1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	ME2125-M082-401
Study Protocol Title:	A multi-center, open-label phase 4 study evaluating the efficacy and safety of safinamide mesilate as add-on therapy to levodopa in Parkinson's Disease patients with motor fluctuation in South Korea
Sponsor:	Eisai Korea Inc. 10F Revessant, 6, Bongeunsa-ro 86-gil, Gangnam-gu, Seoul, 06163, Korea
Sponsor's Investigational Product Name:	Equfina Film Coated Tab. 50 mg (safinamide mesilate)
Indication:	Parkinson's Disease
Phase:	4
Approval Date:	V5.0 24 January 2022
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.: ME2125

Name of Active Ingredient: safinamide mesilate

Study Protocol Title

A multi-center, open-label phase 4 study evaluating the efficacy and safety of safinamide mesilate as add-on therapy to levodopa in Parkinson's Disease patients with motor fluctuation in South Korea

Sites

Approximately 20 sites

Study Period and Phase of Development

Approximately 13 months (may be shortened or extended depending on registration status)

Phase 4

Objectives

Primary Objective

To evaluate the change at the 18th week from baseline in daily "off" time measured by subject diary and Parkinson's Disease Questionnaire-39 (PDQ-39) in patients with Parkinson's Disease who are receiving levodopa.

Secondary Objective

- To evaluate the change at the 18th week from baseline in below assessments:
  - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 3
  - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 4
  - King's Parkinson's disease Pain Scale (KPPS)
  - Mini-Mental State Examination (MMSE)
- To evaluate the safety of safinamide mesilate in Parkinson's Disease patients who are receiving levodopa
- To evaluate the change at the 18th week from baseline in daily "on" time without dyskinesia in patients with Parkinson's Disease who are receiving levodopa

Study Design

This is a multi-center, open-label, single-arm, interventional study in Parkinson's Disease patients who are receiving levodopa.

After providing written informed consent, subjects will enter the Screening Period for maximum 21 days and then Baseline Period for 1 day. If subjects are eligible, Treatment Period will begin in which subjects will be treated with safinamide mesilate (hereinafter, study drug) for 18 weeks.

After the Treatment Period, subjects' participation in the study will be completed after the completion of Visit 4 (EOT), which is the End of Treatment Visit. At Visit 4(EOT), the subjects who require tapering will enter a Taper Period for 1 week. The Taper Period may be omitted if the subject's daily dose of study drug at the end of treatment is 50mg, if subjects will continue to take the study drug after the completion of the trial, or if it is considered not required by an investigator.

[Screening Period]

At Visit 1(Screening), 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. A medical history interview, identification of prior and concomitant medications, identification of concomitant therapies, height, weight, physical examination, urine pregnancy test (females of childbearing potential only), 12-lead electrocardiogram (ECG; if deemed necessary by the investigator), vital signs, clinical laboratory tests (hematology, chemistry, and urinalysis), and adverse events (AE) assessment will be conducted for evaluation of eligibility criteria, and will include confirmation that the subject meets diagnostic criteria for Parkinson's Disease.

At Visit 1(Screening), subjects perform the Mini-Mental State Examination (MMSE) among the efficacy assessments. Also, a diary will be handed out to subjects and/or their caregivers, and investigator will train them how to complete the diary. Subjects who meet the eligibility criteria of the study will be instructed to complete the diary for 3 consecutive days prior to Visit 2 (Baseline).

If subjects have previously taken medications such as Catechol-O-methlytransferase (COMT) inhibitor and/or Monoamine oxidase-B (MAO-B) inhibitor, they have to take appropriate wash-out period for each medication (3 days for COMT inhibitor; 14 days for MAO-B inhibitor).

[Baseline Period]

At Visit 2 (Baseline), subjects will return to the site after they have completed the diary for at least 3 consecutive days. At Visit 2 (Baseline), safety assessments including AE assessment, vital signs, weight (if deemed necessary by an investigator), and physical examination will be conducted.

Efficacy assessments including Parkinson's Disease Questionnaire-39 (PDQ-39), Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 and Part 4, and King's Parkinson's disease Pain Scale (KPPS) will be conducted. Investigators will also review the completed subject diary with subjects.

The study drug will be distributed to the subjects who meet the eligibility criteria at Visit 2 (Baseline). Subjects will be instructed to take the study drug every day starting from the day after Visit 2 (Baseline).

[Treatment Period]

Subjects will take the study drug daily for 18 weeks.

The dose of the study drug is 50 mg once a day for 2 weeks (14 days) starting from the next day after Visit 2 (Baseline), and 100 mg once a day afterwards. Subjects who need to increase the dose at the discretion of an investigator shall visit the site (unscheduled) prior to the dose increase.

Subjects whose dose cannot be increased to 100 mg/day within 4 weeks following Visit 2 (Baseline) will be dropped out from the clinical trial.

If Adverse Events (AE) occur in subjects who have increased the dose, the dose may be reduced back to 50 mg/day at the discretion of an investigator through unscheduled site visit or phone visit. After reduction from 100mg/day to 50mg/day, the dose may be increased back to 100 mg/day at the discretion of an investigator.

