1 TITLE PAGE

Clinical Study Protocol

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
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US
Sponsor's Investigational Product Name:	E2027
Indication:	Dementia with Lewy bodies and Parkinson's disease dementia
Phase:	2
Approval Date:	V1.0 19 Nov 2020 (original protocol)
IND Number:	123614
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2027

Name of Active Ingredient: 7-(2-Methoxy-3,5-dimethylpyridin-4-yl)-1-[(3S)-tetrahydrofuran-3-yl]-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one maleate (IUPAC)

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

Sites

Approximately 30 investigational sites in the United States (US) and Canada

Study Period and Phase of Development

Approximately 9 months for the study

Phase 2

Objectives

Primary Objective

- 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

Secondary Objective

- To evaluate the safety and tolerability of E2027 in subjects with DLB and PDD

Exploratory Objectives

- 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

Study Design

This is a multicenter, open-label study in subjects with DLB or PDD who will be treated with E2027 for 12 weeks. Four subgroups of subjects will be 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 is defined as ratio of plasma concentration of amyloid-β (Aβ)42/Aβ40 <0.092 (based on the C2N Preclivity assay).

The study design allows for add-on therapy of E2027 to standard of care for DLB and PDD, which includes acetylcholinesterase inhibitor (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 to participate in this study but are not permitted to start such medications during the study. It is required that in each subgroup there should be at least 1 subject who is not receiving AChEI or memantine during the study. Subjects should be on stable doses of medications for the treatment of Parkinson's disease, maintained without change during the study.

For all subjects, study participation will comprise 2 Phases: Pretreatment (Screening Period [up to 6 weeks] and Baseline Period [up to 1 week]) and Treatment (Treatment Period [12 weeks] and Follow-up Period [4 weeks]).

Pretreatment Phase

Screening Period: Screening will occur between Day -49 and Day -8. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. All subjects will be assessed for eligibility through review of medical history, physical examination (including neurological examination), laboratory tests, vital signs, and ECGs.

Subjects with DLB will be assessed on clinical scales of cognition and depression, safety magnetic resonance imaging (MRI) of the brain and dopamine transporter (DAT) brain imaging or myocardial scintigraphy (^{123}I-meta-iodobenzylguanidine [MIBG]) (if indicated in individual subjects and not previously performed) to confirm that they meet the diagnostic criteria and severity for DLB.

Subjects with PDD will be assessed on clinical scales of cognition and depression, safety MRI of the brain and DAT brain imaging or MIBG (if indicated in individual subjects and not previously performed) to support their diagnosis of Parkinson's disease (and not other extrapyramidal or cerebrovascular diseases).

Eligibility assessments at Screening will be conducted in 6 tiers, and subjects will need to satisfy eligibility criteria in each tier before proceeding to the next tier.

The scores of various clinical scales (including NPI, Short Fluctuation Questionnaire [SFQ], CFI, and Unified Parkinson's Disease Rating Scale Part III: Motor Examination [UPDRS-III]) and cognitive tests (MMSE, MoCA) at Screening will be reviewed by a central process. Subjects who are diagnosed by the investigator with DLB or PDD but whose scores on clinical scales or cognitive tests are found not to be consistent with the diagnosis during central review will be discussed with the investigator to determine their eligibility.

All subjects who have completed screening assessments and are deemed eligible for the study will have a baseline CSF sample collected by lumbar puncture (LP). The CSF sample will be collected in the morning, either in the fasted state or at least 2 hours after breakfast. In subjects who require DAT or MIBG scan, the CSF collection should be at least 1 week after the scan.

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 clinical assessments on cognition and depression) and at least 1 week after CSF collection. Study assessments should be conducted in the morning (whenever possible). Cognition will be assessed by the MoCA, which must be the first clinical scale to be administered before any invasive procedures, followed by the WAIS-IV DSC and then the Clinician Interview Based Impression of Severity Plus Caregiver Input (CIBIS-Plus). The caregiver or informant will also complete the CIBIS-Plus, NPI, CFI, SAPS-PD, and FAQ. The rater administering the CIBIS-Plus should be independent of the rater(s) who administer the other clinical scales.

At the Baseline Visit subjects will be assessed regarding other medical conditions and concomitant medications (including medications for DLB or PDD) to ensure that these remain stable with no changes to treatment required and that they do not interfere with their safety or study procedures. Other safety assessments including vital signs, ECGs, laboratory tests, and Columbia Suicide Severity Rating Scale (C-SSRS) will also be conducted.

Treatment Phase

Treatment Period: After completing study assessments at the Baseline Visit, subjects who continue to be eligible will proceed to the Treatment Period on E2027 (50 mg once daily [QD]). They will be provided with 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 3, 6, 9, and 12 weeks on E2027. Efficacy assessments will be performed after 6 and 12 weeks on E2027 and should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first efficacy assessment to be administered, followed by the WAIS-IV DSC (after 12 weeks only), then the CIBIC-Plus and finally the MMSE (after 12 weeks only). Whenever possible, a subject should have the same rater administering the MoCA and the CIBIC-Plus throughout his/her participation in the study. The rater administering the CIBIC-Plus should be independent of the rater(s) who administer the other clinical scales. The caregiver or informant will also complete the CIBIC-Plus, NPI, CFI, SAPS-PD (after 12 weeks only) and FAQ (after 12 weeks only). Safety assessments will be conducted at these visits, including review of adverse events (AEs), vital signs, ECG, laboratory safety tests, C-SSRS, and UPDRS-III. The investigator will review all the efficacy endpoints and safety data at the visits after 6 and 12 weeks on study drug and formulate the CGIC of the subject's clinical status from baseline.

After subjects have completed 9 weeks of treatment with E2027 will have a 2nd CSF sample collected. The CSF sample will be collected in the morning at approximately the same time as at Screening, either in the fasted state or at least 2 hours after breakfast. A 2nd plasma sample for biomarkers will also be collected.

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

The end of study is defined as the last subject completing the Follow-Up Visit.

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. At these originally scheduled visits that take place after the ED Visit, blood PK samples, plasma biomarker samples, and CSF samples will not be collected.

Conduct of the Study During the COVID-19 Pandemic and Other Extenuating Circumstances

All study assessment and visit information affected by any extenuating circumstances (eg, the COVID-19 pandemic) will be collected on the electronic case report forms (eCRFs). These include but are not limited to any visits or assessments that are missed or not done, any assessments that are performed remotely/offsite or in person/onsite, and any home delivery of investigational product.

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

- An extension of the Screening Period from 6 weeks to up to 10 weeks is allowed with sponsor approval on a subject by subject basis.
- If subjects cannot visit the study site, all procedures which require physical contact with the subjects (eg, vital signs, ECGs, blood tests, physical examination, UPDRS-III) may be conducted via home visit (if feasible) with sponsor approval. The brain or cardiac imaging during the Screening Visit must be conducted at the study site. The CSF collection at the Screening Visit and Visit 6 (Week 9) must be conducted at the study site. Other study procedures including all the efficacy endpoints, AEs, and concomitant medications review may be conducted remotely via telephone, sponsor approved telehealth, or home visit. If it is not possible for subjects to attend the study site for the CSF collection Visit 6 (Week 9), this can be performed at an Unscheduled Visit as soon as possible after Week 9. Study drug may be delivered to subjects' homes if it is not possible to visit the study site to collect the study drug.

Number of Subjects

Approximately 64 subjects will be screened to provide a maximum of 32 treated subjects, with 8 subjects in each of the 4 subgroups (DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology, and PDD with amyloid copathology). Allowing for a 25% dropout rate there will be 24 treated subjects completing the study treatment, with 6 subjects in each subgroup. Further subjects may be screened and treated with E2027 if there are less than 6 completers in any of the subgroups.

Inclusion Criteria

1. Male or female, age 50 to 85 years, inclusive at time of consent
2. Meet criteria for probable DLB (as defined by the 4th report of the DLB Consortium) or meet criteria for probable PDD (as defined by the task force of the Movement Disorder Society). Specific situations regarding the use of imaging are described below:
   a. DLB subjects who have 1 core clinical feature only by the investigator and who do not have previous reports of DAT brain imaging scan, MIBG scan or polysomnography (PSG) will undertake DAT brain imaging scan or MIBG scan as organized by the investigator.
   b. DLB subjects who have 2 or more core clinical features by the investigator but who are judged as having only 1 core clinical feature by central reviewer and who do not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor.
   c. DLB subjects who have 2 or more core clinical features by the investigator and the central reviewer and who do not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the

sponsor medical monitor if the investigator considers that imaging is necessary to confirm the diagnosis.

d. PDD subjects with clinical features that are consistent with the diagnostic criteria of probable PDD but in whom the investigator considers that there may be other diagnoses, DAT brain imaging scan or MIBG scan may be conducted after discussion with the sponsor medical monitor.

3. MMSE $\geq$14 and $\leq$26 at Screening Visit
4. For DLB subjects, have experienced visual hallucinations since onset of their DLB
5. If receiving AChEIs, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment-naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs from Screening to the end of the study.
6. If receiving memantine, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment naïve subjects can be entered into the study but there should be no plans to initiate treatment with memantine from Screening to the end of the study.
7. If receiving Parkinson's disease medications, must have been on a stable dose for at least 4 weeks before Screening Visit, with no plans for dose adjustment during the study.
8. Must have an identified caregiver or informant who is willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, not be suffering from cognitive impairment, be sufficiently familiar with the subject and spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant should normally be residing with the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. As a guide the caregiver or informant should have contact with the subject on at least 4 days a week and each day for a total of at least 5 hours. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At all visits caregivers or informants need to attend the visit in person along with the subject.
9. Provide written informed consent. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, as required in accordance with local laws, regulations and customs, plus the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). In countries where local laws, regulations, and customs do not permit subjects who lack capacity to consent to participate in this study, they will not be enrolled.

Exclusion Criteria

1. Any neurological condition that may be contributing to cognitive impairment above and beyond those caused by the subject's DLB or PDD, including any comorbidities detected by clinical assessment or MRI (identification of amyloid copathology is not exclusionary)
2. History of transient ischemic attacks or stroke within 12 months of Screening
3. Modified Hachinski Ischemic Scale >4
4. Parkinsonian (extrapyramidal) features with Hoehn and Yahr Scale (HYS) stage IV or higher

5. Any major psychiatric diagnosis, including schizophrenia, bipolar disorder and current major depressive disorder as per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
6. Geriatric Depression Scale (GDS) score >8
7. Severe visual or hearing impairment that may interfere with the subject study assessments including cognitive testing
8. The following exclusions apply in relation to CSF sampling by LP:
   - A bleeding disorder that is not under adequate control (including a plate count <50,000, international normalized ratio [INR] >1.5 or partial thromboplastin time [PTT] >upper limit of normal [ULN])
   - Any contraindications to LP (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, obesity to the extent that it makes LP technically difficult, or inability to cooperate with LP due to cognitive impairment or motor symptoms)
9. History of deep brain stimulation or other neurosurgical procedure for Parkinson's disease
10. Has thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects whether or not they are taking thyroid supplements.
11. Abnormally low serum vitamin B12 levels (less than the lower limit of normal [LLN]) for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory). Low levels of vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, (if available in region) and excluded only if MMA levels are also >ULN.
12. Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or positron emission tomography (PET) scanning as per local guidelines need not be excluded
13. Evidence of other clinically significant lesions that suggest a dementia diagnosis other than DLB or PDD on brain MRI at Screening. All MRIs will be acquired using a standardized procedure that will be outlined in the Imaging Charter and Imaging Acquisition Guidelines and will be read by an approved centralized reader.
14. Other significant pathological findings on brain MRI at Screening, including but not limited to: any macrohemorrhage (greater than 10 mm at greatest diameter); an area of superficial siderosis; evidence of cerebral contusion, encephalomalacia, aneurysms, arteriovenous malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than or equal to 1 cm at their greatest diameter need not be exclusionary)
15. Hypersensitivity to E2027 or any of the excipients
16. A prolonged corrected QT interval calculated using Fridericia's formula (QTcF) as demonstrated by triplicate ECG at the Screening or Baseline Visit (ie, mean value >450 msec)
17. Had symptomatic orthostatic hypotension or symptomatic orthostatic tachycardia which resulted in hospitalization or urgent medical review in hospital in the past 12 months before Screening

18. Any other clinically significant abnormalities that in the opinion of the investigator, require further investigation or treatment or that may interfere with study procedures or safety in the following:
    a. Physical examination, ECG, vital signs at Screening or Baseline Visit
    b. Laboratory tests at Screening Visit
19. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma of the skin, or localized prostate cancer in male subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
20. Has a "yes" answer to C-SSRS suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
21. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
22. Any other medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator may affect the subject's safety or interfere with the study assessments
23. Taking any of the prohibited medications or not meeting the requirements regarding stable doses of permitted medications
24. Participation in a clinical study involving any investigational drug/device for DLB or PDD within 6 months before Screening or any other investigational drug/device in the 8 weeks or 5 half-lives (whichever is longer) of the study medication before Screening unless it can be documented that the subject was in a placebo treatment arm
25. Planned surgery which requires general, spinal or epidural anesthesia that will take place during the study. Planned surgery that requires only local anesthesia and can be undertaken as a day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.
26. Males who have not had a successful vasectomy (confirmed azoospermia) if their female partners are of childbearing potential and are not willing to use a highly effective contraceptive method throughout the study period and for 98 days after study drug discontinuation. No sperm donation is allowed during the study period and for 98 days after study drug discontinuation.
27. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test) with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Females of childbearing potential who:
    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device or intrauterine hormone-releasing system

- a contraceptive implant
- an oral contraceptive (Subject must have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of oral contraceptive throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation

(NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing].)

Study Treatment

E2027 should be administered QD orally in the morning with or without food. Subjects will be instructed to take their other concomitant medications at the usual time.

Test drug: E2027

E2027 will be administered in size #2 hypromellose (HPMC) capsules containing 25 mg of E2027.

All subjects will take 2 × E2027 25 mg capsules.

Comparator Drug: Not applicable

Duration of Treatment

The total duration of study participation of each subject is approximately 23 weeks:

- Up to 6 weeks for Screening Period
- Up to 1 week for Baseline Period
- Treatment Period of 12 weeks
- Follow-up Period of 4 weeks

Concomitant Drug/Therapy

Prohibited and Restricted Concomitant Medications:

Unless otherwise specified, the following medications are prohibited from a period of 14 days (or 5 half-lives, whichever is longer) before the Baseline Visit (Visit 2) until the Follow-Up Visit to avoid the risk of interaction with E2027. Subjects who start any of these medications during the study will be discontinued.

- Drugs known to be strong inhibitors of cytochrome P450 (CYP) 3A (CYP3A), grapefruit, grapefruit juice, and grapefruit products
- Drugs known to be moderate to strong inducers of CYP3A. Herbal preparations containing St. John's Wort is prohibited for 4 weeks before the Baseline Visit (Visit 2) until the Follow-Up Visit
- Drugs known to cause prolongation of the QT interval, including but not limited to drugs that may cause cardiac arrhythmias. For drugs which may cause QTcF prolongation, subjects need not be excluded if at Screening the subjects are already on stable doses for at least 4 weeks and their mean QTcF on triplicate ECGs at Screening and Baseline Visit is not >450 msec (Exclusion Criterion 16).

- Drugs that are phosphodiesterase inhibitors (eg, theophylline, aminophylline, sildenafil, tadalafil, vardenafil, dipyridamole, roflumilast, apremilast, inamrinone, milrinone, and enoximone)

The following medications are prohibited to avoid the risk of interference with study assessments or procedures. Subjects who start these medications during the study will be discontinued unless otherwise specified.

