STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2027-A001-203
Study Protocol Title:	An Open-Label Study To Evaluate the Pharmacodynamic Effects, Efficacy, Safety, and Tolerability of E2027 in Subjects With Dementia With Lewy Bodies or Parkinson's Disease Dementia With or Without Amyloid Copathology
Date:	10 February 2022
Version:	Final Version 2.0

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AChEI	acetylcholinesterase inhibitor
AE	adverse event
ATC	anatomical therapeutic class
BMI	body mass index
BP	Blood pressure
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CI	confidence interval
CIBIC-Plus	Clinician's Interview Based Impression of Change Plus Caregiver Input
CFI	Cognitive Fluctuation Inventory
CGIC	Clinician Global Impression of Change
cGMP	cyclic guanosine monophosphate
CRF	case report form
CSF cGMP	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	coefficient of variation
DBP	Diastolic blood pressure
DLB	Dementia in Lewy Bodies
ED	Early Discontinuation
FAQ	Functional Assessments Questionnaire
FAS	full analysis set
LLT	lower level term
LS	least squares
MDS	Movement Disorders Society
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NPI	Neuropsychiatric Inventory

Abbreviation	Term
NPI-D	Neuropsychiatric Inventory – Distress symptoms
PD	pharmacodynamic
PDD	Parkinson's Disease Dementia
PK	pharmacokinetic
PT	Preferred term
QTcB	corrected QT interval calculated using Bazett's formula
QTcF	corrected QT interval calculated using Fridericia's formula
RBD	REM sleep behavior disorder
SAE	serious adverse event
SAP	statistical analysis plan
SAPS-PD	Scale for Assessment of Positive Symptoms in Parkinson's Disease
SBP	Supine blood pressure
SE	standard error
SI	Système International
SOC	System organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III: Motor Examination
WAIS-IV DSC	Wechsler Adult Intelligence Scale-4th Edition Digit Symbol Coding
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

Table 1 Summary of Changes (Version 2)

Changes in Version 2	Rationale
5.2.1 Definitions of Analysis Sets Addition to the definition of subjects being excluded from the PD Analysis Set, based on low drug compliance/PK concentrations at Week 9.	Subjects with low PK concentrations, and therefore low drug compliance at Week 9 had outlying cGMP percentage change from baseline values. This was not helpful in determining proof of concept and hence they are to be excluded from the PD Analysis Set, and kept in all other analysis sets.
5.2.4 Demographic and Other Baseline Characteristics and 5.3.4 Examination of Subgroups Update to cutpoint for CSF Aβ42/40 ratio and CSF p-tau181/Aβ(1-42) ratio	In correct cutpoints were referenced. CSF Aβ42/40 ratio was changed from 0.0597 to 0.0571. CSF p-tau181/Aβ(1-42) ratio was changed from 0.0749 to 0.083.
5.3.4 Examination of Subgroups and 5.6.2 Adverse Events Removal of subgroups for: On AChEI at baseline (Yes or No), Hoehn & Yahr stage (0&I&II or III), Baseline MMSE subgroup (≥14 total score ≤19, ≥20 total score ≤26), Age (<65, ≥ 65), NPI hallucination sub-item score (≥median/<median), Caregiver's time per week to spend with subject (≥median/<median).	Due to the number of subjects, it was not useful to subgroup the data in this detail.
8.2.3 Duplicate PD Tests Wording added to implement derivation for any duplicate PD tests received.	Added for completion for derivation of a sigle value if duplicate tests received.
8.3.2 Treatment Duration for Safety Analyses Footnote d added to Table 5	Footnote d added for clarity.
8.4 Algorithms for Efficacy Parameters NPI total scores are set to zero if any part	To be consistent with the derivation from Study 201

is missing, changed from set to missing if any part is missing.	

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 for Eisai E2027-A001-203.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to demonstrate the Pharmacodynamic (PD) effects of E2027 on cerebrospinal fluid (CSF) cyclic guanosine monophosphate (cGMP) in subjects with dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) with and without amyloid copathology after 9 weeks of treatment.

3.1.2 Secondary Objective

The secondary objective of the study is to evaluate the safety and tolerability of E2027 in subjects with DLB and PDD.