Subjects will return to the site at 8 weeks and 18 weeks for Visit 3 and Visit 4 (EOT), respectively. The "windows" permitted for Visit 3 (8 weeks) will be -4 weeks and +2 weeks; for Visit 4 (18 weeks: EOT) will be +/- 2 weeks. Safety assessments including AE assessment, 12-lead ECG (if deemed necessary by an investigator), vital signs, weight, physical examination, clinical laboratory tests (hematology, chemistry, and urinalysis), and urine pregnancy test (females of childbearing potential only) will be conducted according to the schedule for each visit during Treatment Period. Efficacy assessments including PDQ-39, MDS-UPDRS Part 3 and Part 4, KPPS, and MMSE will be conducted at Visit 4 (EOT). Subjects will complete the diary for at least 3 consecutive days prior to Visit 4 (EOT), and investigators will review the completed diary together with subjects at Visit 4 (EOT).

[Taper Period]

Of the subjects who have completed 18 weeks of treatment, those who require tapering will enter a Taper Period for 1 week. After the completion of the Taper Period, subjects will return to the site for Visit 5. At Visit 5, safety assessments including AE assessment, vital signs, weight (if deemed necessary by an investigator), and physical examination will be conducted. For those subjects participating in the Taper Period, their participation in the study will be completed after the completion of Visit 5.

Taper Period may be omitted if the subject's daily dose of the study drug at the end of treatment is 50mg, if subjects will continue to take the study drug after the completion of the trial, or if it is considered not required by an investigator. For the subjects who do not require the Taper Period, their participation in the study will be completed after the completion of Visit 4 (EOT).

Premature Discontinuation of Study Drug

A subject who prematurely discontinues taking the study drug should return to the site as soon as practicable after discontinuing study drug (preferably within 7 days) to complete Premature Discontinuation Visit. Following the completion of Premature Discontinuation Visit, subjects who require taper will undergo a Taper Period for 1 week. Then the subjects will return to the site for Visit 5. For the subjects who do not require the Taper Period, Premature Discontinuation Visit would be their last visit in the study.

Number of Subjects

Approximately 199 subjects will be enrolled in the trial.

Inclusion Criteria

To be eligible for inclusion into this trial, the subjects must fulfill all of the following criteria:

1. Male or female, age ≥19 years at the time of informed consent
2. Patients who meet the clinical diagnostic criteria of Movement Disorder Society (MDS) diagnosis criteria 2015 for Parkinson's disease, have motor fluctuations with ≥1.5 hours of "off"

time throughout the day which is confirmed at the time of Screening, and take levodopa 3 or more times a day

3. Parkinson's Disease patients who are receiving levodopa without COMT inhibitor and/or MAO-B inhibitor

CCI [redacted]

4. Be able to maintain an accurate and complete diary with the help of a caregiver as needed, recording "on" time, "on" time with dyskinesia, "off" time, and time asleep
5. Be able to provide written informed consent
6. Patients whose cognitive function, at the discretion of an investigator, is at a level appropriate to participate in the clinical trial (i.e., with a GDS score of 3 or less or a CDR of 0.5 or less within 3 months prior to Screening)

Exclusion Criteria

To be eligible for inclusion into this trial, the subjects must not meet any of the following criteria:

1. Females who are planning for pregnancy, pregnant or breastfeeding.
2. Prior use of safinamide
3. If patients have previously taken medication such as COMT inhibitor and/or MAO-B inhibitor, they have to take appropriate wash-out period for each medication (3 days for COMT inhibitor; 14 days for MAO-B inhibitor)
4. Use of medications for depression or psychosis within 5 weeks prior to Screening Visit
5. History of allergic response to levodopa, or other anti-Parkinsonian agents
6. Hypersensitivity or contraindications to MAO-B inhibitors
7. Confirmed ophthalmologic history including any of the following conditions: albino subjects, family history of hereditary retinal disease, progressive and/or severe diminution of visual acuity (i.e., 20/70 on Snellen Chart), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or diabetic retinopathy
8. Patients who did not consent to having at least 7 days of washout period prior to Visit 2, if known to take narcotic analgesics 7 days prior to Screening Visit (eg, pethidine hydrochloride-containing products, tramadol hydrochloride, or tapentadol hydrochloride)
9. History of serotonergic medications administration (eg, tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–noradrenaline reuptake inhibitors, selective noradrenaline reuptake inhibitor, or noradrenergic and serotonergic antidepressant) within 5 weeks prior to Screening Visit
10. Administering central nervous system stimulants (eg, methylphenidate hydrochloride, lisdexamfetamine mesilate)
11. Administering dextromethorphan
12. Patients with clinically significant liver function abnormalities defined as > 1.5 times of the upper limit of the normal range of total bilirubin or > 3 times of the upper limit of the normal

range of ALT or AST; re-examination and re-screening are allowed once within the screening period

13. Have a history of hypersensitivity to any of the ingredients of the product
14. Currently enrolled in another clinical trial or used any investigational drug/biologics or device within 30 days or 5 × the half-life, whichever is longer, preceding informed consent

Study Drug

Safinamide mesilate as add-on therapy

- A white film-coated tablet contains 50 mg of safinamide

Duration of Treatment

18 weeks

Concomitant Drug/Therapy

- Addition and dose adjustment of anticholinergic and/or amantadine during the study period will be based on the judgment of an investigator.

- CCI [redacted]

Prohibited concomitant medications and therapies are listed below.

