DLB and acetylcholinesterase inhibitors (AChEIs) are often used as part of standard care in patients with DLB. Therefore, the study design allows for add-on therapy to standard of care for DLB, which includes AChEI and/or memantine at stable doses, except for any prohibited medications specified in this protocol. Subjects who are not receiving AChEI or memantine are also eligible, but are not permitted to start such medications during the study. Randomization will be stratified based on whether subjects are on a stabilized dose of AChEI or not and by geographical region (ie, North America, Europe, or Japan). Subjects will be randomly assigned to placebo or E2027 (50 mg QD) in a ratio of 1:1

For all subjects, study participation will comprise 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last for up to 6 weeks and will include a

Screening Period (up to 5 weeks) and a Baseline Period (1 week). The Randomization Phase will last for 16 weeks and will include a Treatment Period (12 weeks) and a Follow-up Period (4 weeks).

Screening will occur between Day -42 and Day -8. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Eligibility assessments at Screening will be conducted in tiers and subjects will need to satisfy eligibility criteria in each tier before proceeding to the next tier. There are total 6 tiers. Subjects who are deemed eligible after passing all tiers at Screening will proceed to the Baseline Visit.

The baseline visit may take place at any time up to 7 days before the first dose of study drug (Day 1, ie, during Day -7 to Day -1, but should take place at least 2 weeks after the Screening Visit Tier 2 assessments).

After completing study assessments at the Baseline Visit, subjects who continue to be eligible will proceed to the Randomization Phase, and will be randomly assigned to placebo or E2027 (50 mg QD). They will be provided with study drug (placebo or E2027) to start administration in the morning of Day 1 at home. They will continue to take study drug for 12 weeks. During the Treatment Period study visits will be conducted after 2, 4, 6, 9 and 12 weeks on study drug. Safety assessments will be conducted at all these visits. Efficacy assessments will be performed after 6 and 12 weeks on study drug and should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning).

After the Treatment Period, subjects will complete a Follow-Up Visit 4 weeks after the final dose of study drug.

The end of study was the date of the last study visit for the last subject.

Early Discontinuation

Subjects who prematurely discontinue study drug for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their final dose of study drug. The safety and efficacy assessments normally performed after 12 weeks of treatment will be conducted at the ED Visit. In addition, subjects who discontinue study drug are expected to continue in the study for the originally scheduled visits, starting with next such visit that is >7 days after the ED Visit. Subjects who prematurely discontinue the study should attend at least 1 originally scheduled visit after the ED Visit.

CSF Substudy

A subset of subjects will participate in a substudy in which CSF will be collected by lumbar puncture (LP) during Screening and again during the Randomization Phase after 9 weeks of treatment on study drug. Participation in the substudy will be voluntary. After they have completed all screening assessments and are deemed eligible for the study, a baseline CSF sample will be collected at least 7 days before the Baseline Visit. After they have completed

9 weeks of treatment, they will have a 2nd CSF sample collected. The CSF samples will be collected in the morning at approximately the same time, either in the fasted state (preferred) or at least 2 hours after breakfast.

As data permit, CSF cGMP will be assayed to evaluate the PD effects of E2027 in these subjects with DLB. Other CSF PD biomarkers related to DLB or E2027 PD effects may also be assayed if appropriate. CSF E2027 concentrations will also be determined.

Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the study is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

4 DETERMINATION OF SAMPLE SIZE

The MoCA scale was assessed in DLB subjects and reported by Biundo et al. (2016). The observed mean change from baseline in the MoCA total score at 1 year in this report is -1.04 points and the corresponding standard deviation (SD) is 1.32 points. An estimation of the mean change from baseline in the MoCA total score at 3 months is approximately -0.26 points using linear interpolation. It is assumed that E2027 would improve the MoCA total score as compared with baseline and achieve a mean treatment difference of approximately 0.6 points between E2027 and placebo at 12 weeks. The SD of change from baseline in the MoCA total score at 3 months is expected to be smaller than that at 1 year. A conservative estimate of the SD of change from baseline in the MoCA total score is 1.3 points at 12 weeks.

In a 12-week donepezil monotherapy study in subjects with DLB (E2020-J081-431), the estimated proportional odds ratio based on the CIBIC-Plus scale for donepezil 10 mg relative to placebo was 6.14. It is assumed that E2027 would achieve a proportional odds ratio of 2.607 relative to placebo (ie, 42% of the effect size observed in the above donepezil study).

With 80 subjects completing per arm (for 91 randomized subjects per arm, assuming a 12% dropout rate), this study will have approximately 80% power to detect the above effect sizes (ie, mean treatment difference of approximately 0.6 points based MoCA total score and proportional odds ratio of 2.607 based on CIBIC-Plus scale for E2027 relative to placebo) in both co-primary endpoints simultaneously. Therefore, the total sample size of 182 randomized subjects is planned, assuming a 12% dropout rate.

The MoCA total score on blinded study data shows SD is 3 points, to keep 80% power and the effect size of 0.46 with 80 subjects completing each arm, the treatment difference would need to be 1.4. A treatment difference of 1.4 has been shown with blinded study data to be similar to a one unit change in CIBIC-Plus, which is clinically meaningful.

CSF Substudy

Participation in the CSF substudy is voluntary. It is estimated that approximately 30% of subjects will participate in the CSF substudy. If the dropout rate in the CSF substudy is 12%, 20%, or 50%, then the number of subjects having final CSF assessment would be approximately 48, 44, or 27, respectively. The estimated standard deviation of percent change from baseline of cGMP concentrations after 9 weeks of treatment from pooled subjects in the CSF substudy is approximately 130%. The width of the 95% CI of the mean difference of percent change from baseline of cGMP concentrations after 9 weeks of treatment between E2027 and placebo for the 3 different sample sizes above would be approximately 74%, 77%, or 96%, respectively. Since mean percent change from baseline of cGMP concentrations after 9 weeks of treatment in the E2027 and placebo groups are expected to be approximately 200% and 5%, respectively, the sample size of the CSF substudy would be adequate to detect the mean difference of percent change from baseline of cGMP concentrations after 9 weeks of treatment between E2027 and placebo groups.

5 STATISTICAL METHODS

All statistical tests will be 2-sided at the 5% significance level unless otherwise stated. All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum, maximum and number of subjects with non-missing data. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

The details of calculating each efficacy endpoint are presented in Section 8.3 ALGORITHMS FOR EFFICACY PARAMETERS. The details of calculating each QoL endpoint are presented in Section 5.7 OTHER ANALYSES.

5.1.1 Primary Endpoints

Change from baseline in the MoCA total score at 12 weeks of treatment

CIBIC-Plus scale at 12 weeks of treatment

5.1.2 Secondary Endpoints

CGIC-DLB scale at 12 weeks of treatment

- Change from baseline at 12 weeks of treatment in the following endpoints:

- CFI score
- MMSE total score
- NPI total score, subscores and caregiver or informant distress score

Safety and tolerability of E2027 as measured by

- Incidence of adverse events including severe AEs, serious AEs, AEs resulting in discontinuation
- Incidence of orthostatic hypotension and orthostatic tachycardia
- Incidence of markedly abnormal laboratory values and shifts from baseline of laboratory values
- Incidence of abnormal ECG parameters and abnormal ECG findings
- Incidence of suicidality based on C-SSRS
- Changes from baseline in the total score of UPDRS-III

5.1.3 Exploratory Endpoint(s)

- Change from baseline at 12 weeks of treatment in the following endpoints:
  - SCOPA-Sleep total score and subscores
- Change from baseline at 12 weeks of treatment in the following endpoints:
  - Total score and domain scores of the DEMQOL and DEMQOL-Proxy
  - EQ-5D utility score and EQ-5D health status rating
- Percentage change from baseline in CSF cGMP concentrations after 9 weeks of treatment
- CIBIC-plus sub-items (Attention, Orientation, Memory, etc) rating

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The Randomized Set is the group of subjects who are randomized to study treatment.

The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 post dose safety assessment. The Safety Analysis Set will be used in the statistical analyses for safety. In the event that a subject received study drug different from the one to which this subject was randomized, the subject's safety data will be analyzed "as actually treated" for the safety analyses.

The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 post dose primary efficacy measurement. In the event that a subject received study drug different from the one to which this subject was

randomized, the subject's efficacy data will be analyzed "as randomized" for the FAS analyses.

The PK Analysis Set is the group of subjects with at least 1 quantifiable E2027 serum concentration with a documented dosing history.

The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

The Per Protocol (PP) Analysis Set is the subset of subjects in the Full Analysis Set who sufficiently complied with the protocol. It may include subjects who complete certain pre-specified minimal exposure to the treatment and have no major protocol violations such as wrong diagnosis, error in treatment assignment, use of prohibited medication and poor compliance. The precise reasons for excluding subjects from the Per Protocol Set will be fully defined and documented before database lock, see Section 5.2.3.

5.2.2 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects by each site will be summarized by treatment group and total.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group, overall and by stratification factors.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on Early Discontinuation from Study Drug eCRF. The number (percent) will be presented by treatment group and total, overall and by stratification factors. Subjects who discontinued study treatment but were followed up for efficacy assessments after treatment discontinuation will also be summarized.

5.2.3 Protocol Deviations

Major protocol deviations for the PP Analysis Set include:

- Subject did not meet Inclusion Criterion #2, which was: 2. Meet criteria for probable DLB (e.g. date of diagnosis of DLB missing).
- Subject met Exclusion Criteria #6, which was: 6. GDS score >8.

- Subject received incorrect study treatment for more than 6 weeks.
- Subject initiated prohibited medications used in the treatment of dementia during the 12 weeks treatment period.

Subject had poor compliance with study treatment (e.g., overall compliance is <80%).

In addition, subjects with treatment duration less than 6 weeks will be excluded from the PP Analysis Set.