3.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the efficacy of E2027 on the following endpoints after 12 weeks of treatment:
  - Montreal Cognitive Assessment (MoCA)
  - Wechsler Adult Intelligence Scale-4th Edition Digit Symbol Coding (WAIS-IV DSC)
  - Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus)
  - Clinician Global Impression of Change (CGIC)
  - Cognitive Fluctuation Inventory (CFI)
  - Mini-Mental State Examination (MMSE)
  - Neuropsychiatric Inventory (NPI)
  - Scale for Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD)
  - Functional Assessments Questionnaire (FAQ)
- To explore the indirect PD effects of E2027 on plasma biomarkers and CSF biomarkers related to DLB and PDD
- To explore the effects of E2027 on CSF cGMP, other plasma and CSF biomarkers, and clinical endpoints using other diagnostic subgroups classifications based on baseline biomarkers
- To characterize the population pharmacokinetics (PK) of E2027 in subjects with DLB or PDD, including evaluation of the effects of intrinsic and extrinsic factors on the PK

- To explore the relationships amongst the PK exposure of E2027 in plasma/CSF and its effects on plasma/CSF biomarkers (including CSF cGMP) as well as clinical efficacy and safety endpoints
- To explore the relationship amongst plasma and CSF biomarkers at baseline and after treatment with E2027
- To collect genomic samples for exploratory investigation on heterogeneity in drug-response and clinical features of disease.

3.2 Overall Study Design and Plan

This is a multicenter, open-label study in subjects with DLB or PDD who were treated with E2027 for 12 weeks. Four subgroups of subjects were enrolled as follows: DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology, and PDD with amyloid copathology. The presence of amyloid copathology was defined as ratio of plasma concentration of Aβ42/Aβ40 <0.092 (based on the C2N PreclivityAD assay).

The study design allowed for add-on therapy of E2027 to standard of care for DLB and PDD, which includes acetylcholinesterase inhibitors (AChEI) and/or memantine at stable doses, except for any prohibited medications specified in this protocol. Subjects who were not receiving AChEI or memantine were also eligible to participate in this study but were not permitted to start such medications during the study. It was required that in each subgroup there was to be at least 1 subject who was not receiving AChEI or memantine during the study. Subjects were required to be on stable doses of medications prescribed for the treatment of Parkinson's disease, maintained without change during the study.

For all subjects, study participation comprised 2 phases: Pretreatment Phase and Treatment Phase. The Pretreatment Phase included a Screening Period and a Baseline Period. The Treatment Phase included a Treatment Period and Follow-up Period. An overview of the study design is presented in Figure 1.

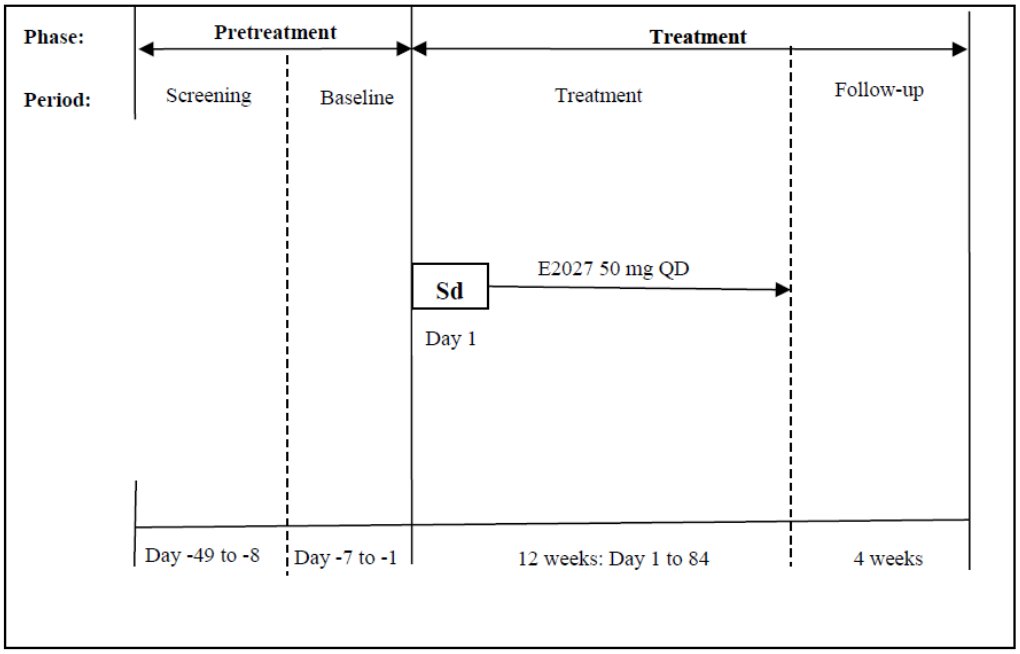

Figure 1 Study Design for Study E2027-A001-203

QD = once daily, Sd = Start of study drug (E2027)

All subjects who have completed screening assessments and are deemed eligible for the study will have a baseline CSF. During the Treatment Period study visits were conducted after 3, 6, 9, and 12 weeks on E2027. Efficacy assessments were performed after 6 and 12 weeks on E2027. After subjects completed 9 weeks of treatment with E2027, a 2nd CSF sample was collected.