Prohibited medications:

- Acetylcholinesterase inhibitors
- COMT inhibitor
- Any investigational drugs/biologics
- All the contraindicated medications listed on the approved label of study drug (Appendix 1)

Prohibited therapies:

- DBS (Deep brain stimulation)
- Surgical treatment
- LCIG (Levodopa-carbidopa intestinal gel) therapy

Prohibited medications and therapies should not be used during the study.

If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study.

Assessments

Efficacy Assessments

The procedure for the efficacy assessments consists of the subject diary and questionnaire examination. Each questionnaire test below (PDQ-39, MDS-UPDRS part 3 and part 4, KPPS, MMSE) is to be performed in the "on" state of the subject, and is tested in the "off" state only when it is difficult to evaluate it in the "on" state.

Subject Diary

Information on daily "off" time and "on" time will be collected by subject diary.

Subjects will complete the diary for at least 3 consecutive days prior to each visit where completed diary review is conducted (Visit 2, Visit 4) and the diary will be maintained by the subject over a 24-hour period each day the diary is being completed. At 30-minute intervals throughout the period, the subject/caregiver will record whether the subject is currently 1) in an "on" phase 2) in an "on" phase with dyskinesia, 3) in an "off" phase, or 4) asleep. Subjects will also check when they take their levodopa throughout the day.

An "off" phase will be defined as lack of mobility, bradykinesia, or akinesia whereas in an "on" phase, the subject will be functioning as well as can be expected for that subject, irrespective of whether or not he/she is having dyskinesia.

The daily "off" time is defined as the mean of the total daily "off" time during the last two 24-hour diary recording periods prior to the visit. The daily "on" time is defined as the mean of the total daily "on" time during the last two 24-hour diary recording periods prior to the visit.

Investigators will review the completed subject diary with subjects at Visit 2 (Baseline) and Visit 4 (EOT).

PDQ-39

To assess the efficacy of non-motor symptoms and motor symptoms in subjects, PDQ-39 will be used. The PDQ-39 comprises 39 questions measuring eight dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). A summary index score can also be calculated. The contents of the instrument were developed on the basis of exploratory in-depth interviews with subjects with Parkinson's Disease, and the reliability, validity and sensitivity to change of the instrument were then assessed in a number of large-scale surveys. The questionnaire will be provided in Korean to the subjects.

MDS-UPDRS Part 3

To assess the efficacy of motor symptoms in subjects, MDS-UPDRS Part 3 will be used. The MDS-UPDRS is a rating tool used to follow the longitudinal course of Parkinson's Disease. It is made up of four parts that assess the following: Part 1 – Non-motor Aspects of Experiences of Daily Living; Part 2 – Motor Aspects of Experiences of Daily Living; Part 3 – Motor Examination; and Part 4 – Motor Complications. The information for these ratings is obtained through an interview with the subject and caregiver if available.

MDS-UPDRS Part 3 evaluates the motor function of the subject. This section of the scale consists of 18 items with 33 separate ratings being performed on a scale from 0 (normal) to 4 (severe). Specific instructions are provided for the testing of each item, which should be followed in all instances. Raters demonstrate while describing tasks the subject is to perform and rate function immediately thereafter. The subject's speech, facial expressions, ability to arise from a chair, posture, gait, postural stability (retropulsion test), and body bradykinesia are assessed. In addition, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements (open/close), rapid alternating movements of hands (pronation/supination), and leg agility are assessed.

MDS-UPDRS Part 4

In MDS-UPDRS Part 4, raters use historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Raters will use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. This section has instructions for the raters and also instructions to be read to the patient, and integrates patient-derived information with the rater's clinical observations and judgments. In Part A, the duration of, disability caused by, and functional impact of any dyskinesias experienced by the subject are rated on a scale from 0 to 4. Clinical fluctuations are assessed in Part B, which includes time spent in the "off" state (estimation of the proportion of the waking day spent in the "off" state), functional impact of fluctuations, the predictability and timing of the subject's "off" periods, and proportion of the "off" state having painful dystonia.

KPPS

To assess pain scale in subjects, KPPS will be used. KPPS is Parkinson's Disease-specific pain scale. Its seven domains include 14 items; each item is scored by severity (0-3) multiplied by frequency (0-4), resulting in a subscore of 0 to 12 with a total possible score range from 0 to 168.

MMSE

To assess cognition in subjects, MMSE will be used. The MMSE is a brief practical screening test for cognitive dysfunction. The test consists of relevant items (awareness of time, awareness of location, memory, attention, ability to calculate, ability to recall, ability to name names, repetition, understanding, reading, writing, and drawing) and has a total possible score of 30. It is useful as a quick method to assess the severity of cognitive dysfunction.

Safety Assessment

Safety assessment will consist of determining and recording all adverse events (AEs) and other events of special interests including pregnancy, breast feeding, overdose, abuse or misuse, lack of therapeutic efficacy, medication error, off label use, occupational exposure, and suspected transmission of an infectious agent; regular clinical laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and the performance of physical examinations.

Statistical Methods

Details of statistical methods and analyses will be specified in the statistical analysis plan (SAP).