- Anticholinergic drugs that have central nervous system (CNS) activity are prohibited from 4 weeks before Screening Visit until the Follow-Up Visit
- Pimavanserin is prohibited for 12 weeks before Screening Visit until the Follow-Up Visit
- Anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) and dual antiplatelet therapy (eg, aspirin and clopidogrel together) are prohibited from Screening Visit until after the 2nd CSF collection at 9 weeks of treatment with E2027

The following restrictions apply to AChEIs (including donepezil, rivastigmine, galantamine) or memantine for treatment of DLB or PDD:

- If a subject is already receiving AChEI or memantine at Screening, they must be on a stable dose for at least 12 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already receiving AChEI or memantine at Screening, then these should not have been used at least 12 weeks before Screening and AChEI or memantine should not be started during the study until the Follow-Up Visit.
- Subjects who start AChEI/memantine or change their dose of AChEI/memantine during the study should undertake an Unscheduled Visit before making such changes in their AChEI/memantine medications to undertake efficacy assessments (MoCA, CIBIC-Plus, NPI, CFI, CGIC) (unless they have been conducted within past 4 weeks). This change in AChEI/memantine medications is considered a protocol deviation; the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in the Statistical Analysis Plan (SAP).

The following restrictions apply to medications for Parkinson's disease or motor symptoms of DLB (except CNS-active anticholinergic drugs that are prohibited as above):

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- Starting or changing the dose of these medications during the study is considered as a protocol deviation; the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in the SAP.

The following restrictions apply to medications for antipsychotic or neuroleptic drugs, hypnotics, anxiolytics or antidepressants:

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.

- Subjects who start or change their dose of these medications should undertake an Unscheduled Visit before making such changes in these medications to undertake efficacy assessments (MoCA, CIBIC-Plus, NPI, CFI, CGIC) (unless they have been conducted within past 4 weeks). This change in such medications is a protocol deviation and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in the SAP.

The following restrictions apply to other medications that the subject is taking at Screening or are started during the study:

- These medications may be permitted if they are not included in the prohibited or restricted medications list above and are considered by the investigator and sponsor medical monitor not to compromise study assessments or subject safety.
- Permitted prior medications should be at a stable dose for at least 4 weeks before Screening and should remain on the same dose throughout the study.
- Subjects who change the dose of their permitted prior medications or who start permitted new medications during the study may continue in the study if the investigator and sponsor medical monitor consider that this will not compromise study assessments or subject safety.
- As needed (PRN) medications required for performing LP for CSF sampling are permitted

Assessments

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 or PDD. The total possible score is 30 points; a score of 26 or above is considered normal.

WAIS-IV DSC

This is the Digit-Symbol Substitution Test from the WAIS-IV. The test consists of small blank squares presented in rows with one of 9 numbers (1-9) randomly printed directly above each blank square. A "key" is printed above the rows of blank squares. The "key" pairs numbers 1 through 9 with an unfamiliar symbol. Following a short series of practice trials, the subject must use the key to fill in the blank squares in order (working from left to right across the rows) with the symbol that is paired with the number over the blank square. The subject must work as fast as possible for 120 seconds. The measure of interest is known as the Digit Symbol Coding, which is the number of squares filled in correctly within the time limit (maximum score=135). This test engages multiple cognitive abilities including attention, psychomotor speed, complex scanning, visual tracking, and immediate memory. Alternate versions will include the identical symbols and digits re-paired.

CIBIC-Plus

The CIBIC-Plus scale is designed to measure various domains that describe subject function: general, mental/cognitive state, behavior, and activities of daily living. It is a semi-structured global rating derived from a comprehensive interview with the subject and caregiver or informant by an independent rater who has no access to the source data or other psychometric test scores conducted postbaseline as part of the given protocol.

At the Baseline Visit, the independent rater will use a related tool, the CIBIS-Plus. This scale, which assesses disease severity on a 7-point scale from 1 = normal to 7 = extremely ill, establishes a point of reference for subsequent interviews using the CIBIC-Plus. During the Treatment Period, the rater will administer the CIBIC-Plus separately to the subject and the caregiver or informant. At the end of each pair of interviews during each of these study visits, the rater alone will determine separately for each of the 4 domains whether the disease has improved, worsened, or

remained unchanged since the evaluation at Baseline. The CIBIC-Plus scores are: 1 (marked improvement), 2 (moderate improvement), 3 (minimal improvement), 4 (no change), 5 (minimal worsening), 6 (moderate worsening), and 7 (marked worsening).

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 also assesses the degree of caregiver or informant distress engendered by each of the symptoms (NPI-D). It is rated from 0 to 144 with high scores meaning a greater neuropsychiatric disturbance. Two subscores will be derived NPI-10 (covering the domains of delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and motor disturbance) and NPI-4 (covering the domains of delusions, hallucinations, apathy, and depression).

SAPS-PD

The SAPS-PD is a structured clinical interview originally designed for use in schizophrenia. It includes 5 domains of positive symptoms: hallucinations, delusions, bizarre behavior, positive formal thought disorder and inappropriate affect. The SAPS-PD is adapted from the Scale for Assessment of Positive Symptoms (SAPS) and includes items that are reflective of the hallucinations and delusions in PDD. It is a 9-item scale adapted from the hallucinations and delusions domains of the SAPS. 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.

MMSE

A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

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 behavior. It is scored based on frequency and severity with a score range of 0 to 12. The scale also assesses the degree of caregiver or informant distress engendered by the symptoms.

CGIC

The CGIC provides an overall clinician-determined summary measure of change from the subject's clinical status at the Baseline Visit that takes into account all available information from the efficacy endpoints above (which include cognitive function, non-cognitive symptoms, behavior and the impact of the symptoms on the patient's ability to function) and safety data.

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').

Pharmacokinetic Assessments

Blood samples will be collected for the determination of plasma E2027 concentrations for PK analysis. Two blood samples for PK will be drawn at Weeks 6, 9, and 12: at predose (within 30 minutes before dosing) and 1 to 4 hours postdose. At these visits, subjects or their caregivers or informants will be instructed not to take their study drug at home on the day the blood samples for PK are collected. Instead, subjects will take their study drug at the clinic after the predose blood draw; then a postdose blood draw will be performed. In addition, subjects or their caregivers or informant will be instructed to record the time of study drug administration for the 2 days before these visits when self-administered at home and this information will be collected and recorded on the eCRFs.

CSF samples will be collected for the determination of CSF E2027 concentrations at Week 9. At this visit, a predose blood sample for PK will be taken first, followed by CSF sampling. Study drug will then be administered to the subjects. Another PK sample will be collected at 1 to 4 hours postdose.

Baseline Biomarker Assessments

A plasma sample will be collected during the Screening Period (Tier 3) to measure biomarkers related to Alzheimer's disease (AD) copathology (including amyloid and p-tau) and other biomarkers related to DLB or PDD. These baseline plasma amyloid Aβ42/Aβ40 ratio will be used to classify subjects into the various categories (DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology and PDD with amyloid copathology). The baseline plasma and CSF biomarkers may also be used to define other subgroups classifications of subjects for subgroup analyses.

A CSF sample will be collected during the Screening Period (at least 7 days before the Baseline Visit) to measure baseline CSF cGMP and biomarkers related to DLB or PDD. These DLB or PDD related biomarkers may be used to define other subgroups classifications of subjects for subgroup analyses.

Pharmacodynamic Assessments

CSF samples will be collected during the Screening Period (at least 7 days before the Baseline Visit) and after 9 weeks on E2027. Both samples should be collected at approximately the same time in the morning, either in the fasted state (preferred) or at least 2 hours after breakfast. The CSF sample during the Treatment Period should be collected after the predose blood draw for PK and plasma biomarker analysis at the study visit after 9 weeks on E2027. The CSF samples will be assayed for cGMP and E2027. Other CSF biomarkers related to DLB or PDD or E2027 PD effects may also be assayed, if appropriate.

A predose plasma sample will be collected at the study visit after 9 weeks on E2027. It will be assayed for plasma biomarkers related to DLB or PDD or E2027 PD effects on these biomarkers if appropriate.

Pharmacogenomic Assessments

Blood samples will be collected as specified in the Schedule of Procedures/Assessments where feasible and in accordance with local regulations. Participation in pharmacogenomic (PGx) assessments is voluntary and subjects must provide a separate informed consent before blood collection for PGx assessments.

The PGx blood samples may be used to genotype common and rare genetic variants (including apolipoprotein E [ApoE] genotype). Data obtained from the PGx analysis will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The deoxyribonucleic acid (DNA) will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample may be stored for up to 15 years, based on country specific regulations to assist in any scientific research questions related to E2027 or DLB or PDD.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs, regular monitoring of hematology, blood chemistry and urinalysis, measurement of vital signs (including orthostatic changes), ECGs, and the performance of physical examinations, C-SSRS, and UPDRS-III. A safety brain MRI may also be performed at Unscheduled Visits if deemed appropriate by the investigator.

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline Visits, every 3 weeks during the Treatment Period, and at the Follow-Up Visit.

MDS UPDRS-III: Motor Examination

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. It is recommended that 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).

Bioanalytical Methods

Plasma concentrations of E2027 and its metabolite HP4 and CSF concentrations of E2027 will be measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay methods.

Plasma concentrations of Aβ42 and Aβ40 will be measured by the validated immunoprecipitation LC-MS/MS C2N Preclivity plasma assay. Plasma concentrations of p-tau 181, glial fibrillary acidic protein (GFAP), and neurofilament light (NFL) will be measured by Quanterix Simoa plasma assay.

CSF concentrations of cGMP will be measured using a validated assay. Other CSF biomarkers represented by Aβ42, Aβ40, tau, p-tau will be measured by Lumipulse platform and CSF NFL, neuregulin (NRG) will be measured by Simoa.

Statistical Methods

Primary Endpoint

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

Secondary Endpoints

- Safety and tolerability of E2027 as measured by the following:
  - Incidence of AEs 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

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

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

Efficacy Analyses

The exploratory efficacy endpoints 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).

Pharmacokinetic, Pharmacodynamic and Pharmacogenomic Analyses

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 and its report, and the results will not be included in the clinical study report.

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). 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 may be analyzed similarly, if appropriate.

The CSF and plasma PD biomarkers will be summarized by subject subgroups, as appropriate. Summaries and figures will be produced exploring the relationships between CSF and plasma PD biomarkers and the efficacy endpoints.

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 and its report, and the results will not be included in the clinical study report.

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 PGx data will be summarized similarly.

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 subgroup and overall.

Interim Analyses

No interim analysis will be conducted.

Sample Size Rationale

Assuming the standard deviation of percentage change from baseline in CSF cGMP at Week 9 is 60 , the sample size of 6 completers per group (for 8 enrolled subjects per arm, assuming a 25% dropout rate), will 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 has approximately 80% power to detect the difference in change from baseline of CSF cGMP of 100% (same assumptions as above). These sample size calculations illustrate the possible differences that could be seen between subgroups. However, without previous data on the differences between subgroups in CSF cGMP, these are for illustration only and it is not expected statistical significance will 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 groups. If the true difference is 100%, there will be 97.8% probability that the observed difference is ≥30%. If the true difference is 60%, the probability is 80.7%. If the true difference is 10%, there will be 28.2% probability that the observed difference is ≥30%.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid-β
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
AE	adverse event
ApoE	apolipoprotein E
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CIBIC-Plus	Clinician's Interview Based Impression of Change Plus Caregiver Input
CIBIS-Plus	Clinician's Interview Based Impression of Severity Plus Caregiver Input
CGIC	Clinician Global Impression of Change
cGMP	cyclic guanosine monophosphate
CFI	Cognitive Fluctuation Inventory
CNS	central nervous system
CRA	Clinical research associate
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
DAT	dopamine transporter
DLB	dementia with Lewy bodies
eCRF	electronic case report form
ED	early discontinuation
FAQ	Functional Assessments Questionnaire
FAS	Full Analysis Set
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GFAP	glial fibrillary acidic protein
hCG	human chorionic gonadotropin
HPMC	hypromellose
HYS	Hoehn and Yahr Scale
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry
LBD	Lewy body dementias
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLN	lower limit of normal

Abbreviation	Term
LNH	low/normal/high
LP	lumbar puncture
LS	least square
MDS	Movement Disorders Society
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	^{123}I-meta-iodobenzylguanidine
MMA	methylmalonic acid
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NFL	neurofilament light
NPI	Neuropsychiatric Inventory
NRG	neuregulin
PD	pharmacodynamic(s)
PDD	Parkinson's disease dementia
PDE9	phosphodiesterase 9
PET	positron emission tomography
PGx	pharmacogenomic
PK	pharmacokinetic(s)
PSG	polysomnography
PT	preferred term
PTT	partial thromboplastin time
QD	once daily
QTcF	corrected QT interval calculated using Fridericia's formula
REM	rapid eye movement
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAPS	Scale for Assessment of Positive Symptoms
SAPS-PD	Scale for Assessment of Positive Symptoms in Parkinson's Disease
SFQ	Short Fluctuation Questionnaire
SOC	system organ class
TEAEs	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory value
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPDRS-III	Unified Parkinson's Disease Rating Scale Part III: Motor Examination
US	United States
WAIS-IV DSC	Wechsler Adult Intelligence Scale-4th Edition Digit Symbol Coding
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

Where appropriate, at the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2018)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or caregiver (or informant), in accordance with applicable professional standards and local laws/regulations, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations.

During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study.

The identified caregiver or informant should also consent to supporting the subject's participation in the study before any study-specific procedures are performed and will be provided with a written ICF for his or her participation in the study. The subject and caregiver or informant do not have to sign their ICF on the same day.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

Subjects who agree to take part in pharmacogenomics (PGx) assessment will also be asked to provide separate written consent for this procedure.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in the United States (US) and Canada.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organizations (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

Lewy body dementias (LBD) are the second most common cause of dementia in subjects over 65 years of age. It comprises dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), which are considered to be different ends of the same spectrum. Both DLB and PDD share a common underlying pathology which involves deposition of cortical and subcortical Lewy bodies within neurons (comprising aggregates of alpha synuclein). Idiopathic Parkinson's disease is a progressive neurodegenerative disorder characterized by tremor, rigidity, bradykinesia, and postural instability, with onset typically in middle to late life. It is thought that up to 80% of patients with Parkinson's disease develop dementia some years after the onset of the motor features and they are classified as having PDD. In DLB, subjects develop dementia prior to or within 12 months

(McKeith, et al., 2017) after the onset of the characteristic motor symptoms associated with Parkinson's disease (Walker, et al., 2015).

LBD (in the form of both DLB and PDD) involve similar profiles of cognitive dysfunction affecting attention, executive function, visuospatial domains and memory (Aarsland, et al., 2003; Walker, et al., 2015; Biundo, et al., 2016). Often, more than 1 aspect of cognition is impaired, interfering with the patient's daily, occupational, or social functioning. While generally progressive, LBD are characterized by fluctuations in cognition and levels of consciousness, visual hallucinations, delusions, depression, anxiety, or other behavioral disturbances. Patients may also have autonomic impairment that may include urinary dysfunction and orthostatic hypotension, with susceptibility to falls early in the disease course.

Although both DLB and PDD are considered to be part of the same spectrum of LBD, there are some clinical differences. DLB subjects develop dementia early in the course of their disease (McKeith, et al., 2017) compared to subjects with PDD. Patients with PDD have motor symptoms for some years with a higher proportion taking medications for Parkinsonian motor symptoms (Noe, et al., 2004). Neuropsychiatric features (such as visual hallucinations) and cognitive fluctuations are more prominent in DLB than in PDD.