Subjects who prematurely discontinued study drug for any reason underwent 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 were conducted at the ED Visit. In addition, subjects who discontinued study drug were expected to continue in the study for the originally scheduled visits, starting with next such visit that was >7 days after the ED Visit.

During the COVID-19 pandemic, and under other extenuating circumstances:

- An extension of the Screening Period from 6 weeks to up to 10 weeks was allowed with sponsor approval on a subject by subject basis.
- If subjects could not visit the study site, all procedures which required physical contact with the subjects (eg, vital signs, ECGs, blood tests, physical examination, Unified Parkinson's Disease Rating Scale Part III: Motor Examination [UPDRS-III]) could be conducted via home visit (if feasible) with sponsor approval. The brain or cardiac imaging during the Screening Visit was to be conducted at the study site. The CSF collection at the Screening Visit and Visit 6 (Week 9) was to be conducted at the study

site. Other study procedures including all the efficacy endpoints, adverse events (AEs), and concomitant medications review could be conducted remotely via telephone, sponsor approved telehealth, or home visit. If it was not possible for subjects to attend the study site for the CSF collection Visit 6 (Week 9), this could be performed at an Unscheduled Visit as soon as possible after Week 9. Study drug was to be delivered to subjects' homes if it was not possible to visit the study site to collect the study drug.

4 DETERMINATION OF SAMPLE SIZE

Assuming the standard deviation of percentage change from baseline in CSF cGMP at Week 9 was 60, the sample size of 6 completers per subgroup (for 8 enrolled subjects per subgroup, assuming a 25% dropout rate), would have approximately 80% power to detect the difference in change from baseline of CSF cGMP of 100% between the DLB without amyloid copathology subgroup and the DLB with amyloid copathology subgroup. The analysis between the PDD without amyloid copathology subgroup and the PDD with amyloid copathology subgroup, also would have approximately 80% power to detect the difference in change from baseline of CSF cGMP of 100% (same assumptions as above). These sample size calculations illustrated the possible differences that could be seen between subgroups. However, without previous data on the differences between subgroups in CSF cGMP, these were for illustration only and it was not expected statistical significance would be reached with 6 subjects per subgroup.

The probability of observing a difference in percentage of CSF cGMP between 2 subgroups (DLB without amyloid copathology subgroup minus DLB with amyloid copathology subgroup, or PDD without amyloid copathology subgroup minus PDD with amyloid copathology subgroup) ≥30% depends on the true difference between the 2 subgroups. If the true difference was 100%, there would be 97.8% probability that the observed difference was ≥30%. If the true difference was 60%, the probability was 80.7%. If the true difference was 10%, there would be 28.2% probability that the observed difference was ≥30%.

5 STATISTICAL METHODS

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

5.1.1 Primary Endpoint

Percentage change from baseline in CSF cGMP at 9 weeks of treatment.

5.1.2 Secondary Endpoints

- Safety and tolerability of E2027 as measured by the following:
  - 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 Columbia Suicide Severity Rating Scale (C-SSRS)
- Changes from baseline in the total score of MDS-UPDRS-III