Study Endpoints

Co-Primary Endpoints

- Change at the 18th week from baseline in daily "off" time
- Change at the 18th week from baseline in PDQ-39 score

Secondary Endpoints

- Change at the 18th week from baseline in below assessments:
  - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 3

- Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 4
- King's Parkinson's disease Pain Scale (KPPS)
- Mini-Mental State Examination (MMSE)

- Safety of safinamide mesilate
- Change at the 18th week from baseline in daily "on" time without dyskinesia

Analysis Set

Safety Analysis Set (SAS)

The SAS is the group of subjects who received at least 1 dose of study drug and completed at least 1 post-dose safety assessment.

Full Analysis Set (FAS)

The FAS is the group of subjects who received at least 1 dose of study drug and had at least 1 post-dose daily "off" time or PDQ-39.

Per Protocol Set (PPS)

It is intended for subjects who have fully complied with the study protocol. The details of the evaluability criteria will be determined prior to database lock and will be specified in the statistical analysis plan.

Efficacy Analyses

All efficacy analysis will use FAS as the primary population and PPS as the secondary population.

Primary efficacy analyses

- To evaluate the change at the 18th week from baseline in daily "off" time

  The daily "off" time will be analyzed using paired t-test on the change at the 18th week from baseline. The descriptive statistics for the daily "off" time will be summarized by each visit.
- To evaluate the change at the 18th week from baseline in PDQ-39

  The PDQ-39 will be analyzed using a paired t-test on the change at the 18th week from baseline.

  The descriptive statistics for the PDQ-39 will be summarized by each visit.

Secondary efficacy analyses

For the following items, the descriptive statistics will be summarized by each visit and it will be analyzed using a paired t-test on the change at the 18th week from baseline.

- Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 3
- Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 4
- King's Parkinson's disease Pain Scale (KPPS)
- Mini-Mental State Examination (MMSE)
- Daily "on" time without dyskinesia

Safety Analyses

All safety analyses will be performed on the SAS. Safety data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety data that will be evaluated include extent exposure, AEs, clinical laboratory results, weights, and vital signs.

Other Analyses

Levodopa dose during the study will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Efficacy analyses will be performed in subgroups based on levodopa dose and details will be described in the SAP.

Sample Size Rationale

The sample size was calculated assuming the efficacy of this study at 18 weeks is comparable to the efficacy of phase 3 clinical study at 24 weeks. The sample size is calculated using each 2 primary endpoints, and a larger sample size is selected conservatively. The sample size for each evaluation variable is as follows:

- Endpoint 1: Paired t-test for "off" time

  Based on the above assumptions, to calculate the number of subjects for the comparison of the "off" time mean change after 24 weeks compared to baseline, sample size was calculated assuming average change (-1.56) and standard deviation (2.35).

  The results were performed through PASS (version 2020), the sample sizes of 31 achieve 90% power and the significance level (alpha) is 0.025.
- Endpoint 2: Paired t-test for PDQ-39 score

  Based on the above assumptions, to calculate the number of subjects for the comparison of the PDQ-39 score mean change after 24 weeks compared to baseline, sample size was calculated assuming average change (-3.17) and standard deviation (10.86).

  The results were performed through PASS (version 2020), the sample sizes of 149 achieve 90% power and the significance level (alpha) is 0.025.

According to the above two endpoints, the sample sizes are 31, 149 at each assumption. The sample size of endpoint 2 is larger than endpoint 1. Therefore, the final sample size obtained considering the drop-out rate of 25% during the study period is 199.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CDR	Clinical Dementia Rating
COMT	Catechol O-methyltransferase
CPK	Creatine phosphokinase
CRA	Clinical Research Associates
CRF	Case Report Form
CRO	Contract Research Organization
ECG	Electrocardiogram
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Global Deterioration Scale
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	Investigational Products
IRB	Institutional Review Board
ISF	Investigator Study File
IxRS	Interactive Voice/Web Response System
KGCP	Korean Good Clinical Practice
KPPS	King's Parkinson’s disease Pain Scale
LAR	Legally Acceptable Representative
LLT	Lower Level Term
NICE	National Institute for Health and Care Excellence

Abbreviation	Term
MAO-B	Monoamine oxidase-B
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MMSE	Mini-Mental State Examination
PDQ-39	Parkinson's Disease Questionnaire-39
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set Statistical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cell
γ-GTP	γ-glutamyl transpeptidase

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 ICH E6 (Good Clinical Practice, GCP), Section 3, Korea Good Clinical Practice (KGCP), and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator 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 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 an investigator or sponsor, depending on local regulatory obligations. If an 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 or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC 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.

In the case of early termination/temporary halt of the study, an investigator should notify the IRB/IEC within the timeline required by each IRB's Standard Operating Procedures (SOP) 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 2013
- ICH E6 Guideline for GCP
- KGCP

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigators must explain to each subject or legally acceptable representative, 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 or course 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 investigator.

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 at Visit 1 (Screening) before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

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 or sponsor's representative 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.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai Korea Inc. at approximately 20 investigational sites in South Korea.

The name and telephone and fax numbers of contact personnel at the sponsor and of the Contract Research Organization (CRO) are listed in the Investigator Study File (ISF) provided to each site.