The number (percentage) of subjects excluded from PP analysis will be summarized by reason for exclusion and treatment group. A listing of subjects excluded from PP analysis will be provided along with the description of reason for exclusion.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for the Safety Analysis Set, FAS and PP Analysis Set will be summarized for each treatment group using descriptive statistics, overall and by stratification factors. Continuous demographic and baseline variables include age, age at diagnosis, age at onset, years since onset of symptoms, MoCA total score, NPI total score, NPI-4 score, NPI-10 score, NPI subscores, MMSE total score, CFI score, body weight, height, disease duration, baseline UPDRS part III score, CSF cGMP, EQ-5D, EQ-5D proxy, EQ-5D VAS score, EQ-5D VAS score proxy, DEMQOL, DEMQOL proxy, SCOPA – Sleep Overall, SFQ Score, average time per day for caregiver to spend with patient, and average days per week for caregiver to spend with patient; categorical variables include age subgroup (< 65, ≥ 65 to <80, ≥ 80), sex, race, ethnicity, region, CIBIS Plus, MMSE total score subgroup (14-19, 20-26), C-CASA, C-SSRS not completed, ongoing treatment with AChEIs (yes or no), treatment with memantine (yes or no), treatment with AChEI and/or memantine (none, AChEI only, memantine only, AChEI and memantine), Hoehn & Yahr stage, relationship of caregiver to patient, caregiver reside with the patient (Yes or Not), have each clinical core feature (hallucination, fluctuation, parkinsonism, RBD) (Yes or Not), and have 2 or more core clinical feature or have only 1 clinical feature (Appendix 1 of protocol: Diagnostic Criteria for Probable Dementia With Lewy Bodies (DLB)), have each clinical supportive feature, have each indicative biomarker. Where Screening values are also collected, these may be summarized also.

Where the date of diagnosis only contains the year of diagnosis, the age of diagnosis will use the year of diagnosis – year of birth.

MEDICAL HISTORY

The medical history verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be coded to the MedDRA (Version 19.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

The number (percent) of subjects will be presented by SOC and PT for each treatment group.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC), and WHO DD preferred term. Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug and continued up to the last dose. Prior and concomitant therapies for DLB and those for non-DLB will be summarized separately, the summaries showing therapies for DLB will also be summarized separately based on AChEI stratification.

The number (percentage) of subjects with changes in AChEI and non-AChEI restricted medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC), and WHO DD preferred term.

5.2.6 Treatment Compliance

Percent compliance will be calculated for the FAS as follows:

$$\text{Compliance} = \frac{\text{Total number of tablets dispensed} - \text{Total number of tablets returned}}{\text{Planned Total number of tablets to be taken}} \times 100\%$$

Overall compliance with study medication will be summarized using descriptive statistics (median, mean, standard deviation, minimum, maximum, and number of subjects with non-missing data) for each treatment group. Subjects will also be categorized by compliance criteria <50%, ≥50%-<80%, ≥80%-≤100%, >100% - ≤120%, >120% and missing. The maximum of planned total number of tablets to be taken will be 84.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

This is a multi-center, international study conducted in three geographic regions, i.e. United States, Europe, and Japan. Sites will be pooled into the three regions, in order to have sufficient number of subjects per treatment group.

5.3.2 Adjustments for Covariates of Interest

The baseline value will be used as a covariate, and stratification variables (on AChEI or not and geographical region (US, Europe, Japan)) will be used as factors in the efficacy models

for analysis of continuous endpoints. Baseline for the primary and secondary efficacy endpoints is defined as the last pre-treatment assessment.

5.3.3 Multiple Comparisons/Multiplicity

There are 2 co-primary endpoints, change from baseline in the MoCA total score at 12 weeks and CIBIC-Plus score at 12 weeks. Overall there are 2 null hypotheses to be tested in the primary efficacy analysis. The study will be considered positive if statistically significant improvement (at level of 0.05 (2-sided) or 0.025 (1-sided)) is observed in both co-primary endpoints in E2027.

5.3.4 Examination of Subgroups

The co-primary and secondary efficacy endpoints, treatment-emergent adverse events, treatment-emergent markedly abnormal laboratory values will be examined for the following subgroups:

- On AChEI at baseline (Yes or Not)
- Region (US, Europe, Japan)
- Receiving memantine at baseline (Yes or No)
- AChEI and/or memantine at baseline (none, AChEI only, memantine only, AChEI+memantine)
- Hoehn & Yahr stage (0&I&II or III)

In addition, the co-primary and secondary efficacy endpoints will also be examined by the following subgroups:

- Baseline MMSE subgroup ($\geq$14 total score $\leq$19, $\geq$20 total score $\leq$26)
- Age (<65, $\geq$ 65 to <80, $\geq$ 80)
- NPI hallucination sub-item score ($\geq$median/<median)
- Caregiver's time per week to spend with subject ($\geq$median/<median)

For other demography and safety data (vital signs, ECGs, etc), the summaries will be subgrouped by stratification factors, as appropriate.

Where subgroups are small, summaries and analyses will be produced, caution will be used in the interpretation of those subgroups.

5.3.5 Handling of Missing Data, Drop-outs, and Outliers

5.3.5.1 Efficacy

For non-EMA registration, for primary and secondary efficacy endpoints, there will be no imputation of missing value. MMRM and GLMM will be used to analyze repeated measures of continuous and ordinal data, respectively.

For EMA registration, for co-primary efficacy endpoint MoCA and all continuous secondary efficacy endpoints, there will be no imputation of missing value at individual level. The statistical estimate will be calculated based on the mean imputation method proposed by Mehrotra et al (2017). For EMA registration, the missing co-primary efficacy endpoint CIBIC-Plus and ordinal secondary efficacy endpoint will be imputed using control-based pattern imputation at subject level (Yuan 2014).

The date of change in AChEIs stable dose during treatment period, Screening and 12 weeks prior to Screening will be used in the sensitivity analysis to determine the censoring time. In case the date of change in AChEIs stable dose is missing, the missing date will be imputed similarly to missing start date of concomitant medication but replacing the First Dose Date by Last Visit Date before the change in AChEIs stable dose as reference date in the imputation. Please refer to AChEIs Stable Dose CRF page to determine the last visit date before the change in AChEIs stable dose. Where non-AChEI restricted medications are changed during the treatment period, Screening and 4 weeks prior to Screening (12 weeks prior to Screening for memantine), the above method will be used similarly.

Post-ED data will be included in all the analyses.

5.3.5.2 Safety

The methods for handling missing start and end dates are described in standard Eisai SDTM Domain Mapping Specifications Template (Appendix 13.4) and documented in SDTM+ specification.

All the listings will display the original missing values.

5.3.6 Other Considerations

Not Applicable.

5.4 Efficacy Analyses

5.4.1 Primary Efficacy Analyses

The treatment effect of interest will be the efficacy as measured by co-primary endpoints that would be observed at 12 weeks regardless of whether or when the assigned treatment was discontinued due to adverse event, lack of efficacy or any other events related to treatment or

study outcome. The target population is DLB subjects defined by inclusion/exclusion criteria.

There are 2 co-primary efficacy endpoints, change from baseline in the MoCA total score at 12 weeks and CIBIC-Plus scale at 12 weeks. Overall there are 2 null hypotheses (H_0) to be tested in the primary analysis:

H_{01}: There is no difference in the mean change from baseline in the MoCA total score at 12 weeks between E2027 and placebo.

H_{02}: The proportional odds ratio based on CIBIC-Plus scale at 12 weeks between E2027 and placebo is equal to 1.

The corresponding 2 alternative hypotheses are that there is a difference in the mean change from baseline in MoCA total score at 12 weeks in this co-primary endpoint between E2027 and placebo and the proportional odds ratio based on CIBIC-Plus scale at 12 weeks between E2027 and placebo is not equal to 1. The study will be considered positive if statistically significant improvement (at level of 0.05 (2-sided) or 0.025 (1-sided)) is observed in both co-primary endpoints in E2027.

Due to correspondence with the FDA during the study, separate analyses will be performed for the non-EMA and EMA registrations, the endpoints remain identical.

Non-EMA Analyses

Co-primary Analysis of Change from Baseline in the MoCA Total Score at 12 Weeks for non-EMA registration

Change from baseline in the MoCA total score at 12 weeks will be analyzed using MMRM. The MMRM model will include baseline variable (corresponding to the response variable in the model) as a covariate, treatment group, visit (Week 6 and Week 12), randomization stratification variables (receiving AChEI or not, geographical region [North America, Europe, Japan]), baseline variable-by-visit interaction, and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be used to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom when unstructured covariance matrix is used. If MMRM fails to converge and a structured covariance matrix is used, the empirical method will be used to compute variance-covariance matrix of the fixed-effects parameters (sandwich estimator).

Sensitivity Analysis of Change from Baseline in the MoCA Total Score at 12 Weeks for non-EMA registration

A sensitivity analysis will be produced to repeat the primary analysis for MoCA but to censor data after changes in AChEI medications.

Co-primary Analysis of the CIBIC-Plus Scale at 12 Weeks for non-EMA registration

CIBIC-Plus scale at 12 weeks will be analyzed using GLMM. The GLMM model will include treatment, visit, randomization stratification variables (receiving AChEI or not, geographical region [North America, Europe, Japan]), and treatment x visit as fixed effects. The model will be fitted using GLMM with a multinomial distribution and a cumulative logit link function. If the proportional odds assumption is contradicted ($p < 0.05$ in Score Test for the Proportional Odds Assumption) by the observed data in either the entire population or any stratum, the GLMM method will be replaced by the nonparametric van Elteren test adjusting 2 randomization stratification variables (on stabilized AChEI dose or not; geographical region [North America, Europe, Japan]).