In DLB approximately 50% to 70% of subjects have concurrent amyloid pathology in the brain similar to that in Alzheimer's disease (AD) (Donaghy, et al., 2015). In PDD the prevalence of concurrent amyloid pathology is lower than DLB, with a positive amyloid positron emission tomography (PET) scan in approximately 34% of PDD patients (Petrou, et al., 2015). Patients with DLB or PDD with concomitant AD amyloid and tau pathology may have shorter disease duration and shorter survival compared to patients without such pathology (Irwin, et al., 2017; Ferman, et al., 2020).

7.1 Compound Overview

7.1.1 Current Therapeutic Options

There are no therapies currently available that alter the underlying neurodegenerative process of LBD. A number of symptomatic therapies can improve patient quality of life, primarily through management of motor symptoms such as bradykinesia, rigidity, and gait disturbance. Levodopa remains the most effective medication available for treating the motor features of Parkinson's disease that occur in LBD. Current therapy for cognitive deficits associated with LBD is largely based on the use of acetylcholinesterase inhibitors (AChEIs), such as rivastigmine and donepezil. Rivastigmine is approved in multiple countries for symptomatic treatment of cognitive deficits in PDD and donepezil is approved in several Asian countries including Japan and the Philippines for symptomatic treatment of DLB. Memantine is also used in the treatment of DLB but its efficacy is small (Aarsland, et al., 2009). With regard to neuropsychiatric symptoms, pimavanserin is approved for these symptoms in Parkinson's disease. AChEIs and antipsychotics such as risperidone, quetiapine, and olanzapine are also commonly used in clinical neurology practice for this purpose. However, the efficacy of AChEI and antipsychotic drugs on cognitive symptoms and neuropsychiatric symptoms is

modest. In addition, there are concerns about worsening of parkinsonism by both AChEI and antipsychotics as well as special concerns about hypersensitivity to antipsychotics. Therefore, there is a need for further treatment benefit.

7.1.2 Therapeutic Pathway

E2027 is a novel highly selective and potent inhibitor of phosphodiesterase 9 (PDE9). PDE9 is primarily responsible for breakdown of cyclic guanosine monophosphate (cGMP) within the brain, a second messenger implicated in synaptic plasticity, learning and memory. Restoring cGMP levels in the brain of DLB patients without amyloid copathology, by inhibiting the PDE9 enzyme, is hypothesized to enhance synaptic plasticity at intact synapses and improve cognition. Recent study results (see below) have prompted the need to conduct this study to understand the effect of E2027 in DLB patients with amyloid copathology relative to those without amyloid copathology.

7.2 Clinical Experience

E2027 is a new chemical entity. E2027 has been evaluated in 5 completed studies (E2027-A001-001[Study 001], E2027-A001-002 [Study 002], E2027-A001-003 [Study 003], E2027-A001-005 [Study 005], and E2027-G000-201 [Study 201]). In the completed Phase 1 studies, 176 subjects received at least 1 dose of E2027 (120 subjects administered single E2027 doses from 10 to 1200 mg in Study 001, Study 003, and Study 005, and 56 subjects administered multiple doses of E2027 from 5 to 400 mg once daily [QD] for up to 6 weeks in Study 002). In the completed Phase 2 study (Study 201), there were 200 subjects with DLB randomized in a 1:1 ratio to receive 50 mg of E2027 or placebo administered QD.

In the Phase 1 studies, E2027 was found to be well-tolerated at doses up to 400 mg QD for 14 days. Doses of E2027 at 50 mg QD or higher resulted in mean cerebrospinal fluid (CSF) cGMP elevation by approximately 200% from baseline at steady state, which was maintained after 6 weeks of treatment. This implied that >80% of subjects had at least 150% CSF cGMP elevation from baseline at a dose of E2027 50 mg QD.

Detailed description of clinical experience with E2027, including pharmacokinetic (PK), pharmacodynamic (PD), metabolism, and safety in Phase 1 studies, is provided in the E2027 Global Investigator's Brochure.

Study 201 was a Phase 2 proof of concept study. It was a randomized, double-blind, placebo-controlled study to determine the efficacy of a dose of E2027 (50 mg QD) compared to placebo in subjects with DLB. The key efficacy endpoints were Montreal Cognitive Assessment (MoCA), Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus), Neuropsychiatric Inventory (NPI-12), and Cognitive Fluctuation Inventory (CFI). Details of the study design of are provided in the E2027 Global Investigator's Brochure.

In Study 201, there were 99 subjects with mild to moderate DLB treated with E2027 50 mg QD and 97 subjects treated with placebo for up to 12 weeks. E2027 was well-tolerated. Most cases of treatment-emergent adverse events (TEAEs) were mild or moderate in

severity. The incidence of severe TEAEs was higher in placebo than E2027 (placebo [6.2%], E2027 [2.0%]). The most common TEAEs in subjects on E2027 were fall (10.1%), visual hallucinations (7.1%), worsening of DLB (5.1%), dizziness (5.1%), and nasopharyngitis (5.1%). The most common TEAEs in subjects on placebo were fall (15.5%), visual hallucination (9.3%), and urinary tract infection (5.2%).

The TEAEs with higher incidence in the E2027 group (>2% and at least 2-fold of that in placebo group) were worsening of DLB (5.1%, compared with 1.0% on placebo), dizziness (5.1%, compared with 1.0% on placebo), somnolence (3.0%, compared with 1.0% on placebo), orthostatic hypotension (3.0%, compared with 1.0% on placebo) and aggression (3.0%, compared with no subjects on placebo).

The incidence of specific treatment-related TEAEs across the treatment groups was generally similar except for a higher incidence in the E2027 group of worsening of DLB, with 1 (1.0%) subject in the placebo group and 5 (5.1%) subjects in the E2027 group. The incidence of mild, moderate and severe treatment-related TEAEs was similar in the placebo group and the E2027 group.

One death occurred during the study, after the final dose; this subject was in the placebo group. No deaths were reported in the E2027 group. A similar percentage of subjects in each treatment group experienced nonfatal other treatment-emergent serious adverse events (SAEs): 9 (9.3%) subjects in the placebo group and 7 (7.1%) subjects in the E2027 group.

There were no clinically significant changes in laboratory test findings, ECGs, Columbia Suicide Severity Rating Scale (C-SSRS), Unified Parkinson's Disease Rating Scale Part III: Motor Examination (UPDRS-III), or vital signs (including orthostatic hypotension and orthostatic tachycardia).

In Study 201, proof of concept was not achieved in the overall study population. There was no treatment benefit of E2027 compared with placebo in the various efficacy endpoints after 12 weeks of treatment, including MoCA, CIBIC-Plus, NPI-12, and CFI. The treatment differences between E2027 and placebo with their confidence intervals are summarized in Table 1.

Table 1 Study E2027-G000-201: Summary of Efficacy of E2027 in Overall Population

Efficacy Endpoint At 12 Weeks	Treatment Difference (95% CI)[a]
MoCA[b]	0.181 (-0.716, 1.078)
CIBIC-Plus[c]	1.018 (0.695, 1.492)
NPI-12[d]	-0.964 (-4.717, 2.788)
CFI[d]	-0.043 (-0.890, 0.804)

CFI = Cognitive Fluctuation Inventory, CIBIC-Plus = Clinician's Interview Based Impression of Change Plus Caregiver Input, GLMM = generalized linear mixed models, LS = least square, MMRM = mixed effects model of repeated measures, MoCA = Montreal Cognitive Assessment, NPI = Neuropsychiatric Inventory.

a: Treatment difference (E2027 minus Placebo) for MoCA, NPI, and CFI is LS means from MMRM analysis. CIBIC-Plus treatment difference is the proportional odds ratio from a GLMM analysis.

b: Positive treatment difference indicates treatment benefit on E2027.

c: Odds ratio >1 indicates treatment benefit on E2027.

d: Negative treatment difference indicates treatment benefit on E2027.

There was a suggestion that subjects who did not take AChEI at baseline showed numerically higher treatment benefit in MoCA and CIBIC-Plus than subjects who took AChEI at baseline.

There were 4 subjects who participated in the optional CSF substudy and they were all treated with E2027. Their CSF cGMP mean change from baseline showed an increase by 168%. There appeared to be a correlation between their CSF cGMP percentage change from baseline with their change from baseline in MoCA and CIBIC-Plus. There was a trend that subjects with lower CSF cGMP percentage change from baseline having less improvement or worsening of their MoCA from baseline, whereas subjects with higher CSF cGMP percentage change from baseline showed greater improvement in MoCA from baseline. Similarly, subjects with higher CSF cGMP percentage change from baseline showed mild improvement or no change in CIBIC-Plus, whereas those with lower CSF cGMP percentage change from baseline showed mild worsening.

As AD-type copathology of amyloid in the brain in DLB is common (occurring in approximately 70% of subjects), plasma amyloid Aβ42/Aβ40 ratio was determined in a subpopulation of subjects in Study 201 (n=113) using the C2N Preclivity assay. A low plasma Aβ42/Aβ40 ratio is known to be associated with amyloid deposition in the brain in subjects with AD as shown by amyloid positive PET scans (Doecke, 2020). The C2N Preclivity assay has 85% sensitivity and 68% specificity for detecting elevated brain amyloid in amyloid PET scans (based on visual read of the scans) in subjects with mild cognitive impairment or mild dementia due to AD (based on data from Eisai's Mission AD Study). Using a cut-off plasma Aβ42/Aβ40 ratio of 0.092 (derived from correlation analysis of plasma Aβ42/Aβ40 ratio with amyloid load on PET scan in Eisai's Mission AD Study), subjects with a ratio <0.092 were defined as a subgroup of DLB with amyloid copathology (n=57, approximately 50% of subjects with plasma amyloid ratio data), whereas subjects with a ratio ≥0.092 were defined as a subgroup of DLB without amyloid copathology (n=56,

approximately 50% of subjects with plasma amyloid ratio data). Efficacy analyses were performed on various endpoints in these 2 subgroups. It was found that numerically there was a trend for treatment benefit of E2027 compared with placebo in the subgroup of DLB without amyloid copathology, in MoCA, CIBIC-Plus, and Clinician Global Impression of Change (CGIC), but there was no treatment difference in the CFI and NPI. In the subgroup of DLB with amyloid copathology, it was considered that there was no treatment benefit of E2027 in MoCA, CIBIC-Plus, CGIC, and CFI, whereas in the NPI there was numerically less worsening from baseline than placebo. None of these treatment differences in either subgroup was statistically significant, but in the DLB subgroup without amyloid copathology, the treatment benefit of E2027 on MoCA was close to nominal statistical significance (P=0.0534). The treatment differences between E2027 and placebo with their confidence intervals are summarized below for each subgroup (Table 2).

Table 2 Study E2027-G000-201: Summary of Efficacy of E2027 in Subgroups With and Without Amyloid Copathology

Efficacy Endpoint After 12 Weeks	Without Amyloid Copathology Treatment Difference (95% CI)[a]	With Amyloid Copathology Treatment Difference (95% CI)[a]
MoCA[b]	1.567 (-0.024, 3.157)	-0.178 (-1.890, 1.534)
CIBIC-Plus[c]	1.596 (0.753, 3.386)	1.022 (0.478, 2.184)
NPI[d]	-0.073 (-6.370, 6.224)	-2.757 (-10.095, 4.581)
CFI[d]	-0.523 (-2.154, 1.109)	0.333 (-1.489, 2.155)
CGIC-DLB[c]	1.170 (0.555, 2.464)	0.620 (0.288,1.339)

CFI = Cognitive Fluctuation Inventory, CIBIC-Plus = Clinician's Interview Based Impression of Change Plus Caregiver Input, CGIC-DLB = Clinician Global Impression of Change in Dementia with Lewy Bodies, GLMM = generalized linear mixed models, LS = least square, MMRM = mixed effects model of repeated measures, MoCA = Montreal Cognitive Assessment, NPI = Neuropsychiatric Inventory.

a: Treatment difference (E2027 minus Placebo) for MoCA, NPI, and CFI is LS means from MMRM analysis. CIBIC-Plus treatment difference is the proportional odds ratio from a GLMM analysis.

b: Positive treatment difference indicates treatment benefit on E2027.

c: Odds ratio >1 indicates treatment benefit on E2027.

d: Negative treatment difference indicates treatment benefit on E2027.

7.3 Study Rationale

Cyclic nucleotides such as cyclic adenosine monophosphate and cGMP work as second messengers in the intracellular signaling cascade, and play a critical role in learning, memory function and induction of hippocampal long-term potential in animal models (Domek-Łopacińska and Strosznajder, 2005). Therefore, increase of cGMP in synaptic regions is expected to enhance long-term potential and consequently improve cognitive function. PDE9 is a cGMP-degrading enzyme and expressed in brain, and its inhibitor is thought to increase neuronal cGMP and enhance cognitive function. Therefore, PDE9 inhibitors such as E2027 may be efficacious in neurodegenerative diseases with cognitive impairment such as DLB and PDD.

Amyloid deposition leads to tau aggregation in neurons and both pathological processes interact synergistically (reviewed in Busche and Hyman, 2020). Specifically, synaptic degeneration due to amyloid and tau accumulation lead to impairment of the cGMP synthesis pathway on the postsynaptic side (Monfort and Felipo, 2010; Park et al., 2020). Thus, intact synapse may be required for optimal increase of cGMP by E2027, since both presynaptic and postsynaptic elements are involved.

It has been found that in DLB subjects with amyloid copathology, their whole brain and hippocampal atrophy rates were similar to AD subjects, whereas DLB subjects without amyloid copathology showed slower brain atrophy rates comparable to healthy age-matched subjects (Nedelska et al., 2015). Thus, in DLB subjects with amyloid copathology, there occurs greater neuronal and synaptic degeneration compared to DLB subjects without amyloid copathology. There may be relative preservation of hippocampal synapses that respond to PDE9 inhibition better in DLB subjects without amyloid copathology and those who have amyloid copathology.

Thus, it is proposed that subjects with DLB with amyloid copathology may have lower response to E2027 in terms of brain cGMP elevation compared to DLB subjects without amyloid copathology. This may then manifest as lower CSF cGMP in DLB subjects with amyloid copathology than DLB subjects without amyloid copathology. Furthermore, a lower brain cGMP response to E2027 in DLB subjects with amyloid copathology may lead to lower efficacy in cognitive endpoints than DLB subjects without amyloid copathology, as suggested by the trends in Study 201. As PDD and DLB are considered part of the same continuum of LBD, it is possible that subjects with PDD with and without amyloid copathology may also respond differently to E2027 treatment.

The proposed study (E2027-A001-203; Study 203) is an open-label study to evaluate the different responses to E2027 in subjects with DLB and PDD who have or do not have amyloid copathology in terms of their CSF cGMP elevation and various cognitive and neuropsychiatric endpoints. The presence of absence of amyloid copathology will be established by their plasma amyloid-β (Aβ)42/Aβ40 ratio (as in Study 201) using the C2N Preclivity assay.

It will also evaluate the safety, tolerability, PK, and other PD effects in biomarkers of E2027 in these subjects. The relationship between CSF cGMP increase and change in efficacy endpoints will be explored. If it is found that in subjects without amyloid copathology there is greater increase in CSF cGMP, associated with improvement in efficacy endpoints, whereas in subjects with amyloid copathology there is less increase in CSF cGMP associated with worsening or no change in efficacy endpoints, then such a correlation will corroborate the results of Study 201 and support the theory that amyloid status affects E2027 drug response and downstream efficacy. The results will guide the selection of subgroups of DLB and PDD subjects (as characterized by presence or absence of amyloid copathology, or other biomarker-defined characteristics) for further evaluation of efficacy of E2027 in Phase 3 studies.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to demonstrate the PD effects of E2027 on CSF cGMP in subjects with DLB and PDD with and without amyloid copathology after 9 weeks of treatment.