5.1.3 Exploratory Endpoints

- The following clinical efficacy endpoints at 12 weeks of treatment
  - Change from baseline in MoCA total score
  - Change from baseline in WAIS-IV DSC score
  - CIBIC-Plus scale
  - CGIC scale
  - Change from baseline in CFI score
  - Change from baseline in MMSE total score
  - Change from baseline in NPI total score, subscores and caregiver distress score
  - Change from baseline in SAPS-PD total score
  - Change from baseline in FAQ total score
- Change from baseline in CSF cGMP at 9 weeks of treatment
- Percentage change and change from baseline at 9 weeks of treatment in other biomarkers in CSF and/or plasma, including using other diagnostic subgroups classifications based on baseline biomarkers (if appropriate)
- PK of E2027 in subjects with DLB or PDD, using population modelling
- Relationships between E2027 in plasma/CSF and its effects on the following variables using PK/PD modelling, if data permit:
  - Plasma/CSF PD biomarkers (including CSF cGMP),
  - Clinical efficacy (including MoCA, WAIS-IV DSC, CIBIC-Plus, NPI, MMSE, CFI, SAPS-PD, FAQ, and CGIC at 12 weeks of treatment),
  - Safety variables
- Relationships of the plasma and CSF PD biomarkers compared to MoCA, WAIS-IV DSC, CIBIC-Plus, NPI, MMSE, CFI, SAPS-PD, FAQ, and CGIC at 12 weeks of treatment, if data permit
- Relationships amongst plasma biomarkers and CSF biomarkers at baseline and after treatment (if appropriate)
- Subgroup analyses based on genotype classification for CSF cGMP changes from baseline and clinical endpoints

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 post baseline safety assessment.

The Full Analysis Set (FAS) is the group of subjects who receive at least 1 dose of study drug and have baseline and at least 1 post baseline MoCA measurement.

The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter. Subjects who have low drug compliance based on their PK results will be excluded from the PD Analysis Set. Lack of drug around the Week 9 CSF will affect the results of the CSF cGMP, and hence distort the primary endpoint interpretation.

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 electronic case report form (eCRF). The distribution of the number of subjects enrolled by each site will be summarized by subgroup and overall.

Study Completion, defined as completing 12 weeks of study and the follow up visit: The number (percent) of 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) eCRF. The number (percent) will be presented by subgroup and total for all subjects.

Completion of Study Treatment, defined as completing 12 weeks of study: The number (percent) of treated subjects who completed study drug and who discontinued from study drug 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 subgroup and total for all subjects. Subjects who discontinued study treatment but were followed up for efficacy assessments after treatment discontinuation will also be summarized.

5.2.3 Protocol Deviations

A summary table and listing will be produced with critical protocol deviations.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each subgroup and overall using descriptive statistics. Continuous demographic and baseline variables include age, age at diagnosis, age at onset, years since onset of symptoms, NPI hallucintaions FxS score, body weight, height, disease duration, baseline MDS-UPDRS part III score, SFQ Score, Modified Hachinski Ischemic Scale, average time per day for caregiver to spend with patient, and average days per week for caregiver to spend with patient. Categorical variables include sex, age group (less than 65 years, age greater than or equal to 65 years), age group at diagnosis, age group at onset, race, ethnicity, treatment with AChEIs (no or yes), Columbia Classification Algorithm for Suicide Assessment (C-CASA), C-SSRS not completed (missing), Hoehn & Yahr stage and subgroups (0, I, II vs III, IV, V), NPI hallucintaions FxS score subgroups (<median, ≥median), relationship of caregiver to patient, caregiver reside with the patient (yes or no), caregiver's time per week to spend with subject (<median, ≥median), have each clinical DLB core feature (hallucination, fluctuation, parkinsonism, rapid eye movement sleep behavior disorder [RBD]) (yes or no), and have 2 or more core clinical DLB 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 of DLB, have each indicative biomarker of DLB, Parkinsonian Symptoms (yes or no), bradykinesia under PDD (Yes, No), at least one of the other clinical features of PDD (muscular rigidity, 4-6 Hz rest tremor, postural instability) (yes or no) , PDD symptoms severe enough to impair work/activities (yes or no).

Biomarker data will be summarized under the PD Analysis Set for each subgroup and overall using descriptive statistics. Continuous variables include CSF cGMP, plasma Aβ42, plasma Aβ40, CSF Aβ42, CSF Aβ40, CSF Aβ42/40 ratio, plasma p-tau181, plasma p-tau181/Aβ(1-42), CSF p-tau181, CSF p-tau181/Aβ(1-42), plasma neurogranin, plasma neurofilament light (NfL), plasma GFAP, CSF neurogranin, CSF neurofilament light, and any other appropriate biomarkers. Categorical variables include Aβ42/40 ratio (<0.092, ≥0.092), CSF Aβ42/40 ratio (<0.0571, ≥0.0571) [Ref 1], ApoE4 (positive, negative), ApoE categories, plasma p-tau181 (<2.2, ≥2.2 µg/mL), plasma p-tau181/Aβ(1-42) ratio (<0.043, ≥0.043), CSF total tau (<400, ≥400 µg/mL), CSF ptau-181 (<52.8, ≥52.8 µg/mL), CSF p-tau181/Aβ(1-42) ratio (<0.083, ≥0.083), CSF total tau/Aβ(1-42) ratio (<0.637, ≥0.637) and other groups of biomarkers as appropriate. If numbers allow, combinations as follows will be calculated:

a) Based on plasma Aβ42/40 and apolipoprotein E4 (ApoE4):