Sensitivity Analysis of the CIBIC-Plus Scale at 12 Weeks for non-EMA registration

A sensitivity analysis will be produced to repeat the primary analysis for CIBIC-Plus but to censor data after changes in both AChEI and non-AChEI medications.

EMA Analyses

Co-primary Analysis of Change from Baseline in the MoCA Total Score at 12 Weeks for EMA registration

The change from baseline of MoCA total score for E2027 dose compared to placebo will be analyzed using the approach proposed by Mehrotra et al (2017) with slight modification based on reasons for missing data. The following is a list of the missing reasons and their missing mechanisms:

Data not observed because of dropouts (primary reason) due to AEs, lack of efficacy or any other intercurrent events related to treatment or study outcome will be considered as missing not at random (MNAR). Where there are other/secondary reasons for dropout that relate to a new drug being taken in response to an AE, this will also be counted as MNAR, even if the primary reasons for drop out may not be classed as not related to treatment or outcome. Where data are not done with the patient continuing study, the data will be considered MNAR where reasons for missingness are related to AEs, the subject is sleepy/drowsy, the subject is delirious, or the subject refused/declined (where refusal was not related to withdrawal of consent).

Data not observed because of dropouts due to intercurrent events definitely not related to treatment or outcome (eg, withdraw consent due to logistical problems) will be considered as missing at random (MAR). Where data are not done with the patient continuing study, the data will be considered MAR where reasons for missingness are not related to AEs, the

subject is sleepy/drowsy, the subject is delirious, or the subject refused/declined, except if the refusal was due to withdrawal of consent.

The missing endpoint values considered as MAR can be imputed using condition distribution from the observed endpoint values and therefore can be handled by MMRM analysis assuming MAR. The mean of missing endpoint values in the E2027 treatment group considered as MAR can be viewed as implicitly imputed using the estimated means of endpoint values of completers and all subjects through MMRM analysis including completers and subjects with missing values considered as MAR in the E2027 treatment group. The mean of missing endpoint values in E2027 treatment group considered as MNAR will be imputed by the mean of the overall endpoint distribution under placebo as described next. The mean of the overall endpoint distribution under placebo will be obtained using mixed effects model of repeated measures (MMRM) within placebo group assuming MAR. Test statistics and the p-value will be obtained as described by Mehrotra, et al. (2017). In the presence of subjects with missing endpoint values considered as MAR, the superscript of "drop" refers to "subjects with missing endpoint values considered as MNAR" and the superscript of "comp" refers to "completers and subjects with missing endpoint values considered as MAR".

Sensitivity Analysis of Change from Baseline in the MoCA Total Score at 12 Weeks for EMA registration

A sensitivity analysis will be produced to repeat the primary analysis for MoCA but to censor data after changes in AChEI medications. For this the following missing mechanism will be added to the above reasons in the primary analysis

The effect had rescue medication not been made available to subjects prior to week 12 is not observable for subjects who initiated prohibited or restricted rescue medication. For these subjects, the data collected after initiation of prohibited rescue medication are assumed to contain no treatment effect in the E2027 treatment group. Technically, response data collected after initiation of new AChEIs or after any change in concomitant AChEIs stable dose will be treated as MNAR such that response data treated as MNAR in the E2027 treatment group would be imputed by the mean response in the placebo treatment group as described by the imputation method below.

In order to generate inputs for proposed primary and sensitivity analyses for the EMA registration, a MMRM will be used in separate MMRM analyses for each treatment group for all randomized subjects as well as completers assuming MAR for both treatment groups. The model will be adjusted for baseline MoCA, visit (Week 6 and Week 12), randomization stratification variables (receiving AChEI or not, geographical region [North America, Europe, Japan]), and baseline MoCA × visit as fixed effects. An unstructured covariance matrix will be used to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous

Compound Symmetry, and Compound Symmetry. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom when unstructured covariance matrix is used. If MMRM fails to converge and a structured covariance matrix is used, the empirical method will be used to compute variance-covariance matrix of the fixed-effects parameters (sandwich estimator). The values of baseline MoCA will be adjusted using the overall baseline mean of all study subjects in computing least square (LS)-means.

Co-primary Analysis of the CIBIC-Plus Scale at 12 Weeks for EMA registration

The primary analysis of the CIBIC-Plus scale at 12 weeks will be based on control-based pattern imputation at subject level (Yang, 2014). The CIBIC-Plus scale at 12 weeks will be imputed as an ordinal response variable. The same missing reasons and corresponding missing mechanism as in the analysis of change from baseline in MoCA total score will be used in this analysis. Only the missing ordinal responses in E2027 treatment group considered as MNAR will be imputed by ordinal responses observed in the placebo group using a pattern-mixture model approach under MNAR assumption. Other missing ordinal responses will be imputed assuming MAR. This can be implemented using multiple imputation in two steps: Step 1: impute E2027 dropouts considered as MAR and placebo dropouts using multiple imputations assuming MAR, e.g., generate N (N = 100 or larger) datasets; Step 2: impute the E2027 dropouts considered as MNAR using placebo data and a pattern-mixture approach under the MNAR assumption for each above imputed dataset in Step 1. In each step, the multiple imputations will be conducted using Proc MI implemented in SAS 9.4. The logistic regression method of classification variables will be specified to impute missing values for CIBIC-Plus scale. In Step 2, an additional MNAR statement will be used to complete the control-based pattern imputation at subject level.

The CIBIC-Plus scale at 12 weeks (observed or imputed) will be analyzed using the proportional odds model, a special case of generalized linear mixed models (GLMM), in multiply imputed data sets. The results obtained from all multiply imputed data sets will be combined for overall inference using Rubin's rules. The GLMM model will include treatment, randomization stratification variables (receiving AChEI or not, geographical region [North America, Europe, Japan]) as fixed effects. The model will be fitted using GLMM with a multinomial distribution and a cumulative logit link function. The proportional odds ratio estimate between E2027 and placebo, the corresponding 95% CI and P-values will be presented.

Sensitivity Analysis of the CIBIC-Plus Scale at 12 Weeks for EMA registration

A sensitivity analysis will be produced to repeat the primary analysis for CIBIC-Plus but to censor data after changes in both AChEI and non-AChEI medications. For this the following missing mechanism will be added to the above reasons in the primary analysis

The effect had rescue medication not been made available to subjects prior to week 12 is not observable for subjects who initiated prohibited or restricted rescue medication. For these subjects, the data collected after initiation of prohibited rescue medication are assumed to contain no treatment effect in the E2027 treatment group. Technically, response data collected after initiation of new AChEIs or non-AChEIs prohibited or restricted medications (as specified in Concomitant Drug/Therapy section in the protocol) or after any change in concomitant AChEIs or non-AChEIs stable dose will be treated as MNAR such that response data treated as MNAR in the E2027 treatment group would be imputed by the mean response in the placebo treatment group as described by the imputation method below.

A sensitivity analysis that excludes all subjects with changes in AChEI or non-AchEI restricted medications will also be performed.

If the proportional odds assumption is contradicted ($p < 0.05$ in Score Test for the Proportional Odds Assumption) by the observed data in either the entire population or any stratum, the GLMM method will be replaced by the nonparametric van Elteren test in both primary analysis and sensitivity analysis. The CIBIC-Plus scale at 12 weeks will be analyzed using van Elteren test adjusting 2 randomization stratification variables (on stabilized AChEI dose or not; geographical region [North America, Europe, Japan]). The H0 corresponding to the van Elteren test is that there is no difference in the location of distribution of the CIBIC-Plus scale at 12 weeks between E2027 and placebo. The corresponding alternative hypothesis is that there is a difference in the location of distribution of the CIBIC-Plus scale at 12 weeks between E2027 and placebo.

Supplementary Analysis for both non-EMA and EMA registrations

Subgroup (eg, region, age group, baseline AChEI status, baseline memantine status, and baseline MMSE subgroup) analyses will be performed for the subgroups defined in Section 5.3.4. The treatment effect within each subgroup and corresponding 95% CI for each co-primary endpoint will be summarized and also depicted using forest plot.

The treatment effect will be also examined using PP Analysis Set for each co-primary endpoint and analysis.

Descriptive statistics and graphical presentation for each co-primary endpoint will be provided.

Table 4 Primary Efficacy Analyses

Score		Analysis for non-EMA Registration	Analysis for EMA Registration
MoCA	Primary	MMRM	Control based mean imputation with Mehrotra

	Sensitivity	As primary, but censor changes in AChEI medication	As primary, but censor changes in AChEI medication
	Supplementary	As primary, subgroups	As primary, subgroups
		As primary, Per Protocol Analysis Set	As primary, Per Protocol Analysis Set
CIBIC-Plus	Primary	GLMM	Proportional odds model with control-based pattern imputation
	Sensitivity	Censor changes in both AChEI and non-AChEI medications	Censor changes in both AChEI and non-AChEI medications
		Exclude subjects with changes/new AChEI and non-AChEI restricted medications	Exclude subjects with changes/new AChEI and non-AChEI restricted medications
	Supplementary	As primary, subgroups	As primary, subgroups
		As primary, Per Protocol Analysis Set	As primary, Per Protocol Analysis Set

5.4.2 Secondary Efficacy Analyses

Table 5 Secondary Efficacy Analyses

Score		Analysis for non-EMA Registration	Analysis for EMA Registration
CGIC-DLB	Secondary analysis	GLMM	Proportional odds model with control-based pattern imputation
	Additional secondary analysis	Proportional odds model with control-based pattern imputation	GLMM
CFI	Secondary analysis	MMRM	Control based mean imputation with Mehrotra
	Additional secondary analysis	Control based mean imputation with Mehrotra	MMRM

MMSE	Secondary analysis	ANCOVA and multiple imputation (MI) assuming MAR	ANCOVA and control-based pattern imputation
NPI	Secondary analysis	MMRM	Control based mean imputation with Mehrotra
	Additional secondary analysis	Control based mean imputation with Mehrotra	MMRM
MoCA	Additional secondary analysis	Control based mean imputation with Mehrotra	MMRM
CIBIC-Plus	Additional secondary analysis	Proportional odds model with control-based pattern imputation	GLMM

Table 5 details the analyses for the secondary endpoints. Further details are described below.