8.2 Secondary Objective

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

8.3 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 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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, open-label study in subjects with DLB or PDD who will be treated with E2027 for 12 weeks. Four subgroups of subjects will be 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 is defined as ratio of plasma concentration of Aβ42/Aβ40 <0.092 (based on the C2N Preclivity assay).

The study design allows for add-on therapy of E2027 to standard of care for DLB and PDD, 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 to participate in this study but are not permitted to start such medications during the study. It is required that in each subgroup there should be at least 1 subject who is not receiving AChEI or memantine during the study. Subjects should be on stable doses of medications for the treatment of Parkinson's disease, maintained without change during the study.

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

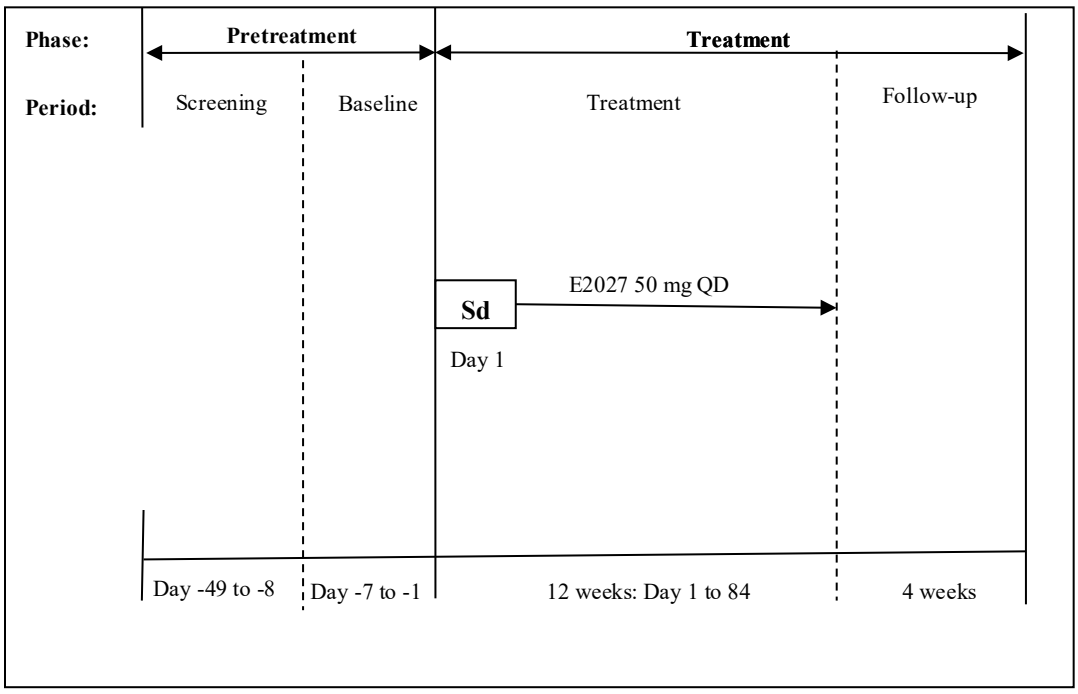

Figure 1 Study Design for Study E2027-A001-203

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

9.1.1 Pretreatment Phase

The Pretreatment Phase will last up to 7 weeks and will include a Screening Period (up to 6 weeks) and a Baseline Period (up to 1 week).

9.1.1.1 Screening Period

Screening will occur between Day -49 and Day -8. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. All subjects will be assessed for eligibility through review of medical history, physical examination (including neurological examination), laboratory tests, vital signs, and ECGs.

Subjects with DLB will be assessed on clinical scales of cognition and depression, safety magnetic resonance imaging (MRI) of the brain and dopamine transporter (DAT) brain imaging or myocardial scintigraphy (^{123}I-meta-iodobenzylguanidine [MIBG]) (if indicated in individual subjects and not previously performed) to confirm that they meet the diagnostic criteria and severity for DLB.

Subjects with PDD will be assessed on clinical scales of cognition and depression, safety MRI of the brain and DAT brain imaging or MIBG (if indicated in individual subjects and not previously performed) to support their diagnosis of Parkinson's disease (and not other extrapyramidal or cerebrovascular diseases).

During Screening, the subject's motor features will be assessed on the Movement Disorders Society (MDS) UPDRS-III and staged by the Hoehn and Yahr Scale (HYS). History of suicidality will be assessed by the C-SSRS. Medical history will also be assessed regarding other medical conditions and concomitant medications to ensure that these are stable with no changes to treatment required and that they do not interfere with subject safety or study procedures.

Eligibility assessments at Screening will be conducted in 6 tiers and subjects will need to satisfy eligibility criteria in each tier before proceeding to the next tier.

- In Tier 1 demographics, medical history (including history of DLB, PDD and other medical conditions) and prior and concomitant medications will be reviewed.
- In Tier 2, clinical assessments on cognition and depression will be conducted in the morning (whenever possible) in subjects in the following order: MMSE then Geriatric Depression Scale (GDS) should be done first, followed by the MoCA. The caregivers or informants will also complete the Short Fluctuation Questionnaire (SFQ), CFI, and NPI. If the eligibility criteria regarding the MMSE and GDS are not met, the other assessments (SFQ, CFI, and NPI) do not have to be performed and the subject should be screen failed.

- In Tier 3, subjects will be assessed with the Modified Hachinski Ischemic Scale, UPDRS-III, HYS, and C-SSRS. A plasma sample will be collected to measure biomarkers related to AD copathology (amyloid, phosphorylated-tau [p-tau]) and other biomarkers related to DLB or PDD. If a sufficient number of subjects in a subgroup has been achieved, a new subject in that subgroup will be screen failed at Tier 3 or at subsequent tiers. While waiting for the result of the subject's plasma Aβ42/Aβ40 ratio, the subject may proceed with subsequent tiers.
- In Tier 4, subjects will undertake physical examination, vital signs, ECG, and clinical laboratory tests.
- In Tier 5, subjects will be assessed by safety MRI for brain abnormalities that may affect eligibility.
- In Tier 6, if indicated as judged by the investigator, individual subjects may also undertake DAT brain imaging scan or myocardial MIBG scan to help establish their diagnosis.

It is recommended that where appropriate Tiers 1 to 4 should be performed on the same day and Tiers 5 and 6 on a separate day. However, the investigator may perform the various tiers on separate days as appropriate for each subject. The scores of various clinical scales (including NPI, SFQ, CFI, and UPDRS-III) and cognitive tests (MMSE, MoCA) at Screening will be reviewed by a central process. Subjects who are diagnosed by the investigator with DLB or PDD but whose scores on clinical scales or cognitive tests are found not to be consistent with the diagnosis during central review will be discussed with the investigator to determine their eligibility.

Due to the intrinsic variability of cognitive functions in DLB or PDD, subjects who screen fail at Tier 2 may be rescreened after at least 30 days, but as a guide, rescreening frequency should not be more frequent than once every 3 months and a subject should not be rescreened more than 2 times under the same version of the eligibility criteria. For subjects who screen fail at Tier 3 or 4 due to their subgroup already having achieved the target number of subjects, they may be rescreened if a new subject is required in their subgroup due to early discontinuation. If this rescreening occurs within 30 days after screen fail, the history of DLB or PDD in Tier 1 and the assessments at Tiers 2, 3, and 4 do not need to be repeated unless clinically indicated in the investigator's judgement.

All subjects who have completed screening assessments in Tiers 1 to 6 and are deemed eligible for the study will have a baseline CSF sample collected by lumbar puncture (LP). The CSF sample will be collected in the morning, either in the fasted state or at least 2 hours after breakfast. In subjects who require DAT or MIBG scan, the CSF collection should be at least 1 week after the scan.

9.1.1.2 Baseline Period

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) and at least 1 week after CSF collection. Study assessments should be conducted in the morning (whenever possible). Cognition will be assessed by the MoCA,

which must be the first clinical scale to be administered before any invasive procedures, followed by the WAIS-IV DSC and then the Clinician Interview Based Impression of Severity Plus Caregiver Input (CIBIS-Plus). The caregiver or informant will also complete the CIBIS Plus, NPI, CFI, SAPS-PD, and FAQ. The rater administering the CIBIS-Plus should be independent of the rater(s) who administer the other clinical scales.

At the Baseline Visit subjects will be assessed regarding other medical conditions and concomitant medications (including medications for DLB or PDD) to ensure that these remain stable with no changes to treatment required and that they do not interfere with their safety or study procedures. Other safety assessments including vital signs, ECGs, laboratory tests, and C-SSRS will also be conducted.

Subjects who complete the Baseline Period and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will last up to 16 weeks and will include a Treatment Period (up to 12 weeks) and a Follow-up Period (up to 4 weeks).

9.1.2.1 Treatment Period

After completing study assessments at the Baseline Visit, subjects who continue to be eligible will proceed to the Treatment Period on E2027 (50 mg QD). They will be provided with 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 3, 6, 9, and 12 weeks on E2027. Efficacy assessments will be performed after 6 and 12 weeks on E2027 and should be performed at approximately the same time of the day as at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first efficacy assessment to be administered, followed by the WAIS-IV DSC (after 12 weeks only), then the CIBIC-Plus and finally the MMSE (after 12 weeks only). Whenever possible, a subject should have the same rater administering the MoCA and the CIBIC-Plus throughout his/her participation in the study. The rater administering the CIBIC-Plus should be independent of the rater(s) who administer the other clinical scales. The caregiver or informant will also complete the CIBIC-Plus, NPI, CFI, SAPS-PD (after 12 weeks only) and FAQ (after 12 weeks only). Safety assessments will be conducted at these visits, including review of AEs, vital signs, ECG, laboratory safety tests, C-SSRS, and UPDRS-III. The investigator will review all the efficacy endpoints and safety data at the visits after 6 and 12 weeks on study drug and formulate the CGIC of the subject's clinical status from baseline.

After subjects have completed 9 weeks of treatment with E2027 will have a 2nd CSF sample collected. The CSF sample will be collected in the morning at approximately the same time as at Screening, either in the fasted state or at least 2 hours after breakfast. A 2nd plasma sample for biomarkers will also be collected.

If during the study, the designated caregiver or informant relinquishes his/her responsibilities as caregiver or informant, a replacement caregiver or informant must be found. It is

recommended that this replacement caregiver or informant should meet the criteria above and have similar knowledge of the subject's clinical status from Baseline throughout the Treatment Period. If a replacement caregiver or informant is found who does not meet the criteria above, then the CIBIC-Plus will not be conducted but subject may continue in the study. If no replacement caregiver or informant is available at all the subject must be discontinued from the study.

9.1.2.2 Follow-Up Period

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

The end of study is defined as the last subject completing the Follow-Up Visit.

9.1.3 Conduct of the Study During the COVID-19 Pandemic and Other Extenuating Circumstances

All study assessment and visit information affected by any extenuating circumstances (eg, the COVID-19 pandemic) will be collected on the electronic case report forms (eCRFs). These include but are not limited to any visits or assessments that are missed or not done, any assessments that are performed remotely/offsite or in person/onsite, and any home delivery of investigational product.

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

- An extension of the Screening Period from 6 weeks to up to 10 weeks is allowed with sponsor approval on a subject by subject basis.
- If subjects cannot visit the study site, all procedures which require physical contact with the subjects (eg, vital signs, ECGs, blood tests, physical examination, UPDRS-III) may be conducted via home visit (if feasible) with sponsor approval. The brain or cardiac imaging during the Screening Visit must be conducted at the study site. The CSF collection at the Screening Visit and Visit 6 (Week 9) must be conducted at the study site. Other study procedures including all the efficacy endpoints, AEs, and concomitant medications review may be conducted remotely via telephone, sponsor approved telehealth, or home visit. If it is not possible for subjects to attend the study site for the CSF collection Visit 6 (Week 9), this can be performed at an Unscheduled Visit as soon as possible after Week 9. Study drug may be delivered to subjects' homes if it is not possible to visit the study site to collect the study drug.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is an open-label study to evaluate the responses to E2027 in CSF cGMP and efficacy endpoints in subjects with DLB or PDD with and without amyloid copathology. The study is open label on E2027 because the main comparison is between subgroups of subjects with and without amyloid copathology rather than comparing against placebo.

Subjects with DLB and PDD will be eligible for this study because DLB and PDD are considered as 2 ends of the same spectrum of LBD with similar clinical features but with different temporal sequence of onset (Aarsland, et al., 2003; Walker, et al., 2015). In a clinical trial of memantine in LBD, subjects with both diagnostic categories were enrolled (Aarsland, et al., 2009). A meta-analysis of efficacy in clinical trials of AChEI in PDD and DLB suggested comparable efficacy effect size in both diagnostic categories (Matsunaga, et al., 2015), which supports investigating both ends of the LBD spectrum within Study 203. Any differential responses to E2027 between subjects with and without amyloid copathology may be seen in both DLB and PDD. Therefore, in this study equal numbers of subjects in each of the 4 subgroups (DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology and PDD with amyloid copathology) will be enrolled.

AChEIs are the current standard treatments for LBD (Walker, et al., 2015); as such, subjects who are established on a stable dose of AChEIs are eligible. As not all subjects will receive AChEI as standard of care, subjects who are not taking AChEI are also eligible. In Study 201, it appeared that subjects not taking AChEI (~20% of randomized subjects) had greater numerical treatment benefit than subjects taking AChEI (~80% of randomized subjects). Therefore, in Study 203 each of the 4 subgroups is required to have at least 1 subject not taking AChEI to be representative of the Study 201 population. The treatment duration with E2027 is 12 weeks. These study design features are the same as in Study 201 such that Study 203 will be able to further evaluate or corroborate the results in Study 201.

The primary endpoint is the percentage change from baseline of CSF cGMP, which is the main PD response to E2027 that may show different responses in subjects with and without amyloid copathology. As it is an objective endpoint, it supports the use of an open-label design. The efficacy endpoints are exploratory endpoints, and they include the MoCA, CIBIC-Plus, CFI, MMSE, NPI, and CGIC which were the efficacy endpoints in Study 201. The use of the same efficacy endpoints after 12 weeks of treatment as in Study 201 enables Study 203 to corroborate the pattern of changes seen in these endpoints on E2027 in Study 201.

For evaluating the CSF cGMP elevation from baseline, CSF samples will be collected at baseline and again after 9 weeks of treatment on E2027 as in Study 201. In Study 002, it was found that CSF cGMP elevation from baseline was similar after 2 weeks and 6 weeks of treatment on E2027, and hence it is considered that after 9 weeks of treatment CSF cGMP elevation will have reached steady state in Study 203. CSF collection and efficacy evaluations will be conducted at separate visits (CSF collection after 9 weeks and efficacy endpoints after 12 weeks of treatment) to avoid CSF collection interfering with subjects' performance in the efficacy evaluations.

In Study 002, the CSF cGMP increased with increasing dose, approaching a saturation level of approximately 200%, which was considered sufficient for procognitive effects based on animal models. In Study 201, the limited data suggested that in this study population (comprising DLB subjects with and without amyloid copathology) the CSF cGMP elevation could be approximately 170% with no overall clinical benefit on cognition. Furthermore,

based on the limited data of the correlation between CSF cGMP percentage change from baseline and change in efficacy endpoints, it was found that subjects with 190% to 200% increase from baseline in CSF cGMP showed improvement in MoCA and CIBIC-Plus, whereas subjects with <170% increase from baseline in CSF cGMP showed no improvement or worsening in these efficacy endpoints. Thus, it is considered that in subjects without amyloid copathology, if their CSF cGMP elevation is >30% higher than in subjects with amyloid copathology, this may be associated with clinically significant differences in efficacy as suggested by the subgroup results in Study 201. The absolute concentrations of CSF cGMP attained after treatment on E2027 between subjects with and without amyloid copathology will also be investigated for potential contribution to the difference in efficacy.