- Aβ42/40 <0.092 and ApoE4 postive,
- Aβ42/40 <0.092 and ApoE4 negative,
- Aβ42/40 ≥0.092 and ApoE4 negative,
- Aβ42/40 ≥0.092 and ApoE4 positive,

b) Based on CSF Aβ42/40 and ApoE4

- CSF Aβ42/40 <0.0571 and ApoE4 postive,

- CSF Aβ42/40 <0.0571 and ApoE4 negative,
- CSF Aβ42/40 ≥0.0571 and ApoE4 negative,
- CSF Aβ42/40 ≥0.0571 and ApoE4 positive.

Clinical efficacy data will be summarized under the FAS for each subgroup and overall using descriptive statistics. Continuous variables include MoCA total score, NPI total score, NPI-4 score, NPI-10 score, NPI-D score, NPI subscores, MMSE total score, CFI score, WAIS-IV DSC, SAPS-PD and FAQ. Catergorical variables include CIBIC Plus and subitems, and MMSE total score subgroup (14-19, 20-26).

Where Screening values are 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 23.1 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 subgroup and total.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2020). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by subgroup and overall, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be 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 up to the date of the last dose. All medications will be presented in subject data listings.

Prior and concomitant medications will be summarized by cognitive and non-cognitive medications categorized under DLB and PDD medications, all other medications not categorized under DLB and PDD medications will be summarized separately.

Restricted medications taken at baseline, and changes in restricted medications taken at any time post baseline will be summarized separately. Prohibited medications will be summarized separately if numbers allow.

Medications taken within the 4-week Follow-Up Period will also be listed.

5.2.6 Treatment Compliance

Percent compliance will be calculated for the Safety Analysis Set as follows:

Compliance = (Total number of capsules dispensed – Total number of capsules returned – Total Number of capsules lost) x 100% / Planned Total number of capsules to be taken

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 subgroup. Subjects will also be categorized by compliance criteria <50%, ≥50% to <80%, ≥80% to ≤100%, >100% to ≤120%, >120% and missing. The maximum of planned total number of capsules to be taken will be 168

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

This is a multi-center study conducted in United States and Canada. Due to the small number of subjects per site and location of sites, subjects from all centers will be pooled for all summaries and analyses.

5.3.2 Adjustments for Covariates

Where statistical analysis models are used, the baseline of the variable will be included as a covariate.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Examination of Subgroups

The primary subject subgroups will be compared for all data:

- DLB without amyloid copathology versus DLB with amyloid copathology, and PDD without amyloid copathology versus PDD with amyloid copathology). Amyloid copathology is defined by the plasma Aβ42/40 ratio: with <0.092, without ≥0.092.

- The above subgroups will be combined to compare with amyloid vs without amyloid copathology, DLB without amyloid vs PDD without amyloid, and DLB with amyloid vs PDD with amyloid).

The demography, MoCA and some of the PD endpoints will be presented by the subgrouping as column headers instead of the amyloid copathology:

- Plasma p-tau181/Aβ(1-42) (<0.043, ≥0.043), by DLB, PDD and Overall

- CSF amyloid status (CSF Aβ42/40 <0.0571, CSF Aβ42/40 ≥0.0571), by DLB, PDD and Overall
- Genotype classification (ApoE4 postive or negative), by DLB, PDD and Overall
- Plasma p-tau181 (<2.2, ≥2.2), by DLB, PDD and Overall
- CSF p-tau181 (<52.8, ≥52.8), by DLB, PDD and Overall
- CSF p-tau181/ Aβ42 (<0.083, ≥0.083), by DLB, PDD and Overall
- CSF total tau/Aβ42 (<0.637, ≥0.637), by DLB, PDD and Overall
- If data permits, combinations of the above overall for DLB+PDD,
  - a) plasma Aβ42/40 <0.092 and ApoE4 postive, Aβ42/40 <0.092 and ApoE4 negative, Aβ42/40 ≥0.092 and ApoE4 negative, Aβ42/40 ≥0.092 and ApoE4 positive.

    b) CSF Aβ42/40 <0.0571 and ApoE4 postive, CSF Aβ42/40 <0.0571 and ApoE4 negative, CSF Aβ42/40 ≥0.0571 and ApoE4 negative, CSF Aβ42/40 ≥0.0571 and ApoE4 positive.
- Other biomarkers, to be determined if data permit (all cutpoints TBD).