The CGIC-DLB scale will be analyzed as ordinal response data in a manner similar to the primary analysis of co-primary endpoint based on CIBIC-Plus, according to both methods for non-EMA and EMA registrations.

CFI is a continuous variable and will be analyzed in a manner similar to the primary analysis of co-primary endpoint based on MoCA, according to both methods for non-EMA and EMA registrations.

For the non-EMA registration, MMSE will be analyzed using ANCOVA with MI assuming MAR. For the EMA registration, MMSE will be analyzed using ANCOVA with control-based pattern imputation at subject level for missing data handling (Yang Yuan, Paper SAS270-2014, SAS Institute Inc.). The ANCOVA model will include corresponding baseline as a covariate, with treatment group and randomization stratification variables as factors.

NPI will be analyzed in a manner similar to the primary analysis of co-primary endpoint based on MoCA, according to both methods for EMA, and non-EMA registrations.

The details of calculating all efficacy endpoints are presented in Section 8.3 ALGORITHMS FOR EFFICACY PARAMETERS.

Additional secondary efficacy analyses will be performed with or without inclusion of efficacy data collected after treatment discontinuation:

- For the non-EMA registration, the change from baseline in the MoCA total score at 12 weeks will be analyzed using the control based mean imputation with Mehrotra as described above in Section 5.4.1 for the primary analysis for EMA registration. This analysis will be repeated for the CFI and NPI.

- For the EMA registration, the change from baseline in the MoCA total score at 12 weeks, change from baseline in the MoCA total score at Follow-up visit and other continuous variables will be analyzed using MMRM, as described above in Section 5.4.1 for the primary analysis for non-EMA registration. This analysis will be repeated for the CFI and NPI.

- For the non-EMA registration, the CIBIC-Plus scale at 12 weeks and other ordinal response variable (CGIC-DLB) will be analyzed using Proportional odds model with control-based pattern imputation, as described above in Section 5.4.1 for the primary analysis for EMA registration.

- For the EMA registration, the CIBIC-Plus scale at 12 weeks and other ordinal response variable (CGIC-DLB) will be analyzed using GLMM, as described above in Section 5.4.1 for the primary analysis for the non-EMA registration.

5.4.3 Exploratory Efficacy Analyses

The sleep endpoint (SCOPA-Sleep total score and subscores) will be analyzed in a manner similar to co-primary endpoint based on MoCA (according to both methods for non-EMA and EMA registration). Endpoints based on CIBIC-plus sub-items (Attention, Orientation, Memory, etc) rating will be analyzed in a manner similar to co-primary endpoint based on CIBIC-plus in the additional secondary analysis (GLMM,). The analyses of quality of life endpoints are described in Section 5.7 Other Analyses. MoCA subscores (Attention Vigilance, Abstraction Score, Orientation Score, Delayed Recall Uncued Score, Language Total, Naming Score and Visuospatial/Executive Score) will also be analyzed similarly to the total score in the primary analysis (according to both methods for non-EMA and EMA registration).

If data permit, the relationship between E2027 PD effects on CSF cGMP (and other biomarkers) and various efficacy endpoints will be explored using correlation analysis. The association between individual CSF cGMP concentration data and individual efficacy data within each treatment group will be examined through scatter plots. The scatter plots including the Pearson correlation coefficient and Spearman correlation coefficient will be produced for each treatment group for percentage change from baseline in CSF cGMP concentrations after 9 weeks of treatment and change from baseline at 12 weeks of treatment of the following efficacy endpoints:

MoCA total score and subscores

NPI total score, subscores and caregiver distress score

MMSE total score

CFI score

CIBIC-plus rating (1 – 7) as continuous variable.

Linear models within each treatment group may be fitted to further quantify the relationship between the changes in efficacy endpoints and the percent changes in CSF cGMP concentrations in case the above scatter plots suggested that the percent changes in CSF cGMP concentrations at 9 weeks of treatment may be predictive to later changes in efficacy endpoints.

5.5 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

The PK Analysis Set will be used for E2027 concentration listings and for summaries of E2027 concentrations in plasma and CSF by visit. A population PK approach will be used to characterize the plasma PK of E2027. For this approach, PK data from this study will be pooled with relevant data from Phase 1 studies. The PD Analysis Set will be used for the summaries and analyses of CSF PD biomarkers. The percentage change from baseline in CSF cGMP and any other PD biomarkers after at least 9 weeks of treatment with study drug post randomization will be analyzed and presented graphically. Summary statistics for CSF PD biomarkers will be summarized by visit If data permit, a population PK/PD approach will be used to characterize the relationship between plasma and/or CSF exposures to E2027 and CSF PD biomarker levels. Further details on analyses of pharmacokinetic/pharmacodynamic data will be described in a separate PK/PD analysis plan.

Analyses of pharmacogenomic data will be described in a separate PGx analysis plan.

5.6 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality (C-SSRS), UPDRS-III, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements (including orthostatic changes) will be summarized by treatment group.

Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

Extent of exposure will be summarized by categories of cumulative weeks as well as by categories of duration of exposure. The number and percent of subjects for each exposure category will be presented by treatment group. Duration of exposure is the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug and will be summarized using descriptive statistics for

continuous variable by treatment group. Overall exposure (number of subject-weeks) is defined as summation over all subjects' exposure durations and will be summarized by treatment group, overall and by stratification factors.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 21.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerged during treatment or within 28 days following the last dose of study drug, having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Only those AEs that are treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-emergent AEs (TEAEs) will be summarized by treatment group, overall and by stratification factors, on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (related and not related).

Summaries of common TEAEs will be produced.

TEAEs will be summarized by the following subgroups: on AChEI at baseline (Yes or Not), region (US, Europe, Japan), receiving memantine (yes or no), age (age < 65, $65 \leq$ age < 80, age ≥ 80 years) and Hoehn & Yahr stage (0&I&II or III), receiving AChEI and/or memantine (none, AChEI only, memantine only, AChEI+memantine).

A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for each treatment group, overall and by stratification factors. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group, overall and by stratification factors. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

TEAEs associated with special situations such as overdose, misuse, abuse, medication error, pregnancy, TEAEs with signal of possible drug abuse potential, and those requiring additional Medical Monitor follow-up will be listed and summarized similarly.

A summary of non-treatment emergent AEs will be produced, these are adverse events which occurred >28 days after final dose of study drug.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in protocol Section 9.5.1.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each post-baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit,treatment group, overall and by stratification factors, using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.5 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post-baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within treatment comparisons for each laboratory parameter will be based on 3-by-3 shift table that compares the baseline LNH classification to the LNH classification at each post-baseline visit and at the end of treatment. Similar shift tables will be used to compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

The Sponsor's Grading for Laboratory Values (see Appendix 13.1) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a laboratory value was determined to be a treatment-emergent markedly abnormal value (TEMAV) if the post-baseline grade increased from baseline and the post-baseline grade was greater than or equal to 2. For phosphate, a laboratory value was determined to be a treatment-emergent markedly abnormal value (TEMAV) if the post-baseline grade increased from baseline and the post-baseline grade was greater than or equal to 3. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, respiration rate, temperature and weight) and changes from baseline for above parameters as well as orthostatic changes for diastolic and systolic blood pressure, pulse will be presented by visit and treatment group, overall and by stratification factors.

Orthostatic hypotension is defined based on the following criteria per protocol:

Drop in standing systolic blood pressure >=20 mmHg compared to supine, or drop in standing diastolic blood pressure >=10 mmHg compared to supine.

Treatment-emergent orthostatic hypotension means if at baseline subject did not have SBP drop>=20 and no DBP drop>=10 compared to supine, but developed one or more of these two events during postbaseline visits.

Orthostatic tachycardia by numerical criteria is defined by the following numerical criteria:

Standing HR increases by >30 beats/min compared to supine AND absolute standing HR is >100 beats/min.

Orthostatic tachycardia without orthostatic hypotension will be considered a true orthostatic tachycardia and an instance of treatment emergent true orthostatic tachycardia is defined below:

1. Orthostatic tachycardia by above numerical criteria

2. No orthostatic hypotension (i.e. neither standing SBP drop by >20 nor standing DBP drop >10 compared to supine) at the same time point.

3. Does not meet criteria #1 and #2 at Baseline.

Additionally, instances of orthostatic hypotension by numerical criteria and treatment-emergent orthostatic hypotension, and instances of orthostatic tachycardia by numerical criteria and treatment-emergent true orthostatic tachycardia will be summarized by treatment group and visit, overall and by stratification factors.

Listing of vital signs including orthostatic changes will be provided.

In addition, the number (percentage) of subjects with clinically notable vital signs will be summarized by treatment group. Table 6 presents the clinical notable ranges.

Table 6 Clinical Notable Ranges for Vital Signs

Vital Sign	Criterion for Low	Criterion for High

Pulse (bpm)	**< 50**	**> 100**
Temperature (°C)	**< 36**	**> 38**
Weight (kg)	**< 45**	**> 100**
Systolic BP	**< 90**	**> 160**
Diastolic BP	**< 60**	**> 100**

5.6.5 Electrocardiograms

12-lead ECG will be performed at the baseline and post-baseline visit. The mean QTcF and other ECG intervals based on triplicate ECG will be obtained. Descriptive statistics for ECG parameters (QTcB, QTcF, PR interval QRS duration and RR interval) and changes from baseline will be presented by visit, treatment group, overall and by stratification factors. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; abnormal, clinically significant) to each post-baseline visit and to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized according to the following categories.