Pharmacogenomic blood samples will be collected to explore if genotypes associated with development or progression of DLB or deposition of amyloid copathology affect the CSF cGMP response to E2027.

9.3 Selection of Study Population

Approximately 64 subjects will be screened at approximately 30 investigational sites in the US and Canada to provide a maximum of 32 treated subjects, with 8 subjects in each of the 4 subgroups (DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology, and PDD with amyloid copathology). Allowing for a 25% dropout rate there will be 24 treated subjects completing the study treatment, with 6 subjects in each subgroup. Further subjects may be screened and treated with E2027 if there are less than 6 completers in any of the subgroups.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Male or female, age 50 to 85 years, inclusive at time of consent
2. Meet criteria for probable DLB (as defined by the 4th report of the DLB Consortium [McKeith, et al., 2017]) or meet criteria for probable PDD (as defined by the task force of the Movement Disorder Society) (Appendix 1). Specific situations regarding the use of imaging are described below:
   a. DLB subjects who have 1 core clinical feature only by the investigator and who do not have previous reports of DAT brain imaging scan, MIBG scan or polysomnography (PSG) will undertake DAT brain imaging scan or MIBG scan as organized by the investigator.
   b. DLB subjects who have 2 or more core clinical features by the investigator but who are judged as having only 1 core clinical feature by central reviewer and who do not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor.

c. DLB subjects who have 2 or more core clinical features by the investigator and the central reviewer and who do not have previous reports of DAT brain imaging scan, MIBG scan or PSG may undertake DAT brain imaging scan or MIBG scan after discussion with the sponsor medical monitor if the investigator considers that imaging is necessary to confirm the diagnosis.

d. PDD subjects with clinical features that are consistent with the diagnostic criteria of probable PDD but in whom the investigator considers that there may be other diagnoses, DAT brain imaging scan or MIBG scan may be conducted after discussion with the sponsor medical monitor.

3. MMSE >14 and <26 at Screening Visit
4. For DLB subjects, have experienced visual hallucinations since onset of their DLB
5. If receiving AChEIs, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment naïve subjects can be entered into the study but there should be no plans to initiate treatment with AChEIs from Screening to the end of the study.
6. If receiving memantine, must have been on a stable dose for at least 12 weeks before Screening Visit, with no plans for dose adjustment during the study. Treatment naïve subjects can be entered into the study but there should be no plans to initiate treatment with memantine from Screening to the end of the study.
7. If receiving Parkinson's disease medications, must have been on a stable dose for at least 4 weeks before Screening Visit, with no plans for dose adjustment during the study.
8. Must have an identified caregiver or informant who is willing and able to provide follow up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, not be suffering from cognitive impairment, be sufficiently familiar with the subject and spend sufficient time with the subject on a regular basis such that the caregiver or informant can reliably fulfill the study requirements and must provide separate written consent. The caregiver or informant should normally be residing with the subject. If the caregiver or informant is not residing with the subject, the investigator has to be satisfied that the subject can contact the caregiver or informant readily during the times when the caregiver or informant is not with the subject. As a guide the caregiver or informant should have contact with the subject on at least 4 days a week and each day for a total of at least 5 hours. If in doubt about whether a subject's care arrangements are suitable for inclusion, the investigator should discuss this with the medical monitor. At all visits caregivers or informants need to attend the visit in person along with the subject.
9. Provide written informed consent. If a subject lacks capacity to consent in the investigator's opinion, the subject's assent should be obtained, as required in accordance with local laws, regulations and customs, plus the written informed consent of a legal representative should be obtained (capacity to consent and definition of legal representative should be determined in accordance with applicable local laws and regulations). In countries where local laws, regulations, and customs do not permit subjects who lack capacity to consent to participate in this study, they will not be enrolled.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any neurological condition that may be contributing to cognitive impairment above and beyond those caused by the subject's DLB or PDD, including any comorbidities detected by clinical assessment or MRI (identification of amyloid copathology is not exclusionary)
2. History of transient ischemic attacks or stroke within 12 months of Screening
3. Modified Hachinski Ischemic Scale >4
4. Parkinsonian (extrapyramidal) features with HYS stage IV or higher
5. Any major psychiatric diagnosis, including schizophrenia, bipolar disorder and current major depressive disorder as per Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
6. GDS score >8
7. Severe visual or hearing impairment that may interfere with the subject study assessments including cognitive testing
8. The following exclusions apply in relation to CSF sampling by LP:
    a. A bleeding disorder that is not under adequate control (including a plate count <50,000, international normalized ratio [INR] >1.5 or partial thromboplastin time [PTT] >upper limit of normal [ULN])
    b. Any contraindications to LP (eg, lower spinal malformation on physical examination, local spinal infection or other abnormality, obesity to the extent that it makes LP technically difficult, or inability to cooperate with LP due to cognitive impairment or motor symptoms)
9. History of deep brain stimulation or other neurosurgical procedure for Parkinson's disease
10. Has thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator. This applies to all subjects whether or not they are taking thyroid supplements.
11. Abnormally low serum vitamin B12 levels (less than the lower limit of normal [LLN]) for the testing laboratory (if subject is taking vitamin B12 injections, level should be at or above the LLN for the testing laboratory). Low levels of vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, (if available in region) and excluded only if MMA levels are also >ULN.
12. Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners). Subjects who require sedation for MRI or PET scanning as per local guidelines need not be excluded
13. Evidence of other clinically significant lesions that suggest a dementia diagnosis other than DLB or PDD on brain MRI at Screening. All MRIs will be acquired using a standardized procedure that will be outlined in the Imaging Charter and Imaging Acquisition Guidelines and will be read by an approved centralized reader.

14. Other significant pathological findings on brain MRI at Screening, including but not limited to: any macrohemorrhage (greater than 10 mm at greatest diameter); an area of superficial siderosis; evidence of cerebral contusion, encephalomalacia, aneurysms, arteriovenous malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than or equal to 1 cm at their greatest diameter need not be exclusionary)
15. Hypersensitivity to E2027 or any of the excipients
16. A prolonged corrected QT interval calculated using Fridericia's formula (QTcF) as demonstrated by triplicate ECG at the Screening or Baseline Visit (ie, mean value >450 msec)
17. Had symptomatic orthostatic hypotension or symptomatic orthostatic tachycardia which resulted in hospitalization or urgent medical review in hospital in the past 12 months before Screening
18. Any other clinically significant abnormalities that in the opinion of the investigator, require further investigation or treatment or that may interfere with study procedures or safety in the following:
    a. Physical examination, ECG, vital signs at Screening or Baseline Visit
    b. Laboratory tests at Screening Visit
19. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma of the skin, or localized prostate cancer in male subjects). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.
20. Has a "yes" answer to C-SSRS suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before Screening, at Screening, or at the Baseline Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
21. Known or suspected history of drug or alcohol dependency or abuse within 2 years before Screening, current use of recreational drugs or a positive urine drug test at Screening. Subjects who test positive in the urine drug screen need not be excluded if in the opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.
22. Any other medical conditions (eg, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which in the opinion of the investigator may affect the subject's safety or interfere with the study assessments
23. Taking any of the prohibited medications or not meeting the requirements regarding stable doses of permitted medications
24. Participation in a clinical study involving any investigational drug/device for DLB or PDD within 6 months before Screening or any other investigational drug/device in the 8 weeks or 5 half-lives (whichever is longer) of the study medication before Screening unless it can be documented that the subject was in a placebo treatment arm
25. Planned surgery which requires general, spinal or epidural anesthesia that will take place during the study. Planned surgery that requires only local anesthesia and can be

undertaken as a day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

26. Males who have not had a successful vasectomy (confirmed azoospermia) if their female partners are of childbearing potential and are not willing to use a highly effective contraceptive method throughout the study period and for 98 days after study drug discontinuation. No sperm donation is allowed during the study period and for 98 days after study drug discontinuation.
27. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test) with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
28. Females of childbearing potential who:
    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device or intrauterine hormone-releasing system
        - a contraceptive implant
        - an oral contraceptive (Subject must have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of oral contraceptive throughout the study and for 28 days after study drug discontinuation.)
        - have a vasectomized partner with confirmed azoospermia
    - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation

    (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing].)

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Subjects who prematurely discontinue study treatment for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their final dose of study treatment. 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 treatment 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. At these originally scheduled visits that take place after the ED Visit, blood PK samples, plasma biomarker samples, and CSF samples will not be collected.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study treatment should be collected. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment

9.4.1 Treatment Administered

E2027 will be administered in size #2 hypromellose (HPMC) capsules containing 25 mg of E2027.

All subjects will take 2 × E2027 25 mg capsules QD for a total dose of 50 mg daily for up to 12 weeks (Table 3).

Table 3 Treatment Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
E2027	25 mg	Capsule	2 × 25 mg capsule QD	12 weeks

QD = once daily

9.4.2 Identity of Investigational Product(s)

E2027 will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name of E2027

- Test drug code: E2027
- Generic name: Not applicable
- Chemical name: 7-(2-Methoxy-3,5-dimethylpyridin-4-yl)-1-[(3S)-tetrahydrofuran-3-yl]-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one maleate (International Union of Pure and Applied Chemistry [IUPAC])
- Molecular formula: $C_{22}H_{22}N_4O_3 \cdot C_4H_4O_4$
- Molecular weight: 506.52 (390.44, free base)

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E2027 will be labeled in accordance with text that is in full regulatory compliance.

9.4.2.4 Storage Conditions

E2027 will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive E2027. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

Based on animal cognition models, a sustained increase in CSF cGMP from baseline by 150% or higher after dosing to steady state is thought to be required for clinical efficacy. In Study 201 a dose of E2027 at 50 mg QD was found to have achieved mean CSF cGMP increase from baseline by 168%. This dose also showed a trend to treatment benefit in the MoCA in DLB subjects without amyloid copathology, and it may be sufficient for precognitive effects in this subgroup of subjects without amyloid copathology, consistent with the animal cognition models. This dose was also found to be well-tolerated in Study 201, with similar incidence of TEAEs and no clinically significant changes in laboratory test findings, ECGs, C-SSRS, UPDRS-III, or vital signs (including orthostatic hypotension and orthostatic tachycardia). Therefore, the dose of E2027 in Study 203 is selected to be 50 mg QD as in Study 201.

9.4.5 Selection and Timing of Dose for Each Subject

E2027 will be administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 will continue for 12 weeks. Subjects should withhold administration of E2027 in the morning of the study visit days that blood will be drawn in the clinic for PK analysis (Table 5). Subjects will be instructed to take their other concomitant medications at the usual time.

9.4.6 Blinding

The study treatment will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded. The AE or medical condition for which the concomitant medication or therapy was administered will be recorded.

9.4.7.1 Drug-Drug Interactions

Instructions for use of medications that may interact with E2027 are described in Section 9.4.7.2.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Unless otherwise specified, the following medications are prohibited from a period of 14 days (or 5 half-lives, whichever is longer) before the Baseline Visit (Visit 2) until the Follow-Up Visit to avoid the risk of interaction with E2027. Subjects who start any of these medications during the study will be discontinued:

- Drugs known to be strong inhibitors of cytochrome P450 (CYP) 3A (CYP3A), grapefruit, grapefruit juice, and grapefruit products
- Drugs known to be moderate to strong inducers of CYP3A. Herbal preparations containing St. John's Wort is prohibited for 4 weeks before the Baseline Visit (Visit 2) until the Follow-Up Visit
- Drugs known to cause prolongation of the QT interval, including but not limited to drugs that may cause cardiac arrhythmias. For drugs which may cause QTcF prolongation, subjects need not be excluded if at Screening the subjects are already on stable doses for at least 4 weeks and their mean QTcF on triplicate ECGs at Screening and Baseline Visit is not >450 msec (Exclusion Criterion 16).
- Drugs that are phosphodiesterase inhibitors (eg, theophylline, aminophylline, sildenafil, tadalafil, vardenafil, dipyridamole, roflumilast, apremilast, inamrinone, milrinone, and enoximone)

The following medications are prohibited to avoid the risk of interference with study assessments or procedures. Subjects who start these medications during the study will be discontinued unless otherwise specified.

- Anticholinergic drugs that have central nervous system (CNS) activity are prohibited from 4 weeks before Screening Visit until the Follow-Up Visit
- Pimavanserin is prohibited for 12 weeks before Screening Visit until the Follow-Up Visit
- Anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) and dual antiplatelet therapy (eg, aspirin and clopidogrel together) are prohibited from Screening Visit until after the 2nd CSF collection at 9 weeks of treatment with E2027

The following restrictions apply to AChEIs (including donepezil, rivastigmine, galantamine) or memantine for treatment of DLB or PDD:

- If a subject is already receiving AChEI or memantine at Screening, they must be on a stable dose for at least 12 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already receiving AChEI or memantine at Screening, then these should not have been used at least 12 weeks before Screening and AChEI or memantine should not be started during the study until the Follow-Up Visit.
- Subjects who start AChEI/memantine or change their dose of AChEI/memantine during the study should undertake an Unscheduled Visit before making such changes in their AChEI/memantine medications to undertake efficacy assessments (MoCA, CIBIC-Plus, NPI, CFI, CGIC) (unless they have been conducted within past 4 weeks). This change in AChEI/memantine medications is considered a protocol deviation, and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in the Statistical Analysis Plan (SAP).

The following restrictions apply to medications for Parkinson's disease or motor symptoms of DLB (except CNS-active anticholinergic drugs that are prohibited as above):

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- Starting or changing the dose of these medications during the study is considered as a protocol deviation, and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in the SAP.

The following restrictions apply to medications for antipsychotic or neuroleptic drugs, hypnotics, anxiolytics, or antidepressants:

- If a subject is already on any of these medications at Screening, then they must be on a stable dose for at least 4 weeks before Screening and remain on the same dose during the study until the Follow-Up Visit.
- If a subject is not already on any of these medications at Screening, then these should not be started during the study until the Follow-Up Visit.
- Subjects who start or change their dose of these medications should undertake an Unscheduled Visit before making such changes in these medications to undertake efficacy assessments (MoCA, CIBIC-Plus, NPI, CFI, CGIC) (unless they have been conducted within past 4 weeks). This change in such medications is a protocol deviation, and the handling of efficacy data collected after the change of these medications in the efficacy analyses is described in the SAP.

The following restrictions apply to other medications that the subject is taking at Screening or are started during the study:

- These medications may be permitted if they are not included in the prohibited or restricted medications list above and are considered by the investigator and sponsor medical monitor not to compromise study assessments or subject safety.
- Permitted prior medications should be at a stable dose for at least 4 weeks before Screening and should remain on the same dose throughout the study.
- Subjects who change the dose of their permitted prior medications or who start permitted new medications during the study may continue in the study if the investigator and sponsor medical monitor consider that this will not compromise study assessments or subject safety.
- As needed medications required for performing LP for CSF sampling are permitted.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, or a completed Investigator and Site Information Form
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572 or Investigator and Site Information Form
- A signed and dated curriculum vitae (CV) of the principal investigator including a copy of the principal investigator's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:
(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site, if applicable. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening Assessments

After the subject has provided informed consent, screening assessments will be performed in 6 tiers as noted in Table 5. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence.

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity. For caregivers or informants, their age, sex, relationship to subject, residential status with the subject, and time spent per week with the subject will be collected at the Screening Visit.

9.5.1.1.2 MEDICAL HISTORY

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions eCRFs. Medical history will include history of DLB or PDD.