Additional subgroup analyses may also be conducted, if deemed 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, Dropouts, and Outliers

5.3.5.1 Efficacy

For the efficacy endpoints, there will be no imputation of missing value.

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 Study Data Tabulation Model (SDTM) Domain Mapping Specifications Template 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

Not applicable.

5.4.2 Secondary Efficacy Analyses

Not applicable.

5.4.3 Other Efficacy Analyses

Exploratory efficacy analyses are described in Section 5.8 Exploratory Analyses.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

E2027 plasma and CSF concentrations were obtained during the dosing period (Week 9 for plasma for biomarkers, Weeks 6, 9 and 12 for plasma for PK and Screening and Week 9 for CSF). Details of the analysis methods for population PK/PD modeling will not be described in this SAP but will be described in a separate analysis plan.

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for E2027 concentration listings and for summaries of E2027 concentrations in plasma and CSF by dose and day.

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 and 2 studies. As appropriate, the effect of covariates on the PK of E2027, such as baseline characteristics/demographics will be evaluated. Derived exposure parameters such as steady state area under the concentration time curve or average concentration of E2027 and other derived parameters may be calculated from the final PK model using the individual posterior estimates of the PK parameters and dosing history. The details will be described in the separately prepared analysis plan.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacodynamic Analyses

The PD Analysis Set will be used for the summaries and analyses of CSF and plasma PD biomarkers. The percentage change from baseline in CSF cGMP at 9 weeks of treatment will be analyzed to compare different subject subgroups (DLB without amyloid copathology vs DLB with amyloid copathology, and PDD without amyloid copathology vs PDD with amyloid copathology). Secondary comparisons will be: total (DLB+PDD) without amyloid vs with amyloid, DLB without amyloid vs PDD without amyloid, and DLB with amyloid vs PDD with amyloid.

Analyses, comparing the different subgroups, of the percentage change from baseline in CSF cGMP will be performed using an analysis of covariance, where baseline CSF cGMP will be included as a covariate. The least square (LS) means, LS mean subgroup differences and 95% CIs will be presented.

The change from baseline in CSF cGMP at 9 weeks of treatment will also be analyzed. Other CSF and plasma PD biomarkers (CSF amyloid, plasma p-tau181, CSF p-tau181, plasma neurogranin, plasma neurofilament, CSF neurogranin, CSF neurofilament, etc) may be analyzed similarly, if appropriate.

The CSF and plasma PD biomarkers (both percentage change and change from baseline at 9 weeks) will be summarized by subgroups, as defined in section 5.3.4.

Summaries and figures will be produced exploring the relationships between CSF and plasma PD biomarkers and the efficacy endpoints. If data permit, the relationship between CSF and plasma PD biomarkers compared to each efficacy endpoint (MoCA, WAIS-IV DSC, CIBIC-Plus, CGIC, CFI, MMSE, NPI [NPI-12, NPI-10, NPI-4 and NPI-D, and each subscore], SAPS-PD and FAQ) and MDS-UPDRS-III will be explored using correlation analysis. The association between individual CSF/plasma biomarker concentration data and individual efficacy data within each subgroup (DLB without amyloid copathology vs DLB with amyloid copathology; PDD without amyloid copathology vs PDD with amyloid copathology; total (DLB+PDD) without amyloid vs with amyloid; DLB without amyloid vs PDD without amyloid; and DLB with amyloid vs PDD with amyloid) will be examined through scatter plots. The scatter plots including the Pearson correlation coefficient and Spearman correlation coefficient will be produced for each amyloid subgroup for both percentage change from baseline and change from baseline (as appropriate) in CSF and plasma PD biomarkers after 9 weeks of treatment and change from baseline at 12 weeks of treatment for the efficacy endpoints. Correlations against CSF and plasma biomarkers at baseline compared to change from baseline at 12 weeks of treatment for the efficacy endpoints may also be explored, by subgroups.

If appropriate, relationships amongst plasma biomarkers and CSF biomarkers (including cGMP) at baseline and after treatment will be explored using summaries, correlation analysis and scatter plots.