Clinically borderline or abnormal ECG results QTc Fridericia will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 msec
- QTcF interval >480 msec
- QTcF interval >500 msec

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 msec
- QTcF interval increases from baseline >60 msec

Plus at least one postbaseline QTcF interval >450 msec and increase from baseline >60 msec.

The number (percentage) of subjects, by treatment group and stratification factor, with at least 1 post-baseline abnormal ECG results during the treatment period, Weeks 2, 4, 6, 9 and 12 and EOT will be summarized according to the following categories:

- QTcF prolongation by >60 ms from baseline and absolute QTcF >450 ms
- QTcF prolongation to >500 ms
- Change from baseline of PR >= 25% to an absolute PR value of > 220 msec
- Change from baseline of QRS >= 25% to an absolute QRS value of > 120 msec.

5.6.6 Other Safety Analyses

5.6.6.1 C-SSRS

The C-SSRS responses will be mapped to C-CASA as suggested by the C-SSRS Columbia website http://www.cssrs.columbia.edu/clinical_trials.html.

Number (percentage) of subjects with any treatment-emergent suicidal ideation, suicidal behavior, and suicidality (suicidal ideation and/or behavior) will be displayed. "Treatment-emergence" is used for any new or worsened events during randomization phase (treatment and follow-up) compared with the baseline C-SSRS assessment. This will be produced for at any point during the study, and by visit.

Shift from baseline to the maximum suicidal ideation severity rating (0=no ideation present to 5=active ideation with specific plan and intent) during randomization phase will assess worsening of suicidal ideation. Any score greater than 0 indicates the presence of suicidal ideation while a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) can be used to indicate serious suicidal ideation.

5.6.6.2 UPDRS-III

Changes from baseline in the total score and four subscores of UPDRS-III will be summarized using descriptive statistics for continuous variable by visit and treatment group.

This scale evaluates extrapyramidal features in motor function in Parkinson's disease. It contains 33 items in 18 categories: (1) speech, (2) facial expression, (3) rigidity, (4) finger tapping, (5) hand movements, (6) supinational and pronation movements of hands, (7) toe tapping, (8) leg agility, (9) arising from chair, (10) gait, (11) freezing of gait, (12) postural stability, (13) posture, (14) body bradykinesia, (15) postural tremor of hands, (16) kinetic tremor of hands, (17) rest tremor amplitude and (18) constancy of rest tremor. Each item is scored 0 to 4, giving a total score range 0 to 132. As far as is practical, the motor assessments should be made with the subject in the "on" state at each visit and at the same time relative to the subject's last dose of Parkinson's disease medication (such as L-dopa). The four subscores are for tremor, rigidity, bradykinesia and postural instability and gait difficulty (PIGD), as calculated per Section 8.4.

The above summary will be repeated where UPDRS and their subscores will be censored if there are changes in the subjects DLB motor medications, censoring will occur at the date of medication change, no imputations will be made.

5.7 Other Analyses

The following endpoints will be analyzed in the FAS using ANCOVA or GLMM as appropriate, with MI assuming MAR:

Change from baseline in the quality of life endpoints (total score and domain scores of DEMQOL and DEMQOL-Proxy, the EQ-5D and EQ-5D Proxy index scores, and EQ VAS scale) at 12 weeks of treatment

Percent change from baseline in CSF cGMP concentrations after 9 weeks of treatment.

The ANCOVA model will include corresponding baseline as a covariate, with treatment group and randomization stratification variables as factors.

Description of DEMQOL and DEMQOL-Proxy:

The DEMQOL is a 28-item scale and DEMQOL-Proxy is a 31-item scale. All items are given a score from 1 to 4 (1 = a lot, 2 = quite a bit, 3 = a little, and 4 = not at all) and summed to produce total score and domain scores (daily activities, memory, negative emotion and positive emotion). However, large score indicates improvement for some items and deterioration for other items. In order to produce total score and domain scores such that a large score indicates improvement, the item score assuming large is deteriorating has to be reversed using the formula: new item score = (5 – current item score) or missing if the current item score is missing. The item score needs to be reversed for the following items:

DEMQOL: item1, item3, item5, item6, and item10;

DEMQOL-Proxy: item1, item4, item6, item8, and item11.

The missing item score will be imputed using developer's algorithm as described in developer's SPSS syntax (Appendix 13.2), i.e., if the number of missing item score for any subject is less than 15, then any missing item score will be imputed by subject's mean item score based on non-missing items; otherwise, the missing item score is still missing and the corresponding domain score and overall score is missing.

The responses for general quality of life item (very good, good, fair and poor) within DEMQOL and DEMQOL-Proxy are unscored and will be analyzed as ordinal response using GLMM.

Description of EuroQol 5 Dimensions (EQ-5D):

The EQ-5D-5L and Proxy version 1 for proxy EQ 5D-5L will be utilized in this study. The EQ-5D-5L scale consists of 5 specific questions (regarding mobility [walking], self-care [washing and dressing], usual activities, pain/discomfort, and anxiety/depression) with 5 levels of responses to each of the 5 questions and 1 overall health rating (EQ VAS). EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system (responses and questions), will be converted into a single index value (or utility score) using conversion matrix from the developer based on country specific value sets, which is stored in the excel file EQ-5D-5L_Crosswalk_Index_Value_Calculator and demonstrated by SAS syntax based on United States (Appendix 13.3). The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of health care interventions. The EQ VAS scale is numbered from 0 (the worst health) to 100 (the best health).

5.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

6 INTERIM ANALYSES

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis.

7 CHANGES IN THE PLANNED ANALYSES

Due to correspondence with the FDA during the study, the primary analyses for the non-EMA registrations were changed during the study to use MMRM for continuous efficacy data and GLMM for categorical efficacy data. The pre-planned analyses were kept for EMA registration, based on pre-study scientific advice from the EMA. The overall change was the ordering of importance of these analyses for each specific registration.

The co-primary analyses of MoCA and CIBIC-Plus will not be censored based on changes in the AChEI and non-AChEI restricted medications. This is based on review of blinded data which showed no improvement on efficacy after the use of this medication. As a sensitivity analysis, changes in AChEI restricted medications will be censored for MoCA and changes in either AChEI or non-AChEI restricted medications will be censored for CIBIC-Plus. The censoring differs based on the clinical interpretation that CIBIC-Plus measures aspects that could change with changes in the non-AChEI restricted medications.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Efficacy data handling

8.1.1 Pre-randomization/Baseline Efficacy

Baseline for all efficacy endpoints is defined as the last pre-treatment assessment. Additional baseline or mean baseline based on the mean of all pre-randomization values at the Screening and Baseline assessment will be explored to assess the potential pre-randomization variability in MoCA.

8.1.2 Treatment Duration for Efficacy Analyses

If additional data are collected other than scheduled visits, the additional data will be mapped to the closest scheduled visit if the data on this scheduled visit is missing.

A treatment visit is defined as occurring between the first dose and Early Discontinuation (ED) Visit (for early discontinuations) or Week 12 visit (for completers). A Post ED visit is defined as occurring after the ED Visit, more detail below.

To allow for the separate analyses where 1) all data is used and 2) only data up to and including ED visit is used, two analysis flags will be presented for efficacy analysis visits. Subjects who have a post ED visit and treatment visit in the same window will flag 1) the one closest to target date out of the two visits for all data, or 2) the treatment visit for data up to ED visit.

Table 7 Mapping of Study Day Ranges to Week for Efficacy

Windowing Period	Study Day Range (Relative to First Dose)	Week
Screening	(-42) ≤ Day ≤ (-8)	
Baseline	(-7) ≤ Day ≤ (-1)	
Analysis Baseline	-	a
Treatment	1 ≤ Day ≤ 63	6 (d)
Treatment	64 ≤ Day ≤ 98	12 (d)
Post ED	1 ≤ Day ≤ 63	6 (e)
Post ED	64 ≤ Day ≤ 98	12 (e)
End of Treatment (EOT)	-	b
Follow up	Follow up visit	c

a: All pretreatment assessments are conducted during Screening/Baseline Periods before Day 1. The Analysis Baseline is the last non-missing value measured during pretreatment phase.

b: For completer, EOT is the Week 12 visit. For early discontinuation, EOT is the Early Discontinuation (ED) visit. If the above visits are missing, then the last non-missing value collected not later than 7 days after the last dose will be used.

c: If follow up visit is missing, there will be no imputed follow up visit. Unscheduled visits can be mapped to follow up for listings, but the CRF follow up visit will be used for analysis.

d: For assessments with no Week 6 planned assessment, the window for the Week 12 assessment is $1 \leq \text{Day} \leq 98$. The data must be within in the date of first dose and date of ED visit (for early discontinuation subjects). For completers, date of last dose is irrelevant, window the visit based on study day range in above table.

e: These subjects have been discontinued from treatment but continue the study untreated. They will be flagged as Post ED in the data listings and datasets. These Post ED visits must be after the early discontinuation visit date. For assessments with no Week 6 planned assessment, the window for the Week 12 assessment is $1 \leq \text{Day} \leq 98$. For the analysis flag based on all data, where subjects have both Week 6 and Week 6 Post ED, the visit closest to the target date will be used, the same is true for Week 12.

8.1.3 Efficacy Data Collected After the ED Visit

Subjects who discontinue study drug are expected to continue in the study for the originally scheduled visits, starting with next such visit that is after the Early Discontinuation (ED) Visit. The scheduled visits post ED will be flagged to reflect its post ED status. The summary statistics by visit will presented twice, 1) for all data including those post ED, and 2) for data up to and including the ED visit.

8.1.4 Censoring of Efficacy Data Based on Changes in Medications

There are two types of censoring as part of the sensitivity analyses of the co-primary endpoints, censoring data based on changes to AChEI medications and censoring data based on changes in both AChEI and non-AChEI restricted medications.