9.5.1.1.3 OTHER SCREENING/BASELINE ASSESSMENTS

The following tests will be performed during Screening or at the Baseline Visit (see Table 5): GDS, SFQ, Modified Hachinski Ischemic Scale, HYS, safety brain MRI, DAT brain imaging and myocardial MIBG scan, vitamin B12 and thyroid function blood tests, urine drug screen, pregnancy tests (as appropriate), and collection of PGx blood sample.

Geriatric Depression Scale (GDS)

This is a self-reported, clinician-assisted scale designed to identify symptoms of depression in the elderly. The scale consists of 15 questions that the subject is asked to answer about how they felt over the past week. Answers to 5 of the items are negatively oriented for depression (eg, Do you feel full of energy?) and 10 positively oriented (eg, Do you often feel helpless ?). One point is given for each appropriate positive or negative answer indicative of a symptom of depression, for a possible total of 15 points. Total scores of 0 to 5 are considered normal and scores of 6 to15 are considered depressed. Subjects with DLB or PDD who have a GDS score >8 are considered to have significant depressive symptoms which may contribute to cognitive deficits and are excluded.

Short Fluctuation Questionnaire (SFQ)

This scale consists of 8 questions as to whether fluctuation occurs in various domains including attention, ability to performance daily functions, orientation, verbal communication

and behavior. It is scored as 1 for presence of fluctuation in each domain and 0 for absence. It has a score range of 0 to 8. Investigators should take into account the SFQ score in deciding if a subject meets one of the core criteria (fluctuating cognition) for diagnosis of DLB and PDD.

Modified Hachinski Ischemic Scale

The modified Hachinski Ischaemic Scale roughly quantifies elements of the history and physical examination relevant to the risk of vascular dementia and helps differentiate between Alzheimer's type dementia and multi-infarct dementia. The questionnaire provides for scoring for abrupt onset of dementia, history of stroke, focal neurological signs and symptoms, stepwise deterioration, somatic complaints, emotional incontinence, and hypertension (past or present). The higher the score, the greater the risk of vascular dementia. Subjects with Modified Hachinski Ischemic Scale >4 are excluded.

Hoehn and Yahr Scale (HYS)

This scale is used to stage (I to V) the severity of motor features in Parkinson's disease. It captures typical patterns of progressive motor impairment. It is based on the extent of anatomical distribution of the extrapyramidal features (unilateral or bilateral, limbs or limbs and trunk) and severity (mild, moderate, severe, loss of mobility). Subjects with Stage IV disease (severe disability but still able to walk or stand unassisted) or worse are excluded.

Safety Brain MRI

Safety brain MRI will be conducted at Screening to identify various exclusionary lesions and other MRI abnormalities which may indicate significant contribution to cognitive impairment from causes other than DLB or PDD (Section 9.3.2). The MRI settings will be described in the MRI manual provided by the central MRI reader, who will also review all MRI scans for eligibility.

DAT Brain Scan

In this brain scan, an intravenous radiopharmaceutical ^{123}I-ioflupane that selectively binds to the striatal DAT in the brain is administered. It is used to visualize the levels of DAT in the striatum (caudate and putamen) using single-photon emission computed tomography brain imaging. In subjects with Parkinsonian syndromes including DLB and PDD, there is reduced DAT signal in the scan in the striatum (caudate and putamen). This pattern may be asymmetrical between left and right sides or there may be diffuse reduction on both sides. DAT scans will be evaluated by a central reader. Subjects who undertake DAT brain imaging are required to have abnormal (low uptake of ^{123}I-ioflupane) in the striatum as one of the eligibility criteria.

MIBG Myocardial Scan

In this cardiac scan, an intravenous radiopharmaceutical ^{123}I-MIBG that is selectively taken up via the norepinephrine transporter into the post-ganglionic sympathetic nerve terminals in

the heart is administered. Uptake into these sympathetic nerve terminals is then visualized using single-photon emission computed tomography imaging. In subjects with Parkinsonian syndromes including DLB and PDD, there is reduced MIBG uptake in the heart such that the ratio of the MIBG signal in the heart to the mediastinum is reduced. MIBG cardiac scans will be evaluated by a central reader. Subjects who undertake MIBG cardiac scans are required to have abnormal (low uptake of MIBG) in the heart as one of the eligibility criteria.

Pregnancy Test

A serum β-hCG test will be performed at Screening and urine β-hCG test will be performed at Baseline for female subjects who are <60 years of age and not surgically sterilized.

Urine Drug Test

A urine sample will be collected at Screening. This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine (PCP), nicotine/cotinine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines. Subjects who test positive in the urine drug screen need not be excluded if in the opinion of the investigator, this is due to the subject taking prior/concomitant medications for a medical condition that is not exclusionary and not due to drug abuse.

Height Measurement

Height (cm) will be recorded at the Screening Visit.

For a detailed description of the sequence in which these assessments are administered at Screening or Baseline Visit, see Section 9.1.1.

9.5.1.2 Efficacy Assessments

Efficacy assessments are summarized in the following sections. At the Baseline Visit cognition will be assessed by the MoCA, which must be the first clinical scale to be administered before any invasive procedures, followed by the WAIS-IV DSC and then the CIBIS-Plus. The caregiver or informant will also complete the CIBIS-Plus, NPI, CFI, SAPS-PD, and FAQ. During the Treatment Period these assessments should be performed at approximately the same time of the day as were done at the Baseline Visit whenever possible (preferably in the morning). The MoCA should be the first efficacy assessment to be administered, followed by the WAIS-IV DSC (after 12 weeks only), then the CIBIC-Plus and finally the MMSE (after 12 weeks only). Whenever possible, a subject should have the same rater administering the MoCA and the CIBIC-Plus throughout his/her participation in the study. The rater administering the CIBIC-Plus should be independent of the rater(s) who administer the other clinical scales. The caregiver or informant will also complete the CIBIC-Plus, NPI, CFI, SAPS-PD (after 12 weeks only) and FAQ (after 12 weeks only). The caregiver or informant will also complete the CIBIC-Plus, NPI, CFI, SAPS-PD (after 12 weeks only) and FAQ (after 12 weeks only).

For a detailed description of the sequence in which these assessments are administered during the Treatment Phase, see Section 9.1.2.

9.5.1.2.1 MONTREAL COGNITIVE ASSESSMENT (MOCA)

The MoCA 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 or PDD. The total possible score is 30 points; a score of 26 or above is considered normal. The MoCA will be assessed as designated in Table 5.

9.5.1.2.2 WECHSLER ADULT INTELLIGENCE SCALE-4TH EDITION DIGIT SYMBOL CODING (WAIS-IV DSC)

This is the Digit-Symbol Substitution Test from the WAIS-IV. The test consists of small blank squares presented in rows with one of 9 numbers (1-9) randomly printed directly above each blank square. A "key" is printed above the rows of blank squares. The "key" pairs numbers 1 through 9 with an unfamiliar symbol. Following a short series of practice trials, the subject must use the key to fill in the blank squares in order (working from left to right across the rows) with the symbol that is paired with the number over the blank square. The subject must work as fast as possible for 120 seconds. The measure of interest is known as the Digit Symbol Coding, which is the number of squares filled in correctly within the time limit (maximum score=135). This test engages multiple cognitive abilities including attention, psychomotor speed, complex scanning, visual tracking, and immediate memory. Alternate versions will include the identical symbols and digits re-paired.

The WAIS-IV DSC will be assessed as designated in Table 5.

9.5.1.2.3 CLINICIAN'S INTERVIEW BASED IMPRESSION OF CHANGE PLUS CAREGIVER INPUT (CIBIC-PLUS)

The CIBIC-Plus scale is designed to measure various domains that describe subject function: general, mental/cognitive state, behavior, and activities of daily living. It is a semi-structured global rating derived from a comprehensive interview with the subject and caregiver or informant by an independent rater who has no access to the source data or other psychometric test scores conducted postbaseline as part of the given protocol.

At the Baseline Visit, the independent rater will use a related tool, the CIBIS-Plus. This scale, which assesses disease severity on a 7-point scale from 1 = normal to 7 = extremely ill, establishes a point of reference for subsequent interviews using the CIBIC-Plus.

During the Treatment Period, the rater will administer the CIBIC-Plus separately to the subject and the caregiver or informant as designated in Table 5. At the end of each pair of interviews during each of these study visits, the rater alone will determine separately for each of the 4 domains whether the disease has improved, worsened, or remained unchanged since the evaluation at Baseline. The CIBIC-Plus scores are: 1 (marked improvement),

2 (moderate improvement), 3 (minimal improvement), 4 (no change), 5 (minimal worsening), 6 (moderate worsening), and 7 (marked worsening).

If during the study, the designated caregiver or informant relinquishes his/her responsibilities as caregiver or informant, a replacement caregiver or informant must be found. If a replacement caregiver or informant is found who does not have similar knowledge of the subject's clinical status from Baseline throughout the Treatment Period, then the CIBIC-Plus will not be conducted but subject may continue in the study. If no replacement caregiver or informant is available at all the subject must be discontinued from the study.

9.5.1.2.4 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 also assesses the degree of caregiver or informant distress engendered by each of the symptoms (NPI-D). It is rated from 0 to 144 with high scores meaning a greater neuropsychiatric disturbance. Two subscores will be derived NPI-10 (covering the domains of delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and motor disturbance) and NPI-4 (covering the domains of delusions, hallucinations, apathy and depression).

The NPI will be assessed as designated in Table 5. The caregiver or informant will complete the NPI at these visits.

9.5.1.2.5 SCALE FOR ASSESSMENT OF POSITIVE SYMPTOMS IN PARKINSON'S DISEASE (SAPS-PD)

The SAPS-PD is a structured clinical interview originally designed for use in schizophrenia. It includes 5 domains of positive symptoms: hallucinations, delusions, bizarre behavior, positive formal thought disorder and inappropriate affect. The SAPS-PD is adapted from the Scale for Assessment of Positive Symptoms (SAPS) and includes items that are reflective of the hallucinations and delusions in PDD. It is a 9-item scale adapted from the hallucinations and delusions domains of the SAPS. 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. The SAPS-PD will be assessed as designated in Table 5.

9.5.1.2.6 MINI-MENTAL STATE EXAMINATION (MMSE)

A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment). The MMSE will be assessed as designated in Table 5.

9.5.1.2.7 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 behavior. It is scored based on frequency and severity with a score range of 0 to 12. The scale also assesses the degree of caregiver or informant distress engendered by the symptoms. The CFI will be assessed as designated in Table 5.

9.5.1.2.8 CLINICIAN GLOBAL IMPRESSION OF CHANGE IN DEMENTIA WITH LEWY BODIES (CGIC)

The CGIC provides an overall clinician-determined summary measure of change from the subject's clinical status at the Baseline Visit that takes into account all available information from the efficacy endpoints above (which include cognitive function, non-cognitive symptoms, behavior and the impact of the symptoms on the patient's ability to function) and safety data. The CGIC will be assessed as designated in Table 5.

9.5.1.2.9 FUNCTIONAL 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'). The FAQ will be assessed as designated in Table 5.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Collection and handling of PK, PD, and PGx samples will be detailed in the central laboratory manual to be provided to clinical sites.

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of plasma E2027 concentrations for PK analysis. Two blood samples for PK will be drawn at Weeks 6, 9, and 12: At predose (within 30 minutes before dosing) and 1 to 4 hours postdose. At these visits, subjects or their caregivers or informants will be instructed not to take their study drug at home on the day the blood samples for PK are collected. Instead, subjects will take their study drug at the clinic

after the predose blood draw; then a postdose blood draw will be performed. In addition, subjects or their caregivers or informant will be instructed to record the time of study drug administration for the 2 days before these visits when self-administered at home and this information will be collected and recorded on the eCRFs.

CSF samples will be collected for the determination of CSF E2027 concentrations at Week 9. At this visit, a predose blood sample for PK will be taken first, followed by CSF sampling. Study drug will then be administered to the subjects. Another PK sample will be collected at 1 to 4 hours postdose.

Plasma concentrations of E2027 and its metabolite HP4 and CSF concentrations of E2027 will be measured using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay methods.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Baseline Biomarker Assessments

A plasma sample will be collected during the Screening Period (Tier 3) to measure biomarkers related to AD copathology (including amyloid and p-tau) and other biomarkers related to DLB or PDD. These baseline plasma amyloid Aβ42/Aβ40 ratio will be used to classify subjects into the various categories (DLB without amyloid copathology, DLB with amyloid copathology, PDD without amyloid copathology and PDD with amyloid copathology). The baseline plasma biomarkers may also be used to define other subgroups classifications of subjects for subgroup analyses.

A CSF sample will be collected during the Screening Period (at least 7 days before the Baseline Visit) to measure baseline CSF cGMP and biomarkers related to DLB or PDD. These DLB or PDD related biomarkers may be used to define other subgroups classifications of subjects for subgroup analyses.

Plasma concentrations of Aβ42 and Aβ40 will be measured by the validated immunoprecipitation LC-MS/MS C2N Preclivity plasma assay. Plasma concentrations of p-tau 181, glial fibrillary acidic protein (GFAP), and neurofilament light (NFL) will be measured by Quanterix Simoa plasma assay.

CSF concentrations of cGMP will be measured using a validated assay. Other CSF biomarkers represented by Aβ42, Aβ40, tau, p-tau will be measured by Lumipulse platform and CSF NFL, neuregulin (NRG) will be measured by Simoa.

Pharmacodynamic Assessments

CSF samples will be collected during the Screening Period (at least 7 days before the Baseline Visit) and after 9 weeks on E2027. Both samples should be collected at approximately the same time in the morning, either in the fasted state (preferred) or at least 2 hours after breakfast. The CSF sample during the Treatment Period should be collected after the predose blood draw for PK and plasma biomarker analysis at the study visit after

9 weeks on E2027. The CSF samples will be assayed for cGMP and E2027. Other CSF biomarkers related to DLB or PDD or E2027 PD effects may also be assayed, if appropriate. CSF concentrations of cGMP and other biomarkers will be measured using validated assays.

A predose plasma sample will be collected at the study visit after 9 weeks on E2027. It will be assayed for plasma biomarkers related to DLB or PDD or E2027 PD effects on these biomarkers if appropriate. Plasma concentrations of Aβ42 and Aβ40 will be measured by the validated immunoprecipitation LC-MS/MS C2N Preclivity plasma assay. Plasma concentrations of p-tau 181, GFAP, and NFL will be measured by Quanterix Simoa plasma assay.

Pharmacogenomic Assessments

Blood samples will be collected as specified in the Schedule of Procedures/Assessments (Table 5) where feasible and in accordance with local regulations. Participation in PGx assessments is voluntary and subjects must provide a separate informed consent before blood collection for PGx assessments.

The PGx blood samples may be used to genotype common and rare genetic variants (including apolipoprotein E [ApoE] genotype). Data obtained from the PGx analysis will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The deoxyribonucleic acid (DNA) will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample may be stored for up to 15 years, based on country specific regulations to assist in any scientific research questions related to E2027 or DLB or PDD.

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular monitoring of hematology, blood chemistry, and urinalysis, measurement of vital signs (including orthostatic changes), ECGs, and the performance of physical examinations, C-SSRS and UPDRS-III as detailed in Table 5. A safety brain MRI may also be performed at Unscheduled Visits if deemed appropriate by the investigator.

9.5.1.4.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2027.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit in the Treatment Phase. Refer to Section 9.5.4.1 for the time period after the end of treatment for SAE collection.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.4.8 for a description of the C-SSRS).