7 INTRODUCTION

7.1 Compound Overview

Levodopa is one of the effective treatments for motor symptoms of Parkinson's Disease.[1, 2] Long-term and high doses of levodopa treatment increase the wearing-off and dyskinesia. Parkinson's Disease patients often need add-on therapy to improve motor fluctuations without dyskinesia to reduce motor and functional disability.[1, 2] Wearing-off is usually improved by dopamine agonist, Monoamine Oxidase-B (MAO-B) inhibitor, and Catechol O-methyltransferase (COMT) inhibitors administered together with dopamine precursor, levodopa.[1, 2]

Safinamide mesilate is a novel oral therapy in the treatment of Parkinson's Disease as an adjunct to levodopa. Mechanism of action of safinamide mesilate includes inhibition of MAO-B, sodium (Na_1) channel blockade, and modulation of stimulated release of glutamate.[1-3] By inhibiting the metabolism of dopamine, Safinamide mesilate enhances endogenous residual dopamine and subsequently increases dopaminergic activity in the brain.[1-3]

7.2 Clinical Experience

Clinical trials with safinamide mesilate, which were 24-week, phase III, double-blind, parallel-group, randomized, multi-center, and multinational trials, demonstrated efficacy and safety in Parkinson's Disease patients with mid-to-late stage experiencing motor fluctuations (NCT01187966 and NCT 00627640).[1,3] According to approved Food and Drug Administration (FDA) label, most common adverse reactions associated with safinamide mesilate treatment in which the incidence for Safnamide mesilate 100 mg/day was at least 2% greater than the incidence for placebo were dyskinesia, fall, nausea, and insomnia (Table 1).[4]

Table 1. Incidence of patients with adverse reaction in the safinamide mesilate 50mg/day and 100 mg/day groups compared to placebo in clinical trials

	Safinamide mesilate 50 mg/day (N=223)	Safinamide mesilate 100 mg/day (N=498)	Placebo (N=497)
Adverse reaction	(%)	(%)	(%)
Dyskinesia	21	17	9
Fall	4	6	4
Nausea	3	6	4

	Safinamide mesilate 50 mg/day (N=223)	Safinamide mesilate 100 mg/day (N=498)	Placebo (N=497)
Adverse reaction	(%)	(%)	(%)
Insomnia	1	4	2
Orthostatic hypotension	2	2	1
Anxiety	2	2	1
Cough	2	2	1
Dyspepsia	0	2	1

In addition, phase II/III clinical trials in Japan indicated the efficacy and safety of safinamide mesilate as add-on therapy to levodopa in Parkinson's Disease patients.[2] In this clinical trial, the most common AEs were nasopharyngitis, dyskinesia, and fall. Among these, the most common adverse drug reaction were dyskinesia and visual hallucinations (Table 2).[2]

Table 2. Incidence of patients with AEs and adverse drug reaction

	Adverse events			Adverse drug reaction		
	Placebo	Safinamide mesilate		Placebo	Safinamide mesilate	
	(N=141)	50 mg/day (N=133)	100 mg/day (N=132)	(N=141)	50 mg/day (N=133)	100 mg/day (N=132)
Nasopharyngitis	11.3	6.8	12.9	-	-	-
Dyskinesia	2.1	8.3	10.6	2.1	8.3	10.6
Fall	5.0	5.3	6.8	2.1	1.5	0.8
Contusion	2.8	3.0	5.3	-	-	-
Visual hallucinations	1.4	3.0	4.5	1.4	3.0	4.5
Back pain	3.5	0.8	3.8	-	-	-
Nausea	0.7	3.0	3.0	0.7	2.3	2.3
Conjunctivitis	0.7	-	3.0	-	-	-
Excoriation	-	-	3.0	-	-	-
Headache	0.7	3.8	1.5	-	2.3	1.5

7.3 Study Rationale

Safinamide mesilate was approved by the U.S. Food and Drug Administration (FDA) in March 2017 based on phase III clinical trials (NCT01187966 and NCT 00627640) as adjunctive treatment to levodopa in patients with Parkinson's Disease experiencing off episodes.[1, 3, 4] In addition, safinamide mesilate was approved by the Ministry of Food and Drug Safety (MFDS) in June 2020 as adjunctive therapy with levodopa-containing products in patients with end of dose motor fluctuations.[6] Previous studies demonstrated that adjunctive therapy of safinamide mesilate to levodopa improves Parkinson's Disease symptoms and "off" time.[7]

The National Institute for Health and Care Excellence (NICE) guideline 2017 regarding managing symptoms of Parkinson's Disease recommends only to add adjuvant therapy to a levodopa regimen, under specialist advice.[5] Subjects with various daily doses of levodopa from 315 mg to 1,273 mg per day were included even in the global phase 3 clinical SETTLE study, so there is no clear agreement on the optimal adjuvant therapy compared to the dose.[2,5]

Furthermore, only limited number of centers and patients from South Korea participated in previous global studies that evaluated the efficacy and safety of safinamide mesilate as an add-on therapy in Parkinson's Disease patients; only 27 Parkinson's Disease patients from 4 centers in South Korea had experienced safinamide mesilate as add-on therapy to stable dose of levodopa.[7] In this situation, to assess the efficacy and safety of safinamide mesilate according to the daily dose of levodopa is needed for Parkinson's Disease patients who need combination therapy with levodopa in South Korea. [1]

8 STUDY OBJECTIVES

8.1 Primary Objective

To evaluate the change at the 18th week from baseline in daily "off" time measured by subject diary and Parkinson's Disease Questionnaire-39 (PDQ-39) in patients with Parkinson's Disease who are receiving levodopa.