Pharmacogenomic Analyses

The percentage change in CSF cGMP at 9 weeks, change in CSF cGMP at 9 weeks and other CSF and plasma PD biomarkers will be summarized by ApoE4 status, using the PD Analysis Set. Other pharmacogenomic data will be summarized similarly.

Pharmacodynamic/Pharmacokinetic Analyses

The correlation amongst plasma and CSF exposure to E2027 and the various efficacy and biomarker endpoints will be explored graphically. The details will be described in the separately prepared 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), MDS-UPDRS-III, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements (including orthostatic changes) will be summarized by subgroup and overall.

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 subgroup and overall. 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 subgroup and overall. Overall exposure (number of subject-weeks) is defined as summation over all subjects' exposure durations and will be summarized by subgroup and overall.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA (Version 21.0 or higher) LLT closest to the verbatim term. The linked MedDRA PT and primary SOC will also be captured in the database.

A 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 subgroup and overall, 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.

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 subgroup and overall. 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 subgroup and overall. 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 AEs 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 9.5.1.4.4. 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, subgroup and overall, using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.4.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline 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 subgroup 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 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 blood pressure [DBP] and systolic blood pressure [SBP], heart rate [HR], 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 subgroup and overall.

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

Drop in standing SBP ≥20 mmHg compared to supine, or drop in standing DBP ≥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 (ie, 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 subgroup and overall and visit.

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 subgroup and overall. Table 2 presents the clinical notable ranges.

Table 2 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 each postbaseline visit. The mean QTc Fridericia (QTcF) and other ECG intervals based on triplicate ECG will be obtained. Descriptive statistics for ECG parameters (QTc Bazett, QTcF, PR interval QRS duration and RR interval) and changes from baseline will be presented by visit, subgroup and overall. 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 postbaseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized according to the following categories.

Clinically borderline or abnormal ECG results QTcF 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 subgroup and overall, with at least 1 postbaseline abnormal ECG results during the treatment period, Weeks 3, 6, 9 and 12 (and ED, as needed) 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.

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 the Treatment 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 the Treatment 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 MDS-UPDRS-III

Changes from baseline in the total score and four subscores of MDS-UPDRS-III will be summarized using descriptive statistics for continuous variable by visit and treatment group. No formal statistical analyses will be performed. Figures will be produced by visit, they will present without amyloid DLB, with amyloid DLB, without amyloid PDD, with amyloid PDD, with amyloid and without amyloid copathology (regardless of DLB/PDD).

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 4 subscores are for tremor, rigidity, bradykinesia and postural instability and gait difficulty (PIGD), as calculated per Section 8.5.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

The exploratory efficacy endpoints, MoCA (and subitems), WAIS-IV DSC, CIBIC-Plus (and subitems), CGIC, CFI, MMSE, NPI (NPI-12, NPI-10, NPI-4 and NPI-D, and each subscore), SAPS-PD and FAQ, will be summarized based on the FAS, by subject subgroup (DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology, and PDD with amyloid copathology). No formal statistical analyses will be performed. Figures will be produced by visit, they will present without amyloid DLB, with amyloid DLB, without amyloid PDD, with amyloid PDD, with amyloid and without amyloid copathology (regardless of DLB/PDD).

The exploratory efficacy endpoint, MoCA will be repeated for subgroups as per Section 5.3.4.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

No changes have been made.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Efficacy data handling

8.1.1 Pretreatment/Baseline Efficacy

Baseline for all efficacy endpoints is defined as the last pretreatment assessment.

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.

Table 3 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)
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 ≤ Day ≤ 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.

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 ED Visit. The scheduled visits post ED will be flagged in the listings and datasets to reflect its post ED status.

8.2 PD data handling

8.2.1 Pretreatment/Baseline PD

Baseline for all PD endpoints is defined as the last pretreatment assessment.

8.2.2 Treatment Duration for PD 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.

Table 4 Mapping of Study Day Ranges to Week for PD

Windowing Period	Study Day Range (Relative to First Dose)	Week
Screening	(-42) ≤ Day ≤ (-8)	
Analysis Baseline	-	a
Treatment	1 ≤ Day ≤ 98	9

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

8.2.3 Duplicate PD Tests

The following rule will be performed if duplicate results are received on biomarker data, if back up samples are tested in addition to the primary samples:

1) Deviation between first and second result ≤ 15 %. Accept first result.