MoCA AChEI only. CIBIC-Plus AChEI and non-AChEI restricted medications are censored. This is due to the type of effects measured by each set of scales and how the effects of changes in the groups of medications may affect these.

8.2 Safety data handling

8.2.1 Baseline Safety

The baseline value for all safety endpoints will be the last non-missing measurement occurring prior to the first dose of the study medication.

8.2.2 Treatment Duration for Safety Analyses

The treatment duration for all safety variables is considered to begin on Day 1 and ends 28 days after the last dose of study medication. Treatment emergent safety data (ie labs, vital signs and ECGs) are defined as observations that were recorded during treatment or within 28 days following the last dose of study drug, these will be flagged in the listings as "off treatment, but treatment emergent". This data will be windowed and summarized as described below. Data after 28 days of last dose will be flagged as Post TE and listed only.

For summaries of safety by time points, the time points will be relative to date of first dose. For standardized reporting, study day windows relative to the first dose (Day 1) in the study will be applied to determine into which week the data will be mapped. All pretreatment assessments are conducted during Screening/Baseline Periods before Day 1. The Analysis Baseline is the last non-missing pretreatment assessments. Scheduled, unscheduled, and early discontinuation visits will be mapped to weeks. Table 8 below gives the mapping of relative day ranges to week for non-AE safety variables. If a subject did not have a recorded observation falling within a given range of days in order to be assigned to a week, the subject's data for that week will be regarded as missing for summarization purposes. If there are two or more assessments in the same window, the following rules will be used:

- If the window is for the screening/baseline assessment, then the latest assessment will be used in the summary tables;
- If the window is for the follow-up assessment, then the latest assessment will be used in the summary tables;
- If the window is not for the screening/baseline or the follow-up assessment, then the assessment closest to the scheduled assessment will be used in the summary tables. Note that if two assessments are equidistant from the scheduled assessment then the last assessment of the two (within the allowable window) will be used.

Table 8 Mapping of Study Day Ranges to Week for Safety

Windowing Period	Study Day Range (Relative to First Dose)	Week
Screening	(-42) ≤ Day ≤ (-8)	
Baseline	(-7) ≤ Day ≤ (-1)	

Analysis Baseline	-	a
Treatment	1 ≤ Day ≤ 21	2
Treatment	22 ≤ Day ≤ 35	4
Treatment	36 ≤ Day ≤ 53	6
Treatment	54 ≤ Day ≤ 74	9
Treatment	75 ≤ Day ≤ 98	12
End of Treatment (EOT)	-	b
Follow up	Follow up visit	c

a: All pretreatment assessments are conducted during Screening/Baseline Periods before Day 1. The Analysis Baseline is the last non-missing value measured during pretreatment phase.

b: For completer, EOT is the Week 12 visit. For early discontinuation, EOT is the Early Discontinuation (ED) visit. If the above visits are missing, then the last non-missing value collected not later than 7 days after the last dose will be used.

c: If follow up visit is missing, there will be no imputed follow up visit.

For subject visits after the treatment emergent period (not defined as a CRF follow up visit) will be labelled as Post TE and listed only.

8.2.3 Handling of Replicate Data

A subject having an AE coded to the same preferred term more than once during the study will be counted only once in the incidence calculations for that AE. Similarly, if a subject has more than one AE in a single body system, the incidence will be counted only once for that body system. If a subject has the same AE more than once, the occurrence that is of greatest severity will be used in the calculation of the incidence of individual AE by severity. Similarly, the AE considered most closely related to study drug will be used in the calculation of incidence of individual AE by relationship in case a subject has the same AE more than once.

For the laboratory, vital signs, ECG, EEG and other safety variables datasets, the measurement noted as the scheduled visit measurement will be used in the analysis. If more than one assessment is present at a scheduled visit, then the nearest assessment for evaluation visit (day) will be used in the summaries of the actual values and changes from baseline. In the event of two assessments being equally close to the scheduled visit (day), the last assessment will be used.

Handling of prior/concomitant medication

If the subject has taken the same concomitant medication (as coded to preferred WHO-drug term) more than once, the subject will be counted only once in the tabulation.

8.2.4 Safety Data Collected After the ED Visit

No post TE data (data collected beyond treatment emergent window) will be summarized separately for safety summaries. If data is within the treatment emergent period, they will be windowed into the visits as above. Data that is not treatment emergent will be flagged in the listings.

8.3 Algorithms for Efficacy Parameters

This section describes the algorithms and missing data handling procedure to derive the totals scores for the efficacy parameters MoCA, NPI, MMSE, CFI, and SCOPA-Sleep.

Montreal Cognitive Assessment (MoCA)

This scale assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It is reported to be useful to characterize global cognitive impairment in DLB. The MoCA scale is composed of 11 assessments. The following are the assessments and possible points earned for each assessment:

Visuoconstructional skills (0 – 5 points), Naming (0 – 3 points), Memory (No points), Attention: Forward/backward digit span (0 – 2 points), Attention: Vigilance (0 – 1 point), Attention: Serial 7s (0 - 3 points), Language: Sentence repetition (0 – 2 points), Language: Verbal fluency (0 – 1 points), Abstraction (0 – 2 points), Delayed recall (0 – 5 points), and Orientation (0 – 6 points).

The MoCA Total Score (range 0 to 30) = sum of all points earned. If any assessment is missing then the Total Score is missing. The lower the total score, the worse the cognitive impairment.

Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus)

This scale is designed to measure various domains that describe subject function: general, mental/cognitive state, behavior, and activities of daily living. The CIBIC-Plus scores will be assigned by clinicians and the possible scores are: 1 (marked improvement), 2 (moderate improvement), 3 (minimal improvement), 4 (no change), 5 (minimal worsening), 6 (moderate worsening) and 7 (marked worsening).

Neuropsychiatric Inventory (NPI)

This scale assesses frequency and severity of 12 neuropsychiatric symptoms commonly described in dementia patients: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors and appetite/eating changes. The scale is composed of 12 items, each item score ranges from 0 to 12.

The NPI Total Score (range 0 to 144) = sum of all item scores. If any item score is missing then the Total Score is missing. The higher the total score, the more severe the symptoms.

A subscore covering the domains of delusions, hallucinations, apathy and depression (NPI-4) will also be derived. The subscore (0 to 48) = sum of 4 corresponding item scores. If any one of the 4 item scores is missing then the subscore is missing.

The caregiver distress (NPI-D) is rated by caregiver based on his or her own stress on a five point scale from 0 - no distress, 1- minimal, 2 - mild, 3 - moderate, 4 - moderately severe, 5 - very severe or extreme.

NPI-10 is the subscore (0-120) of all items except night-time behavior and appetite/eating changes. If any one of the 10 item scores are missing then the subscore is missing.

Mini-Mental State Examination (MMSE)

The MMSE is composed of 30 questions group into domains, see Table 9. For each of the MMSE domains add the correct responses. If a domain has missing data then the domain is missing. From the domains compute the six items as show in Table 9. If any domain is missing then the item is missing. The MMSE Total Score (range 0 to 30) = sum of the six items. If any item score is missing then the Total Score is missing. The lower the total score, the worse the impairment.

Table 9 MMSE Domains and Items

Domain	Score Range	Item	Score Range
1. Orientation to Time	0 to 5	1. Orientation to Time	0 to 5
2. Orientation to Place	0 to 5	2. Orientation to Place	0 to 5
3. Registration	0 to 3	3. Registration	0 to 3
4. Attention and Calculation[a]	0 to 5	4. Attention and Calculation	0 to 5
5. Recall	0 to 3	5. Recall	0 to 3
6. Naming	0 to 2	6. Language (Sum of Naming, Repetition, Comprehension, Reading, Writing, and Drawing)	0 to 9

7. Repetition	0 to 1		
8. Comprehension	0 to 3		
9. Reading	0 to 1		
10. Writing	0 to 1		
11. Drawing	0 to 1		
		Total Score	**0 to 30**

Cognitive Fluctuation Inventory (CFI)

This scale assesses cognitive fluctuation with the same format as the NPI. It evaluates fluctuation in various domains including attention, ability to performance daily functions, orientation, verbal communication and behaviour. It is scored based on frequency and severity with a score range of 0–12. The scale also assesses the degree of caregiver/informant distress engendered by the symptoms.

Scales for Outcome in Parkinson's disease—Sleep (SCOPA-Sleep)

There are sections for night time and daytime sleep. There are 5 questions for night time sleep: (1) trouble falling asleep, (2) awakening during the night, (3) episodes lying awake too long at night, (4) early morning waking and (5) patient's impression whether they had adequate duration of sleep at night. There are 6 questions for daytime sleep, (1) falling asleep unexpectedly during the day or evening, (2) falling asleep while sitting peacefully, (3) while watching television or reading, (4) while talking to someone, (5) trouble staying awake during the day or evening, and (6) experiencing falling asleep as a problem.

8.4 Algorithms for Safety Parameters

UPDRS-III subscores are defined as follows:

Tremor: sum of MDS-UPDRS-III category 3.15 to 3.18 (sum of 10 items from 4 categories: 3.15 Postural Tremor of the Hands, 3.16 Kinetic Tremor of the Hands, 3.17 Rest Tremor Amplitude, 3.18 Constancy of Rest Tremor).

Rigidity: sum of MDS-UPDRS-III category 3.3 (sum of 5 items from 1 category: 3.3 Rigidity).

Bradykinesia: sum of category 3.4 to 3.8 and 3.14 (sum of 11 items from 6 categories: 3.4 Finger Tapping, 3.5 Hand Movements, 3.6 Pronation-Supination Movements of Hands, 3.7 Toe Tapping, 3.8 Leg Agility, 3.14 Global Spontaneity of Movement [Body Bradykinesia]).

Postural instability and gait difficulty (PIGD): sum of category 3.9 to 3.13 (sum of 5 items from 5 categories: 3.9 Arising from Chair, 3.10 Gait, 3.11 Freezing of Gait, 3.12 Postural Stability, 3.13 Posture).