8.2 Secondary Objective

- To evaluate the change at the 18th week from baseline in below assessments:
    - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 3
    - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 4
    - King's Parkinson's disease Pain Scale (KPPS)
    - Mini-Mental State Examination (MMSE)

- To evaluate the safety of safinamide mesilate in Parkinson's Disease patients who are receiving levodopa

- To evaluate the change at the 18th week from baseline in daily “on” time without dyskinesia in patients with Parkinson’s Disease who are receiving levodopa

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multi-center, open-label, single-arm, interventional study in Parkinson's Disease patients who are receiving levodopa. Approximately 199 patients will be enrolled and will receive safinamide mesilate (hereinafter, study drug) for approximately 18 weeks (Figure 1).

This study consists of a Screening Period, Baseline Period, Treatment Period, and Taper Period. The investigators will obtain informed consent at Visit 1 (Screening Visit). Subjects who are eligible for this study can enter the study. During the Screening Period, if subjects have previously taken medication such as COMT inhibitor and/or MAO-B inhibitor, they have to undergo an appropriate wash-out period for each medication before conducting Visit 2 (Baseline). During the Treatment Period, subjects will take the study drug daily for 18 weeks, and scheduled study visits will be Visit 3 and Visit 4 (18 weeks: EOT).

Subjects will complete their participation in the clinical trial after they complete Visit 4 (EOT). For subjects who require tapering at the time of Visit 4 (EOT), they will enter a Taper Period for 1 week. The Taper Period may be omitted if the subject's daily dose of the study drug at the end of treatment is 50mg, if subjects will continue to take the study drug after the completion of the trial, or if it is considered not required by an investigator.

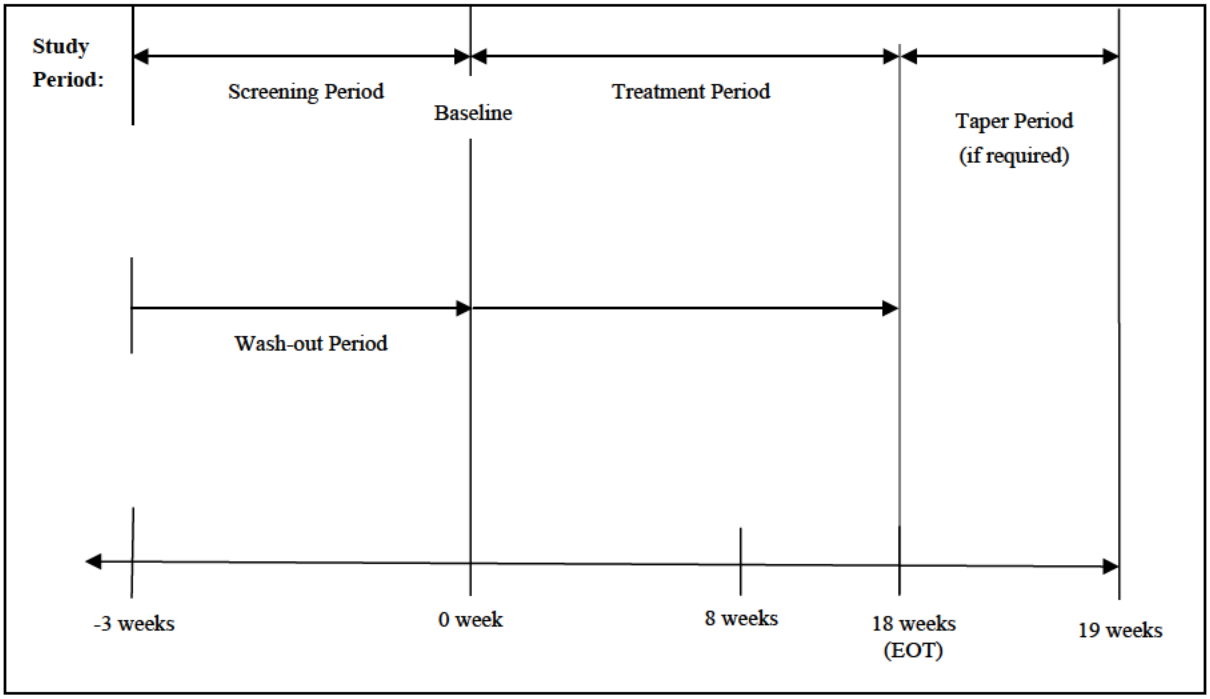

Figure 1 Overall Study Design

EOT: End of Treatment

9.1.1 Screening Period

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. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of Parkinson's Disease and receive levodopa at a stable dose for at least 4 weeks prior to the screening visit. After signed informed consent is obtained from the subject or for subjects from Legally Acceptable Representatives (LARs), a medical history interview, identification of prior and concomitant medications, identification of concomitant therapies, height, weight, physical examination, urine pregnancy test (females of childbearing potential only), 12-lead electrocardiogram (ECG; if deemed necessary by an investigator), vital signs, clinical laboratory tests (hematology, chemistry, and urinalysis), and Adverse Events (AE) assessment will be conducted for evaluation of eligibility criteria, and will include confirmation that the subject meets diagnostic criteria for Parkinson's Disease.