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.4.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the eCRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.4.3 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events, fall, syncope, skin rash considered to be related to study drug, AEs that may signal drug abuse potential, and a "yes" answer to Type 4 or 5 suicidal ideation, or a "yes" response to any suicidal behavior on the C-SSRS, should always be considered adverse events and reported on the Adverse Event eCRF and on the event-specific eCRFs designed to collect additional information on specific events. It is the responsibility of the investigator to review the results of the C-SSRS and determine if any result constitutes an AE.

These AEs will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study.

Skin Rash Considered Related to Study Drug

If a subject develops a skin rash that is considered by the investigator not to be related to study drug, then the study drug should continue. If a subject develops a skin rash that is considered by the investigator to be possibly a drug rash related to study drug, the study drug should be temporarily stopped and a PK sample should be collected. The subject should be referred to a dermatologist for evaluation. If it is concluded after dermatologist review that the skin rash is not drug rash due to study drug, study drug treatment may be resumed.

If it is concluded after dermatologist review that the skin rash is likely to be a drug rash due to study drug, then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity
- A moderate to severe nonbullous rash

If it is concluded after dermatologist review that the skin rash is likely to be a drug rash due to study drug, but does not meet the above criteria for discontinuation, then study drug may be resumed after the rash has resolved.

If the rash that is considered by the investigator to be related to study drug but has resolved before the dermatologist review then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity
- A moderate to severe nonbullous rash

Otherwise, the study drug may be resumed after the rash has resolved.

Adverse Events that May Signal Drug Abuse Potential

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. Similarly, AEs reported during the 28 days following the last dose of study drug (Follow-up Period) that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs that fall into the categories listed below. Examples of such AEs are provided in Appendix 2 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation of study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines). As neuropsychiatric symptoms are common in DLB, the investigator should exercise clinical judgement in deciding if a neuropsychiatric AE [such as those described in Appendix 2] constitute an AE of abuse potential.

Euphoria-related terms:

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood:

- Somnolence
- Mood disorders and disturbances

Dissociative/psychotic terms:

- Psychosis
- Aggression

- Confusion and disorientation
- Dissociative state

Related terms not captured elsewhere:

- Drug tolerance
- Habituation
- Substance related disorders

Physical dependence or withdraw (only for events observed within the first 4 weeks after the last dose of study drug):

- Drug withdrawal syndrome

9.5.1.4.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Coagulation[a]	INR derived from the prothrombin time, PTT
Chemistry	
Electrolytes	Calcium, chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid, TFT[a] (TSH, free triidothyronine, and free thyroxine), vitamin B12[a]
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

INR = international normalized ratio, PTT = partial thromboplastin time, RBC = red blood cell, TFT = thyroid function test, TSH = thyroid stimulating hormone, WBC = white blood cell.

a: Screening only.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of

collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the eCRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF (see Section 9.5.4.3.2).

9.5.1.4.5 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic blood pressure [BP] and diastolic BP [mmHg] including orthostatic evaluations, pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), height (m), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 5) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 10 minutes in the supine position. Blood pressure and pulse will be measured again after standing up for 2 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained on the same day as PK or other blood samples, the vital sign measurements will be performed prior to drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

Orthostatic (postural) hypotension will be defined as either asymptomatic orthostatic hypotension (change in BP upon standing without lightheadedness) or symptomatic orthostatic hypotension (change in BP upon standing accompanied by lightheadedness).

Orthostatic hypotension will be recorded based on the following criteria:

- Drop in systolic BP ≥20 mmHg, or
  Drop in diastolic BP ≥10 mmHg

Occurrences of orthostatic hypotension as defined above that also meet any of the following criteria are considered clinically significant and will be reported as AEs in this study:

- Postural lightheadedness noted upon standing (ie, symptomatic orthostatic hypotension)
- Requires intervention (eg, resumption of recumbent position, IV fluids, etc.)

Postural lightheadedness upon standing if accompanied by orthostatic BP changes meeting the above criteria of orthostatic hypotension should be reported as AE of orthostatic hypotension.

9.5.1.4.6 PHYSICAL EXAMINATIONS

Complete and brief physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5). Documentation of the physical examinations will be

included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AE eCRF.

A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region.

In the brief physical examination, health status will be assessed by brief evaluation of the chest (including heart and lungs), abdomen and limbs, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.1.4.7 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/ Assessments (Table 5). Triplicate ECG will be performed after subject has been resting in the supine position for at least 10 minutes. The mean QTcF and other ECG intervals will be determined.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events eCRF.

9.5.1.4.8 OTHER SAFETY ASSESSMENTS

Columbia Suicide Severity Rating Scale (C-SSRS)

An assessment of suicidality using the C-SSRS will be performed at Screening and Baseline Visits, every 3 weeks during the Treatment Period, and at the Follow-Up Visit, as designated in the Schedule of Procedures/Assessments (Table 5).

Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III (MDS UPDRS-III): Motor Examination

The MDS UPDRS 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. It is recommended that 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).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the study.

Table 5 Schedule of Procedures/Assessments in Study E2027-A001-203

Phase	Pretreatment		Treatment							
Period	Screening	Baseline	Treatment					Follow-Up (FU)	Early Discontinuation (ED)[d]	Unscheduled[e]
Visit[a]	1[b]	2[c]	3[c] Telephone	4	5	6	7	8		
Day	-49 to -8	-7 to -1	1	21	42	63	84	112		
Weeks Elapsed Since Start of Treatment			0	3	6	9	12	16		
Assessments										
Informed consent	X									
Inclusion and exclusion criteria	X	X								
Demographics	X (Tier 1)									
Medical history	X (Tier 1)									
History of DLB or PDD	X (Tier 1)									
Prior and concomitant medications	X (Tier 1)	X	X	X	X	X	X	X	X	X
MMSE[g]	X (Tier 2)						X		X	X
GDS	X (Tier 2)[f]									
MoCA[g]	X (Tier 2)[f]	X			X		X		X	X
SFQ	X (Tier 2)[f]									
CFI[g]	X (Tier 2)[f]	X			X		X		X	X
NPI[g]	X (Tier 2)[f]	X			X		X		X	X
CIBIS-Plus[g]		X								
CIBIC-Plus[g]					X		X		X	X
WAIS-IV DSC[g]		X					X		X	X
SAPS-PD[g]		X					X		X	X
FAQ[g]		X					X		X	X
CGIC					X		X		X	X
Modified Hachinski Ischemic Scale	X (Tier 3)									
UPDRS-III	X (Tier 3)						X	X	X	X
HYS	X (Tier 3)									
C-SSRS	X (Tier 3)	X		X	X	X	X	X	X	X
Blood for plasma biomarkers	X (Tier 3)					X[p]				
Height	X (Tier 4)									
Weight	X (Tier 4)						X		X	X

Table 5 Schedule of Procedures/Assessments in Study E2027-A001-203

Phase	Pretreatment		Treatment							
Period	Screening	Baseline	Treatment					Follow-Up (FU)	Early Discontinuation (ED)[d]	Unscheduled[e]
Visit[a]	1[b]	2[c]	3[c] Telephone	4	5	6	7	8		
Day	-49 to -8	-7 to -1	1	21	42	63	84	112		
Weeks Elapsed Since Start of Treatment			0	3	6	9	12	16		
Assessments										
Vital signs[h]	X (Tier 4)	X		X	X	X	X	X	X	X
Complete physical examination	X (Tier 4)									
Brief physical examination		X					X	X	X	X
12-lead ECG[i]	X (Tier 4)	X		X	X	X	X	X	X	X
Blood and urine for clinical laboratory tests[j]	X (Tier 4	X [j]			X		X		X	X
Blood for vitamin B12 test	X (Tier 4)									
Blood for thyroid function tests[k]	X (Tier 4)									
Urine drug screen	X (Tier 4)	X								X
Serum pregnancy test[l]	X (Tier 4)									
Urine pregnancy test[l]		X								
Safety brain MRI[m]	X (Tier 5)									X[m]
DAT brain imaging, MIBG scan[n]	X (Tier 6)									
CSF sample by LP for PK and PD biomarkers[o]	X					X				
Plasma sample for PK[p]					X	X	X		X	X
PGx sample[q]		X								
Adverse events	X	X	X	X	X	X	X	X	X	X
Start open-label treatment on E2027 50 mg QD[c]			X							
Dispense study drug		X		X	X	X				

AE = adverse event, CFI = Cognitive Fluctuation Inventory, CGIC = Clinician Global Impression of Change, CIBIC-Plus = Clinician's Interview Based Impression of Change Plus Caregiver Input, CIBIS-Plus = Clinician Interview Based Impression of Severity plus Caregiver Input, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, DAT = dopamine transporter, DLB = dementia with Lewy bodies, ECG = electrocardiogram, ED = early discontinuation, FAQ = Functional Assessments Questionnaire, FU = follow-up, GDS = Geriatric Depression Scale, HYS = Hoehn and Yahr Scale, INR = international normalized ratio, LP = lumbar puncture, MIBG = ^{123}I-meta-iodobenzylguanidine, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PD = pharmacodynamic, PDD = Parkinson's disease dementia, PGx = pharmacogenomic, PK = pharmacokinetic, PTT = partial thromboplastin time, QD = once daily, SAPS-PD = Scale for Assessment of Positive Symptoms in Parkinson's Disease, SFQ = Short Fluctuation Questionnaire, UPDRS-III = Unified Parkinson's Disease Rating Scale Part III, WAIS-IV DSC = Weischler Adult Intelligence Scale-4th Edition Digit Symbol Coding

Table 5 Schedule of Procedures/Assessments in Study E2027-A001-203

Phase	Pretreatment		Treatment							
Period	Screening	Baseline	Treatment					Follow-Up (FU)	Early Discontinuation (ED)[d]	Unscheduled[e]
Visit[a]	1[b]	2[c]	3[c] Telephone	4	5	6	7	8		
Day	-49 to -8	-7 to -1	1	21	42	63	84	112		
Weeks Elapsed Since Start of Treatment			0	3	6	9	12	16		
Assessments										

a: A window of ±4 days will be permitted for Visit 4 to 8 (Follow-Up) inclusive. If under extenuating circumstances (eg, the COVID-19 pandemic), a subject is not able to visit the study site for scheduled safety and efficacy assessments, then any assessments not performed during the scheduled visit may be performed remotely (if feasible) with sponsor approval.

b: The Screening Period takes place over a period of up to 6 weeks. Subjects who complete screening assessments in less than 6 weeks may proceed to the Baseline Period. At Screening, assessments are grouped into tiers and should be performed sequentially. It is recommended that where appropriate Tiers 1 to 4 should be performed on the same day and Tiers 5 and 6 on a separate day. However, the investigator may perform the various tiers on separate days as appropriate for each subject. Subjects will need to satisfy the eligibility criteria in each tier before proceeding to the next tier. Subjects who cannot complete screening within 6 weeks should be discussed with the sponsor for extension of the Screening Period by up to 1 week.

c: Visit 2 is the Baseline Visit and may be conducted up to 1 week before the first dose of study drug (ie, from Day -7 to Day -1). The Baseline Visit should be at least 2 weeks after the day of Screening Visit Tier 2 assessments and at least 1 week after CSF collection. After completion of study assessments subjects who are eligible will be dispensed with study drug (E2027) before leaving clinic at Visit 2. Visit 3 (Day 1) will be conducted by telephone. On Day 1 the subject will start taking study drug in the morning at home. The site study staff will telephone the subject/caregiver to check that the subject has taken study drug and to elicit information about any AEs. Subjects who develop acute illnesses which make it inappropriate to start taking study drug may have their Baseline Period extended by 1 week after discussion with the sponsor medical monitor.

d: Subjects who discontinue study drug prematurely for any reason will undergo an Early Discontinuation (ED) Visit within 7 days of their final dose of study drug. In addition, subjects who prematurely 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. At these originally scheduled visits that take place after the ED Visit, blood PK samples, plasma biomarker samples, and CSF samples will not be collected.

e: Unscheduled visits may be conducted at any time as clinically indicated in the judgment of the investigator or as specified in the protocol. Not all assessments indicated under Unscheduled Visits need to be conducted – actual assessments needed will be determined by the investigator or as specified in the protocol and will be based on the specific visit.

f: Tier 2 screening assessments in subjects should be performed in the following order: MMSE and GDS first; then MoCA. The caregivers or informants should complete the SFQ, CFI, and NPI. Subjects who do not meet eligibility criteria on MMSE and GDS should be screen failed and the other assessments do not need to be performed. The above assessments should be completed before more invasive procedures (eg, physical examination, ECG, blood draws). Assessments at all other tiers are not required to be performed in any prespecified order. The caregiver or informant must normally attend in person with the subject. However, under extenuating circumstances only, and only with the approval of the sponsor (eg, during the COVID-19 pandemic), the assessments may be administered remotely via telephone, sponsor-approved telehealth, or home visit.

g: Visit 2, 5, 7, ED Visit and FU study assessments should be conducted at approximately the same time of the day whenever possible (preferably in the morning). The MoCA should be administered first, followed by the WAIS-IV DSC (not at Visit 5), then the CIBIS/CIBIC-Plus and finally the MMSE (not at Visit 5). The caregiver or informant will also complete the CIBIS/CIBIC-Plus, NPI, CFI, SAPS-PD (not at Visit 5) and FAQ (not at Visit 5). The caregiver or informant must normally attend in person with the subject. The CIBIS-Plus and CIBIC-Plus should be performed by an independent rater from other scales. Efficacy assessments should be completed before more invasive

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Weeks Elapsed Since Start of Treatment			0	3	6	9	12	16		
Assessments										

procedures (eg, physical examination, ECG, blood draws) unless otherwise specified. At Visits 5, 7 and ED Visit the MoCA should be the first clinical scale to be administered postdose and before the first postdose PK sample. At Visits 5, 7, and ED Visit the investigator should complete the CGIC after reviewing all the subject's efficacy endpoints. The caregiver or informant must normally attend in person with the subject. However, under extenuating circumstances only, and only with the approval of the sponsor (eg, during the COVID-19 pandemic), the assessments may be administered remotely via telephone, sponsor-approved telehealth, or home visit.

h: Single measurements of vital signs will be performed after the subject has been resting supine for at least 10 minutes. Vital signs include temperature, respiratory rate, supine blood pressure and pulse. Blood pressure and pulse will be measured again after standing up for 2 min. For the visits at which PK sampling is also scheduled (ie, Week 6 [Visit 5], Week 9 [Visit 6], and Week 12 [Visit 7], or ED Visit) vital signs will be taken at 1 – 4 hours postdose, before PK sampling.

i: Triplicate ECG will be performed after subject has been resting supine for at least 10 min. The mean QTcF and other ECG intervals will be determined.

j: Clinical laboratory tests consist of hematology (complete blood count), clinical chemistry, and urinalysis. In all subjects clotting screen (prothrombin time, PTT, INR) will also be performed only at the Screening Visit with the other clinical laboratory tests.

k: Thyroid function tests include thyroid stimulating hormone, free triidothyronine, and free thyroxine.

l: Female subjects who are <60 years of age and not surgically sterilized.

m: Safety MRI of the brain will be acquired using a standardized procedure that will include gradient echo, long tau inversion recovery, and diffusion-weighted imaging sequence images at screening. MRI of the brain will be read by an approved central reader. Safety MRI of the brain may be performed at Unscheduled Visits if deemed appropriate by the investigator but is not required for all Unscheduled Visits. Subjects who are rescreened do not need to have a new MRI at rescreening if there was an MRI within 90 days before rescreening that did not have exclusionary characteristics.

n: DAT brain imaging scan or myocardial MIBG scan will be performed by the local hospital radiology department in accordance with local procedures and must be performed at least 7 days before CSF collection. The rules regarding when DAT brain imaging or MIBG scan will be performed are specified in Inclusion Criterion 2.

o: CSF will be collected by LP in all subjects. During Screening CSF may be collected at any time after completion of screening procedures and a subject is deemed eligible, at least 1 week after DAT or MIBG imaging and at least 1 week before Visit 2. CSF will be collected again at Visit 6. CSF will be collected in the morning at approximately the same time, either fasted (preferred) or at least 2 h after breakfast. The timing of the Screening CSF collection needs to be scheduled carefully such that subsequent collection (at Visit 6) can be performed at a similar time of day (±2 hours) for each individual subject. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation as per local guidelines. At Week 9 (Visit 6), a predose blood sample for PK and a blood sample for plasma biomarkers will be taken first, followed by LP. Subjects will then be dosed with study drug and a PK sample will be collected at 1 – 4 hours postdose. If Visit 6 occurs after an ED Visit, blood PK samples, plasma biomarker sample and CSF will not be collected.

p: The day before the visits at which PK sampling will be done, the site study team will phone the subject and caregiver/informant to remind the subject not to take the study drug in the morning of the visit on the next day. In the morning of the day of the visit, the subjects should take breakfast at home as normal, if applicable. Thereafter, a predose PK sample will be taken in clinic. Study drug will be administered and 1 postdose PK sample will be taken: 1 - 4 hours postdose at Week 6 (Visit 5) and Week 12 (Visit 7) (or ED Visit). At Week 6 (Visit 5) and Week 12 (Visit 7) (or ED Visit) study drug will be administered before efficacy assessments are performed. A predose PK sample and a blood sample for plasma biomarkers will be collected at Week 9 (Visit 6), followed by CSF collection. The subject will then be dosed with study drug and a

Table 5 Schedule of Procedures/Assessments in Study E2027-A001-203

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Day	-49 to -8	-7 to -1	1	21	42	63	84	112		
Weeks Elapsed Since Start of Treatment			0	3	6	9	12	16		
Assessments										

PK sample will be collected at 1 - 4 h postdose. In addition, subjects or their caregivers/ informants will need to record the time of dosing of study drug at home for 2 days before these visits. If these visits take place after the ED Visit, blood PK samples, plasma biomarker sample and CSF samples will not be collected.

q: A blood sample for genomic DNA will be collected at the Baseline Visit. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 5 for the timings of the procedures and assessments to be performed during the study. See Sections 9.1 and 9.5 for a full description of the procedures and assessments, respectively, to be performed during this study.