2) deviation between first and second result > 15% and ≤ 30%. Report the mean of the first and second result.

3) Deviation between first and second result > 30%. Present as missing data.

Deviation= 100%* (second result – first result)/first result

8.3 Safety data handling

8.3.1 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.

8.3.2 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 5 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 2 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 2 assessments are equidistant from the scheduled assessment then the last assessment of the 2 (within the allowable window) will be used.

Table 5 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 ≤ 32	3
Treatment	33 ≤ Day ≤ 53	6
Treatment	54 ≤ Day ≤ 74	9
Treatment	75 ≤ Day ≤ 98	12 (d)
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.

d: For assessments with no Week 3/6/9 planned assessments (ie UPDRS), the window for the Week 12 assessment is 1 ≤ Day ≤ 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. For Lab data (and other similar data) where only Week 6 and 12 are performed, the window for W eek 6 is 1 ≤ Day ≤ 53, and Week 12 the window is 54 ≤ Day ≤ 98.

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.

8.3.3 Handling of Replicate Data

A subject having an AE coded to the same PT 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.

8.3.4 Safety Data Collected After the ED Visit

Post TE data (data collected beyond treatment emergent window) will be summarized separately for for non-TEAEs only, otherwise no post TE data will be summarized. 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.

8.4 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, WAIS-IV DSC, SAPS-PD and FAQ.

<u>Montreal Cognitive Assessment (MoCA)</u>

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 it is set to zero. 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 it is set to zero

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 it is set to zero.

Mini-Mental State Examination (MMSE)

The MMSE is composed of 30 questions grouped into domains, see Table 6. For each of the MMSE domains the correct responses are added. If a domain has missing data then the domain is missing. From the domains compute the six items as show in Table 6. 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 6 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 perform 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. If any one of the domain scores are missing then the score is missing.

Wechsler Adult Intelligence Scale-4th Edition Digit Symbol Coding (WAIS-IV DSC)

The measure of interest in the WAIS-IV is known as the Digit Symbol Coding, which is the number of squares filled in correctly within the time limit of 120 seconds (score range of 0 to135). This test engages multiple cognitive abilities including attention, psychomotor speed,

complex scanning, visual tracking, and immediate memory. If any part of the test is missing (subject unable or unwilling) then the score is missing.

Scale for Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD)

There are 5 items for hallucinations (including auditory, voices conversing, somatic/tactile, visual and global hallucinations) and 4 items for delusions (including persecutory, jealousy, reference and global delusions). Each item is scored on a scale of 0 to 5, with 0 being none and 5 representing severe and frequent symptoms. Therefore, the SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. If any one of the item scores are missing, then the total score is missing.

Funtional Assessments Questionnaire (FAQ)

On the basis of interviews with the caregivers/informants, subjects will be rated for ability to carry out ten complex activities of daily living: (1) manage finances, (2) complete forms, (3) shop, (4) perform games of skill or hobbies, (5) prepare hot beverages, (6) prepare balanced meal, (7) follow current events, (8) attend to television programs, books, and magazines, (9) remember appointments, and (10) travel out of the neighborhood. Each activity will be rated as 0 (normal, does without difficulty), 1 (has difficulty but does by self), 2 (requires assistance), or 3 (dependent). Scores will be summed across items to provide a total disability score (higher scores = greater impairment; maximum score = 30). If an activity was never or very rarely performed premorbidly, it will be marked as "Not Applicable" and will not be included in the score. A proportional score will be derived for subjects who mark any activity as 'Not Applicable' as follows (achieved score/(30 – 3 times the number of activities marked 'Not Applicable').

8.5 Algorithms for Safety Parameters

MDS-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).

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 using SAS Version 9.4 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

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. Table 4 in PERFORMANCE OF CSF AD BIOMARKERS IN PREDICTING AMYLOID PET POSITIVITY IN EARLY AD: DATA FROM EISAI'S MISSIONAD PROGRAM, Kaplow et al, Presented at the 15th International Conference on Alzheimer's and Parkinson's Diseases: Mechanisms, Clinical Strategies and promising Treatments of Neurodegenerative Diseases. (AD PD 2021), March 9-14, 2021, Virtual Event. Poster Board Number: P220.

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 3.

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	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/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 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/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	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
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 – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
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×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
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)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	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; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120 - 124 mmol/L regardless of symptoms	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = gamma-glutamyl transferase, LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0.

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