DEMQOL subscores are defined as follows:

Daily activities contains items 20 to 28, memory contains items 14 to 19, negative emotion contains items 2, 4, 7, 8, 9, 11, 12 and 13 and positive emotion contains items 1, 3, 5, 6, and 10.

DEMQOL-Proxy subscores are defined as follows:

Daily activities contains items 21 to 31, memory contains items 12 to 20, negative emotion contains items 2, 3, 5, 7, 9 and 10 and positive emotion contains items 1, 4, 6, 8, and 11.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed by Eisai Inc., using SAS Version 9.4 or later.

11 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

1. Mehrotra D, Liu F. Permutt T. Missing data in clinical trials: control-based mean imputation and sensitivity analysis. Pharmaceutical Statistics. 2017; 16:378–392..
2. Yuan Y. Sensitivity Analysis in Multiple Imputation for Missing Data. SAS Global Forum 2014 Proceedings. Paper SAS270-2014.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 2.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value:	Fasting glucose value:	>250 – 500 mg/dL;	>500 mg/dL; >27.8 mmol/L;

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>13.9 – 27.8 mmol/L; hospitalization indicated	life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL	>300 – 500 mg/dL	>500 – 1000 mg/dL	>1000 mg/dL >11.4 mmol/L

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
	1.71 – 3.42 mmol/L	>3.42 – 5.7 mmol/L	>5.7 – 11.4 mmol/L	life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

13.2 SPSS Syntax Files for DEMQOL and DEMQOL-Proxy

The SPSS syntax files present the developer's algorithm to handle the missing item score in DEMQOL and DEMQOL-Proxy.

APPENDIX 13.2.1 SPSS Syntax File for DEMQOL

```
***SPSS SYNTAX FILE FOR RECODING PWD DEMQOL DATA - JUNE 2005 ***

***DO NOT MODIFY***

*****

***RAW DATA SHOULD BE ENTERED AS FOLLOWS:

***A LOT = 1; QUITE A BIT = 2; A LITTLE = 3; NOT AT ALL = 4

*****

****

***CREATE A SEPARATE FILE FOR EACH TIME POINT (EG BASELINE, 6
MONTHS AND 12

***MONTHS) AND CODE IT UP SEPARATELY.

***IF YOU WANT TO MERGE THE FILES TOGETHER AFTER CODING, SO AS TO
LOOK AT

***CHANGE OVER TIME, YOU WILL NEED TO

***RENAME THE 6 MONTH AND 12 MONTH SCORES TO INDICATE WHICH TIME
THEY ARE

***FROM (EG DEMTOT_S AND DEMTOT_T).

***BUT DO NOT DO THIS UNTIL YOU HAVE FULLY SCORED AND CODED THE
DATA USING

***THE SYNTAX GIVEN HERE

*****

***CODING SYNTAX

**********************************************************************
```

```
***1. CHANGE VARIABLE NAMES SO THAT: QUESTION 1 = DEM1, QUESTION 2 =
DEM2,

***QUESTION 3 = DEM3 ETC

***THEN CHECK THAT -99 IS SET AS THE MISSING VALUE

**********************************************************************

**********************************************************************
**

***2. RECODE ALL THE POSITIVE ITEMS FOR DIRECTION, SO THAT

***FOR ALL ITEMS A HIGHER SCORE MEANS BETTER HRQL

**********************************************************************
***

***TO RECODE FOR DIRECTION ITEMS IN THE PATIENT DEMQOL***

RECODE dem1 dem3 dem5 dem6 dem10 dem29

(1=4) (2=3) (3=2) (4=1).

EXECUTE.

**********************************************************************
****

***3. IMPUTE MISSING DATA >=50% FOR ONLY THE 28 ITEMS THAT
CONTRIBUTE TO

***THE SCORE

***IE EXCLUDING THE GLOBAL QUESTION (#29)

**********************************************************************
****

COMPUTE missall= NMISS (dem1, dem2, dem3, dem4, dem5, dem6, dem7, dem8, dem9,

dem10, dem11,

dem12, dem13, dem14, dem15, dem16, dem17, dem18, dem19, dem20, dem21, dem22,

dem23, dem24,
```

```
dem25, dem26, dem27, dem28).
EXECUTE.
COMPUTE meanall = MEAN (dem1, dem2, dem3, dem4, dem5, dem6, dem7, dem8, dem9,
dem10, dem11,
dem12, dem13, dem14, dem15, dem16, dem17, dem18, dem19, dem20, dem21, dem22,
dem23, dem24,
dem25, dem26, dem27, dem28).
EXECUTE.
IF (MISSING (dem1) & missall < 15) dem1 = meanall .
EXECUTE .
IF (MISSING (dem2) & missall < 15) dem2 = meanall .
EXECUTE .
IF (MISSING (dem3) & missall < 15) dem3 = meanall .
EXECUTE .
IF (MISSING (dem4) & missall < 15) dem4 = meanall .
EXECUTE .
IF (MISSING (dem5) & missall < 15) dem5 = meanall .
EXECUTE .
IF (MISSING (dem6) & missall < 15) dem6 = meanall .
EXECUTE .
IF (MISSING (dem7) & missall < 15) dem7 = meanall .
EXECUTE .
IF (MISSING (dem8) & missall < 15) dem8 = meanall .
EXECUTE .
```

```
IF (MISSING (dem9) & missall < 15) dem9 = meanall .
EXECUTE .
IF (MISSING (dem10) & missall < 15) dem10 = meanall .
EXECUTE .
IF (MISSING (dem11) & missall < 15) dem11 = meanall .
EXECUTE .
IF (MISSING (dem12) & missall < 15) dem12 = meanall .
EXECUTE .
IF (MISSING (dem13) & missall < 15) dem13 = meanall .
EXECUTE .
IF (MISSING (dem14) & missall < 15) dem14 = meanall .
EXECUTE .
IF (MISSING (dem15) & missall < 15) dem15 = meanall .
EXECUTE .
IF (MISSING (dem16) & missall < 15) dem16 = meanall .
EXECUTE .
IF (MISSING (dem17) & missall < 15) dem17 = meanall .
EXECUTE .
IF (MISSING (dem18) & missall < 15) dem18 = meanall .
EXECUTE .
IF (MISSING (dem19) & missall < 15) dem19 = meanall .
EXECUTE .
IF (MISSING (dem20) & missall < 15) dem20 = meanall .
EXECUTE .
```

```
IF (MISSING (dem21) & missall < 15) dem21 = meanall .
EXECUTE .
IF (MISSING (dem22) & missall < 15) dem22 = meanall .
EXECUTE .
IF (MISSING (dem23) & missall < 15) dem23 = meanall .
EXECUTE .
IF (MISSING (dem24) & missall < 15) dem24 = meanall .
EXECUTE .
IF (MISSING (dem25) & missall < 15) dem25 = meanall .
EXECUTE .
IF (MISSING (dem26) & missall < 15) dem26 = meanall .
EXECUTE .
IF (MISSING (dem27) & missall < 15) dem27 = meanall .
EXECUTE .
IF (MISSING (dem28) & missall < 15) dem28 = meanall .
EXECUTE .
*********************************************
***4. TO COMPUTE OVERALL DEMQOL SCORE
***NOTE THAT THE SCORE CONSISTS OF ITEMS 1-28 ONLY.
***QUESTION 29 DOES NOT CONTRIBUTE TO THE SCORE
*********************************************
COMPUTE demtot = dem1+ dem2 +dem3 + dem4 + dem5 + dem6 +dem7 + dem8 + dem9 +
dem10 + dem11+
dem12 + dem13 + dem14 + dem15 + dem16 + dem17+ dem18 + dem19 + dem20 + dem21 +
```

dem22 + dem23 + dem24 +

dem25 + dem26 + dem27 + dem28.

EXECUTE.

APPENDIX 13.2.2 SPSS Syntax File for DEMQOL-Proxy

SPSS SYNTAX FILE FOR RECODING DEMQOL-PROXY DATA - JUNE 2005

DO NOT MODIFY

*****

***RAW DATA SHOULD BE ENTERED AS FOLLOWS:

***A LOT = 1; QUITE A BIT = 2; A LITTLE = 3; NOT AT ALL = 4

*****

****

***CREATE A SEPARATE FILE FOR EACH TIME POINT (EG BASELINE, 6 MONTHS AND 12

***MONTHS) AND CODE IT UP SEPARATELY.

***IF YOU WANT TO MERGE THE FILES TOGETHER AFTER CODING, SO AS TO LOOK AT

***CHANGE OVER TIME, YOU WILL NEED TO

***RENAME THE 6 MONTH AND 12 MONTH SCORES TO INDICATE WHICH TIME THEY ARE

***FROM (EG CDEMTOT_S AND CDEMTOT_T).

***BUT DO NOT DO THIS UNTIL YOU HAVE FULLY SCORED AND CODED THE DATA USING

***THE SYNTAX GIVEN HERE

*****

***CODING SYNTAX

****

***1. CHANGE VARIABLE NAMES SO THAT: QUESTION 1 = CDEM1, QUESTION 2 = CDEM2,

***QUESTION 3 = CDEM3 ETC FOR CARER VERSION

***THEN CHECK THAT -99 IS SET AS THE MISSING VALUE

****

****

***2. RECODE ALL THE POSITIVE ITEMS FOR DIRECTION, SO THAT

***FOR ALL ITEMS A HIGHER SCORE MEANS BETTER HRQL

****

TO RECODE FOR DIRECTION OF ITEMS IN CARER DEMQOL

RECODE cdem1 cdem4 cdem6 cdem8 cdem11 cdem32 (1=4) (2=3) (3=2) (4=1).

EXECUTE.