At Visit 1 (Screening), subjects will perform the Mini-Mental State Examination (MMSE) among the efficacy assessments. Also, a daily will be handed out to subjects and/or their caregivers, and investigator will train them how to complete the diary. Subjects who meet the eligibility criteria of the study will be instructed to complete the diary for 3 consecutive days prior to Visit 2 (Baseline).

If subjects have previously taken medication such as COMT inhibitor and/or MAO-B inhibitor, they have to undergo an appropriate wash-out period for each medication (3 days for COMT inhibitor; 14 days for MAO-B inhibitor).

9.1.2 Baseline Period

At Visit 2 (Baseline), subjects will return to the site after they complete the diary for at least 3 consecutive days. At Visit 2 (Baseline), safety assessments including AE assessment, vital signs, weight (if deemed necessary by an investigator), and physical examination will be conducted.

Efficacy assessments including Parkinson's Disease Questionnaire-39 (PDQ-39), Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 and Part 4, and King's Parkinson's disease Pain Scale (KPPS) will be conducted. The investigators will also review the completed subject diary with subjects.

The study drug will be distributed to subjects who meet the eligibility criteria at Visit 2 (Baseline). The subjects will be instructed to take the study drug every day starting from the next day after Visit 2 (Baseline).

9.1.3 Treatment Period

Subjects whose screening assessments including the wash-out period and evaluations are completed and reviewed by the investigators and who continue to meet all of the inclusion/exclusion criteria will enter the Treatment Period. Subjects will take the study drug every day for 18 weeks.

The dose of the study drug is 50 mg once a day for 2 weeks (14 days) starting from the next day after Visit 2 (Baseline), and 100 mg once a day afterwards. Subjects who need to increase the dose at the discretion of an investigator shall visit the site (unscheduled) prior to the dose increase.

Subjects whose dose cannot be increased to 100 mg/day within 4 weeks following Visit 2 (Baseline) will be dropped out from the clinical trial.

If Adverse Events (AE) occur in subjects who have increased the dose, the dose may be reduced back to 50 mg/day at the discretion of an investigator through unscheduled site visit or phone visit. After reduction from 100mg/day to 50mg/day, the dose may be increased back to 100 mg/day at the discretion of an investigator.

Subjects will return to the site at 8 weeks and 18 weeks for Visit 3 and Visit 4 (EOT), respectively. The "windows" permitted for Visit 3 (8 weeks) will be -4 weeks and +2 weeks; for Visit 4 (18 weeks: EOT) will be +/- 2 weeks. Safety assessments including AE assessment, 12-lead ECG (if deemed necessary by an investigator), vital signs, weight, physical examination, clinical laboratory tests (hematology, chemistry, and urinalysis), and urine pregnancy test (females of childbearing potential only) will be conducted according to the schedule for each visit during Treatment Period. Efficacy assessments including PDQ-39, MDS-UPDRS Part 3 and Part 4, KPPS, and MMSE will be conducted at Visit 4 (EOT). Subjects will complete the diary for at least 3 consecutive days prior to Visit 4 (EOT), and the investigators will review the completed diary together with subjects at Visit 4 (EOT).

9.1.4 Taper Period

Of the subjects who have completed 18 weeks of treatment, those who require tapering will enter a Taper Period for 1 week. After the completion of the Taper Period, subjects will return to the site for Visit 5. At Visit 5, safety assessments including AE assessment, vital signs, weight (if deemed necessary by an investigator), and physical examination will be conducted. For those subjects participating in the Taper Period, their participation in the study will be completed after the completion of Visit 5.

The Taper Period may be omitted if the subject's daily dose of the study drug at the end of treatment is 50mg, if subjects will continue to take the study drug after the completion of the trial, or if it is considered not required by an investigator. For the subjects who do not require the Taper Period, their participation in the study will be completed after the completion of Visit 4 (EOT).

9.2 Discussion of Study Design

This study is a multi-center, open-label, single-arm, interventional study to evaluate the efficacy and safety of the study drug as add-on therapy to levodopa in subjects with Parkinson's Disease according to standard clinical practice. The study drug has dopaminergic and non-dopaminergic pathways so it improves motor symptoms as well as non-motor symptoms. For this reason, this study will evaluate the "off" time and PDQ-39 as co-primary endpoints.

9.3 Selection of Study Population

Approximately 199 subjects will be enrolled at approximately 20 sites in South Korea. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to participate in this study.

9.3.1 Inclusion Criteria

To be eligible for inclusion into this trial, the subjects must fulfill all of the following criteria:

1. Male or female, age ≥19 years at the time of informed consent
2. Patients who meet the clinical diagnostic criteria of Movement Disorder Society (MDS) diagnostic criteria 2015 for Parkinson's disease, have motor fluctuations with ≥1.5 hours of "off" time throughout the day which is confirmed at the time of Screening and take levodopa 3 or more times a day
3. Parkinson's Disease patients who are receiving levodopa without COMT inhibitor and/or MAO-B inhibitor

4. Be able to maintain an accurate and complete diary with the help of a caregiver as needed, recording "on" time, "on" time with dyskinesia, "off" time, and time asleep
5. Be able to provide written informed consent
6. Patients whose cognitive function, at the discretion of an investigator, is at a level appropriate to participate in the clinical trial (i.e., with a GDS score of 3 or less or a CDR of 0.5 or less within 3 months prior to Screening)