Table 6 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations.

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Number of Time Points × Volume per Collection (mL)			Total Volume (mL)
		Screening Visit	Baseline Visit (predose)	Treatment and Follow-Up Periods	
Blood					
Chemistry	4	1 × 2.5	1 × 2.5	2 × 2.5	10.0
Vitamin B12	1	1 × 1.3	None	None	1.3
TSH, T4, T3, β-hCG	1	1 × 2.5	None	None	2.5
Hematology	4	1 × 2.0	1 × 2.0	2 × 2.0	8.0
INR, prothrombin time, PTT	1	1 × 2.0	None	None	2.0
PD (biomarkers)	2	1 × 6.0	None	1 × 6.0	12.0
PK	6	None	None	6 × 6.0	36.0
PGx	1	None	1 × 6.0	None	6.0
Total blood volume to be collected		**16.3**	**10.5**	**51.0**	**77.8**
CSF					
PK and PD	2	1 × 7.0	None	1 × 7.0	14.0
Total CSF volume to be collected		**7.0**	None	**7.0**	**14.0**

β-hCG = beta-human chorionic gonadotropin, CSF = cerebrospinal fluid, INR = international normalized ratio, PD = pharmacodynamic, PGx = pharmacogenomics, PK = pharmacokinetic(s), PTT = partial thromboplastin time, TSH = thyroid stimulating hormone, T3 = triiodothyronine, T4 = thyroxine.
Note: Actual volumes may be less, based on regional differences in Central Laboratories.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of LBD and other forms of dementia. The primary endpoint is the percentage change from baseline of CSF cGMP, which is the main PD response to E2027 that may show different responses in subjects with and without amyloid copathology. Further discussion of the selection of the efficacy endpoints is provided in Section 9.2.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations,

neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and UPDRS-III. Safety MRI of the brain may be performed at Unscheduled Visits if deemed appropriate by the investigator.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit in the Treatment Phase. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any relevant follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the relevant follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor or its designee to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, (or any partner's pregnancy of a male subject in which the estimated date of conception is either before the last visit or within

98 days of last study treatment), or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional Overdose, even if asymptomatic, are always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious

criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory value that is greater than or equal to 3× the upper limit of normal (ULN)

  AND

- Elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN

  AND AT THE SAME TIME

- Alkaline phosphatase lab value that is less than 2× the ULN

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 5).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, pregnancy, withdrawal of consent, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition eCRF.

If any of the subgroups have fewer than 6 subjects completing at least 9 weeks of treatment and the posttreatment CSF sample, then further subjects may be screened and treated with E2027.

There are no safety signals identified in clinical studies conducted to date to warrant specific discontinuation criteria for individual subjects based on safety data. Most adverse events on E2027 were mild to moderate and there were no subjects who discontinued treatment due to adverse events. Therefore, the investigator should exercise clinical judgement to decide if a subject should be discontinued, except for specific situations described below.

Skin Rash

As already described in Section 9.5.1.4.3, in subjects with skin rash, if it is concluded after dermatologist review that the skin rash is likely to be a drug rash due to study drug, then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity
- A moderate to severe nonbullous rash

As already described in Section 9.5.1.4.3, in subjects with skin rash, if the rash is considered by the investigator to be related to study drug but has resolved before the dermatologist review then the study drug should be permanently discontinued if the rash has any of the following characteristics:

- A bullous rash regardless of severity
- A moderate to severe nonbullous rash

Prolongation of QTcF Interval on ECG

Subjects who have mean QTcF on triplicate ECG >500 msec should be discontinued.

Use of Prohibited Medications

As per Section 9.4.7.2, subjects who start treatment with any of the following medications during the study will be discontinued due to the risk of PK or PD interactions:

- Drugs known to be strong inhibitors of CYP3A, grapefruit juice, and grapefruit products
- Drugs known to be moderate to strong inducers of CYP3A
- Drugs known to cause prolongation of the QT interval, including but not limited to drugs that may cause cardiac arrhythmias
- Drugs that are phosphodiesterase inhibitors (eg, theophylline, aminophylline, sildenafil, tadalafil, vardenafil, dipyridamole, roflumilast, apremilast, inamrinone, milrinone, and enoximone)

As per Section 9.4.7.2, subjects who start treatment with any of the following medications during the study will be discontinued due to interference with efficacy assessments or safety:

- Anticholinergic drugs that have CNS activity
- Pimavanserin
- Subjects who start anticoagulants (eg, heparin, heparin derivatives, non-heparin derivatives, warfarin, dabigatran) or dual antiplatelet therapy (eg, aspirin and clopidogrel together) before their 2nd CSF collection at 9 weeks of treatment, will not undertake the 2nd CSF collection but may continue in the study. However, they will not be considered as completers of the study.

Decline to Loss of Capacity to Consent

During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study.

Contraception Requirement

Subjects who are in the treatment period and who meet the criteria that requires them (and the female partners of male subjects) to practice contraception as specified in Section 9.3.2, but who cannot comply or are unwilling to do so, will be discontinued from study drug.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.4.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the eCRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 or Investigator and Site Information Form must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate SAP, which will be finalized before database lock.

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

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

9.7.1.1.2 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 C-SSRS
  - Changes from baseline in the total score of UPDRS-III

9.7.1.1.3 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

9.7.1.2 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.

9.7.1.3 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 subjects enrolled by each site will be summarized by subgroup and overall.

Study Completion: 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: 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.

9.7.1.4 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, MMSE total score; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, treatment with AChEIs (no or yes), and treatment with memantine (no or yes).

9.7.1.5 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 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.

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

9.7.1.6 Efficacy Analyses

The exploratory efficacy endpoints 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).

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 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 and its report, and the results will not be included in the clinical study report.

9.7.1.7.2 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 versus PDD with amyloid copathology). 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 may be analyzed similarly, if appropriate.

The CSF and plasma PD biomarkers will be summarized by subject subgroups, as appropriate. Summaries and figures will be produced exploring the relationships between CSF and plasma PD biomarkers and the efficacy endpoints.

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 and its report, and the results will not be included in the clinical study report.

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 PGx data will be summarized similarly.

9.7.1.8 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 subgroup and overall.

9.7.1.8.1 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 percentage 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.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is 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.

The TEAEs will be summarized by subgroup and overall. 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 an SOC and PT, even if the subject experienced more than 1 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 (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs, treatment-emergent SAEs and TEAEs leading to discontinuation from study drug will be also summarized by SOC and PT. Subject data listing for each above type of AEs and AEs leading to death will also be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate.

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 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will

also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 3 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and subgroup and overall.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and subgroup and overall. ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) will be presented by visit and subgroup and overall using frequency count. The number (percentage) of subjects with postbaseline abnormal ECG result in QTcF will be summarized by subgroup and overall.

9.7.1.8.6 OTHER SAFETY ANALYSES

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS responses will be mapped to the Columbia-classification algorithm of suicide assessment (C-CASA). The incidence of suicidal ideation or suicidal behavior will be summarized by subgroup and overall. Continuous variables will be summarized by descriptive statistics; number of subjects, mean, standard deviation, median, minimum, and maximum and categorical variables by number (percentage) of subjects.

Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III (MDS UPDRS-III): Motor Examination

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

9.7.2 Determination of Sample Size

Assuming the standard deviation of percentage change from baseline in CSF cGMP at Week 9 is 60, the sample size of 6 completers per group (for 8 enrolled subjects per arm, assuming a 25% dropout rate), will 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 has approximately 80% power to detect the difference in change from baseline of CSF cGMP of 100% (same assumptions as above). These sample size calculations illustrate the possible differences that could be seen between subgroups. However, without previous data on the differences between subgroups in CSF cGMP, these are for illustration only and it is not expected statistical significance will 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 groups. If the true difference is 100%, there will be 97.8% probability that the observed difference is ≥30%. If the true difference is 60%, the probability is 80.7%. If the true difference is 10%, there will be 28.2% probability that the observed difference is ≥30%.

9.7.3 Interim Analysis

No interim analysis will be conducted.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays, and other imaging reports (eg, sonograms, CT scans, MRI, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source
- Electronic Patient-Reported Outcome (eCOA) by self-reported measures

11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

Efficacy or safety assessments are evaluated based on the data entered into eCOA. The applicable data are input directly by each subject from the viewpoint of his/her health condition without the interpretation of the investigator.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents. For the following items, the data recorded directly on the eCRF are to be considered source data:

- Reasons for discontinuation of study treatment
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

- Reasons for dose modification
- Indication for prior/concomitant medication
- Sampling times for drug concentrations
- Sampling times for clinical laboratory tests

The data collected by eCOA are also considered source data.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 15 years following the completion of the study.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor’s Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor’s standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used

and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the

sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Diagnostic Criteria for Probable Dementia With Lewy Bodies and Probable Parkinson's Disease Dementia

The diagnostic criteria for probable dementia with Lewy bodies (DLB) require:

- Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions or with usual daily activities.
- Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progress.
- Deficits on tests of attention, executive function and visuospatial ability may be prominent and occur early.
- At least 2 core clinical features, or 1 core clinical feature and at least 1 indicative biomarker.

The core clinical features are:

- Fluctuating cognition with pronounced variations in attention and alertness.
- Recurrent visual hallucinations that are typically well formed and detailed.
- Rapid eye movement (REM) sleep behavior disorder which may precede cognitive decline.
- One or more spontaneous cardinal features of Parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor or rigidity.

The onset of dementia should not be greater than 1 year after onset of Parkinsonism. The investigator should determine the time of onset of Parkinsonian motor features based on clinical evaluation.

For assessment for cognitive function, the investigator should take into account scores of the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) used at screening.

In evaluation of the core clinical features, the investigator should take into account the scores in the Short Fluctuation Questionnaire (SFQ), Cognitive Fluctuation Inventory (CFI), Neuropsychiatric Inventory (NPI), and Unified Parkinson's Disease Rating Scale Part III: Motor Examination (UPDRS-III) for cognitive fluctuation, hallucinations and parkinsonian motor features respectively.

Indicative biomarkers include:

- Reduced dopamine transporter uptake (DAT) in the basal ganglia on DAT brain scan
- Abnormal (low uptake) in meta-iodobenzylguanidine (MIBG) cardiac scan
- Polysomnography (PSG) confirmation of REM sleep without atonia

When Parkinsonism is the only core feature of DLB in a patient with dementia, reduced DAT uptake warrants a probable DLB diagnosis provided that other disorders associated with cognitive impairment and reduced DAT uptake can be excluded.

Clinicians should carefully interpret MIBG results in the light of possible confounding causes, including ischemic heart disease, heart failure, diabetes mellitus, peripheral neuropathies, and medications that may cause reduced uptake including labetalol, reserpine, tricyclic antidepressants, and over-the-counter sympathomimetics.

The diagnosis of probable Parkinson's disease dementia (PDD) require the following:

- Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria.
- Dementia developing in the context of established Parkinson's disease (ie, dementia onset >12 months after onset of Parkinson's disease) with cognitive impairment in more than one domain and severe enough to impair daily life.
- Impairment in at least 2 of the 4 cognitive domains below:
  - Attention, which may fluctuate
  - Executive function
  - Visuospatial function
  - Memory (in the form of free recall, which may improve with cueing)
- Behavioral features listed below support the diagnosis but absence of such features does not exclude the diagnosis:
  - Apathy
  - Depression
  - Anxiety
  - Hallucinations
  - Delusions
  - Excessive daytime sleepiness
- Diagnosis of PDD cannot be made if any of the following criteria are met:
  - Cognitive and behavioral symptoms appear solely in the context of other conditions such as systemic diseases, drug intoxication or major depression.
  - Patient meets criteria for probable vascular dementia

For assessment for cognitive function, the investigator should take into account scores of the MMSE and MoCA used at screening.

In evaluation of the clinical features, the investigator should take into account the scores in the SFQ, CFI, and NPI for cognitive fluctuation, behavioral and neuropsychiatric symptoms.

Appendix 2 Examples of Adverse Events That May Signal Drug Abuse Potential

Examples of Adverse Events That May Signal Drug Abuse Potential

Categories			Examples[a]	
Euphoria-related terms	1	Euphoric mood	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	Elevated mood	Elevated mood	Elation
			Mood elevated	
	3	Feeling abnormal	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	Feeling drunk	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	Feeling of relaxation	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	Dizziness	Dizziness	
	7	Thinking abnormal	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts
	8	Hallucination	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	Inappropriate affect	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood	10	Somnolence	Somnolence	
	11	Mood disorders and disturbances	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress

Examples of Adverse Events That May Signal Drug Abuse Potential

Categories			Examples[a]	
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere	**16**	**Drug tolerance**	Drug tolerance	
	17	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical dependence or withdrawal[b]	**19**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the electronic Case Report Form Completion Guidelines.

b: Only for events observed within the first 4 weeks of last dose of study drug.

Appendix 3 Sponsor's Grading for Laboratory Values

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				
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
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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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
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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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.

PROTOCOL SIGNATURE PAGE

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
Investigational Product Name:	E2027
IND Number:	123614

SIGNATURES

Authors:

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Neurology Business Group, Eisai Ltd. Date

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Neurology Business Group, Eisai Inc Date

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Neurology Business Group, Eisai Inc Date

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Neurology Business Unit, Eisai Ltd. Date

INVESTIGATOR SIGNATURE PAGE

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
Investigational Product Name:	E2027
IND Number:	123614

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>		
Investigator	Signature	Date