****

***3. TO IMPUTE MISSING DATA >=50% FOR ONLY THE 31 ITEMS IN MAIN INSTRUMENT,

***EXCLUDING THE GLOBAL QUESTION (#32)

****

COMPUTE missall = NMISS (cdem1, cdem2, cdem3, cdem4, cdem5, cdem6, cdem7, cdem8,

cdem9, cdem10, cdem11,

cdem12, cdem13, cdem14, cdem15, cdem16, cdem17, cdem18, cdem19, cdem20, cdem21,

cdem22, cdem23, cdem24,

cdem25, cdem26, cdem27, cdem28, cdem29, cdem30, cdem31).

```
EXECUTE.

COMPUTE meanall = MEAN (cdem1, cdem2, cdem3, cdem4, cdem5, cdem6, cdem7,
cdem8,

cdem9, cdem10, cdem11,

cdem12, cdem13, cdem14, cdem15, cdem16, cdem17, cdem18, cdem19, cdem20, cdem21,

cdem22, cdem23, cdem24,

cdem25, cdem26, cdem27, cdem28, cdem29, cdem30, cdem31).

EXECUTE.

IF (MISSING (cdem1) & missall < 16) cdem1 = meanall .

EXECUTE .

IF (MISSING (cdem2) & missall < 16) cdem2 = meanall .

EXECUTE .

IF (MISSING (cdem3) & missall < 16) cdem3 = meanall .

EXECUTE .

IF (MISSING (cdem4) & missall < 16) cdem4 = meanall .

EXECUTE .

IF (MISSING (cdem5) & missall < 16) cdem5 = meanall .

EXECUTE .

IF (MISSING (cdem6) & missall < 16) cdem6 = meanall .

EXECUTE .

IF (MISSING (cdem7) & missall < 16) cdem7 = meanall .

EXECUTE .

IF (MISSING (cdem8) & missall < 16) cdem8 = meanall .

EXECUTE .
```

```
IF (MISSING (cdem9) & missall < 16) cdem9 = meanall .
EXECUTE .
IF (MISSING (cdem10) & missall < 16) cdem10 = meanall .
EXECUTE .
IF (MISSING (cdem11) & missall < 16) cdem11 = meanall .
EXECUTE .
IF (MISSING (cdem12) & missall < 16) cdem12 = meanall .
EXECUTE .
IF (MISSING (cdem13) & missall < 16) cdem13 = meanall .
EXECUTE .
IF (MISSING (cdem14) & missall < 16) cdem14 = meanall .
EXECUTE .
IF (MISSING (cdem15) & missall < 16) cdem15 = meanall .
EXECUTE .
IF (MISSING (cdem16) & missall < 16) cdem16 = meanall .
EXECUTE .
IF (MISSING (cdem17) & missall < 16) cdem17 = meanall .
EXECUTE .
IF (MISSING (cdem18) & missall < 16) cdem18 = meanall .
EXECUTE .
IF (MISSING (cdem19) & missall < 16) cdem19 = meanall .
EXECUTE .
IF (MISSING (cdem20) & missall < 16) cdem20 = meanall .
EXECUTE .
```

```
IF (MISSING (cdem21) & missall < 16) cdem21 = meanall .

EXECUTE .

IF (MISSING (cdem22) & missall < 16) cdem22 = meanall .

EXECUTE .

IF (MISSING (cdem23) & missall < 16) cdem23 = meanall .

EXECUTE .

IF (MISSING (cdem24) & missall < 16) cdem24 = meanall .

EXECUTE .

IF (MISSING (cdem25) & missall < 16) cdem25 = meanall .

EXECUTE .

IF (MISSING (cdem26) & missall < 16) cdem26 = meanall .

EXECUTE .

IF (MISSING (cdem27) & missall < 16) cdem27 = meanall .

EXECUTE .

IF (MISSING (cdem28) & missall < 16) cdem28 = meanall .

EXECUTE .

IF (MISSING (cdem29) & missall < 16) cdem29 = meanall .

EXECUTE .

IF (MISSING (cdem30) & missall < 16) cdem30 = meanall .

EXECUTE .

IF (MISSING (cdem31) & missall < 16) cdem31 = meanall .

EXECUTE .

**************************************************

***4. TO COMPUTE OVERALL DEMQOL -PROXY SCORE
```

***NOTE THAT THE SCORE CONSISTS OF ITEMS 1-31 ONLY.

***QUESTION 32 DOES NOT CONTRIBUTE TO THE SCORE

****

COMPUTE cdemtot = cdem1 + cdem2 + cdem3 + cdem4 + cdem5 + cdem6 + cdem7+ cdem8 +

cdem9 + cdem10 + cdem11+

cdem12 + cdem13 + cdem14 + cdem15 + cdem16 + cdem17 + cdem18 + cdem19 + cdem20 +

cdem21 + cdem22 + cdem23 + cdem24 +

cdem25 + cdem26 + cdem27+ cdem28 + cdem29 + cdem30 + cdem31.

EXECUTE.

13.3 EQ-5D-5L_Crosswalk_Index_Value_Calculator and SAS Syntax File for EQ-5D

The excel file EQ-5D-5L_Crosswalk_Index_Value_Calculator.v2 includes a data matrix to represents the relationship between 5L profile and the single index value (or utility score) based on country specific value sets. The SAS syntax file, SAS syntax crosswalk values EQ-5D-5L Unit.docx, presents the developer's algorithm to convert EQ-5D-5L health states into a single index value (or utility score) using the United States (US) value set. These documents are saved separately.

13.4 Imputation of Missing Start and End Dates for AE and Concomitant Medication

Adverse Event Start & End Date Imputation

Description of Incomplete *AE End Date*		Imputed date
Day missing (YearMonth only) and Date of Death is not missing		
YearMonth earlier than YearMonth of Date of Death	→	Impute to the last day of the month
YearMonth equals YearMonth of Date of Death	→	Date of Death
Month missing (Year) and Date of Death is not missing		
Year earlier than Year of Date of Death	→	Impute to the last day of the year
Year equals Year of Date of Death	→	Date of Death
ALL is missing and Date of Death is not missing		
	→	Date of Death
Day missing (YearMonth) and Date of Death is missing		
YearMonth		Impute to the last day of the month
Month missing (Year) and Date of Death is missing		
Year	→	Impute to the last day of the year
ALL is missing and Date of Death is missing		
	→	No imputation

Description of Incomplete *AE Start Date*		Imputed date
Day missing (YearMonth Only)		
YearMonth earlier than YearMonth of First Dose Date	→	Impute to first of the month
YearMonth equal YearMonth of First Dose Date	→	Impute to First Dose Date or AE End Date, whichever is earlier
YearMonth greater than YearMonth of First Dose Date	→	Impute to first of the month
Month missing (Year)		
Year earlier than Year of First Dose Date	→	Impute to first of the year
Year equal Year of First Dose Date	→	Impute to First Dose Date or AE End Date, whichever is earlier
Year greater than Year of First Dose Date	→	Impute to first of the year
ALL is missing		
	→	Impute to First Dose Date or AE End Date, whichever is earlier

Description of Incomplete *AE Start Time*		Imputed Time
Hour Missing (no Time present)	→	Impute to 0
Minutes Missing (hour only)	→	Impute to 0
note: seconds not imputed		

Description of Incomplete *AE Stop Time*		Imputed Time
Hour Missing (no Time present)	→	Impute to 23
Minutes Missing (hour only)	→	Impute to 59
note: seconds not imputed		

Medication Start & End Date Imputation

There is clear evidence the drug was STOPPED **BEFORE** the Screening Visit (from Prior Meds page)

Description of Incomplete *Med End Date*		**Imputed date**
Day missing (YearMonth) and Date of Screening is not missing		
YearMonth earlier than YearMonth of Date of Screening	→	Impute to the last day of the month
YearMonth equals YearMonth of Date of Screening	→	Date of Screening
Month missing (Year) and Date of Screening is not missing		
Year earlier than Year of Date of Screening	→	Impute to the last day of the year
Year equals Year of Date of Screening	→	Date of Screening
ALL is missing and Date of Screening is not missing		
	→	Date of Screening

There is NO clear evidence the drug was STOPPED **BEFORE** the Screening Visit

Description of Incomplete *Med End Date*		**Imputed date**
Day missing (YearMonth only) and Date of Death is not missing		
YearMonth earlier than YearMonth of Date of Death	→	Impute to the last day of the month
YearMonth equals YearMonth of Date of Death	→	Date of Death
Month missing (Year) and Date of Death is not missing		
Year earlier than Year of Date of Death	→	Impute to the last day of the year
Year equals Year of Date of Death	→	Date of Death
ALL is missing and Date of Death is not missing		
	→	Date of Death
Day missing (YearMonth) and Date of Death is missing		
YearMonth		Impute to the last day of the month
Month missing (Year) and Date of Death is missing		
Year	→	Impute to the last day of the year
ALL is missing and Date of Death is missing		
	→	No imputation

Description of Incomplete *Med Start Date*		**Imputed date**
Day missing (YearMonth Only)		
YearMonth earlier than YearMonth of First Dose Date	→	Impute to first of the month
YearMonth equal YearMonth of First Dose Date	→	Impute to First Dose Date or Med End Date, whichever is earlier
YearMonth greater than YearMonth of First Dose Date	→	Impute to first of the month
Month missing (Year)		
Year earlier than Year of First Dose Date	→	Impute to first of the year
Year equal Year of First Dose Date	→	Impute to First Dose Date or Med End Date, whichever is earlier
Year greater than Year of First Dose Date	→	Impute to first of the year
ALL is missing		
	→	Impute to First Dose Date or Med End Date, whichever is earlier

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Biostatistics Approval	14-Apr-2020 15:02 GMT-04
	Biostatistics Approval	14-Apr-2020 15:05 GMT-04
	Clinical Approval	14-Apr-2020 15:11 GMT-04