9.3.2 Exclusion Criteria

To be eligible for inclusion into this trial, the subjects must not meet any of the following criteria:

1. Females who are planning for pregnancy, pregnant or breastfeeding
2. Prior use of safinamide
3. If patients have previously taken medication such as COMT inhibitor and/or MAO-B inhibitor, they have to take appropriate wash-out period for each medication.(3 days for COMT inhibitor; 14 days for MAO-B inhibitor)
4. Use of medications for depression or psychosis within 5 weeks prior to Screening Visit
5. History of allergic response to levodopa, or other anti-Parkinsonian agent
6. Hypersensitivity or contraindications to MAO-B inhibitors
7. Confirmed ophthalmologic history including any of the following conditions: albino subjects, family history of hereditary retinal disease, progressive and/or severe diminution of visual acuity (i.e., 20/70 on Snellen Chart), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or diabetic retinopathy.
8. Patients who did not consent to having at least 7 days of washout period prior to Visit 2, if known to take narcotic analgesics 7 days prior to Screening Visit (eg, pethidine hydrochloride-containing products, tramadol hydrochloride, or tapentadol hydrochloride)
9. History of serotonergic medications administration (eg, tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–noradrenaline reuptake inhibitors, selective noradrenaline reuptake inhibitor, or noradrenergic and serotonergic antidepressant) within 5 weeks prior to the Screening Visit
10. Administering central nervous system stimulants (eg, methylphenidate hydrochloride, lisdexamfetamine mesilate)
11. Administering dextromethorphan
12. Patients with clinically significant liver function abnormalities defined as > 1.5 times of the upper limit of the normal range of total bilirubin or > 3 times of the upper limit of the normal range of ALT or AST; re-examination and re-screening are allowed once within the screening period
13. Have a history of hypersensitivity to any of the ingredients of the product
14. Currently enrolled in another clinical trial or used any investigational drug/biologics or device within 30 days or 5 × the half-life, whichever is longer, preceding informed consent

9.3.3 Removal of Subjects from Therapy or Assessment

The investigators may withdraw the subjects from the study at any time for safety or administrative reasons and noncompliance with study procedures (e.g., omission of efficacy evaluation, omission of subject diary completion, use of prohibited medication or therapy, deviation from the dose limitation of concomitant medication, deviation from the dose increase

schedule of study drug, etc.) Also, subjects whose dose of study drug cannot be increased to 100 mg/day within 4 weeks of Visit 2 (Screening) will be withdrawn from the study. Subjects may stop the study drug administration or withdraw from the study at any time for any reason.

Subjects who prematurely discontinue the administration of the study drug should visit the site as soon as practicable (preferably within 7 days) to complete the Premature Discontinuation Visit.

9.4 Treatment

9.4.1 Treatment Administered

Subjects who are enrolled in this study will be treated with the study drug for approximately 18 weeks. The dose and administration of the study drug is as follow:

The dose of the study drug is 50 mg once a day for 2 weeks (14 days) starting from the next day after Visit 2 (Baseline), and 100 mg once a day afterwards. Subjects who need to increase the dose at the discretion of an investigator shall visit the site (unscheduled) prior to the dose increase.

If Adverse Events (AE) occur in subjects who have increased the dose, the dose may be reduced back to 50 mg/day at the discretion of an investigator through unscheduled site visit or phone visit. After reduction from 100mg/day to 50mg/day, the dose may be increased back to 100 mg/day at the discretion of an investigator.

If, following the dose increase to 100mg/day, moderate or severe hepatic impairment occurs according to Child-Pugh classification, study drug should be administered as per below guideline.

- Moderate hepatic impairment (Child-Pugh B): Do not exceed 50 mg once daily
- Severe hepatic impairment (Child-Pugh C): Contraindicated (Termination of study drug required)

[Child-Pugh Classification][8]

Parameter	Abnormal value or degree	Grade Score
Encephalopathy*	None 1 and 2 3 and 4	1 2 3
Ascites	None Mild Moderate	1 2 3
Total bilirubin (mg/dL)	< 2 2 - 3 > 3	1 2 3

Albumin (g/dL)	> 3.5 2.8 - 3.5 < 2.8	1 2 3
Prothrombin Time (seconds)	< 4 4 - 6 > 6	1 2 3

*Grade 0: Normal values for cognition, behavior, neurological examination and ECG
Grade 1: Anxiety, sleep disorder, easily irritated/excited, tremor, dysgraphia, 5 cps wave
Grade 2: Narcolepsy, confusion of time, inappropriate behavior, asterixis, ataxia, decreased triphasic wave
Grade 3: Narcosis, stupor, confusion of sense of space, excessive reflection, contracture, decreased brain wave
Grade 4: Coma, lack of personality/action, decerebrate rigidity, slow delta wave of 2-3 cps

Total Score	Class	Seriousness
5 - 6	A	Mild
7 - 9	B	Moderate
10 -15	C	Severe

9.4.2 Identity of Investigational Products

Study drug will be provided in a strength of 50 mg only. Subjects whose daily dose of study drug is 100 mg will be instructed to take 2 tablets of study drug at once daily. No comparator will be used in this study.

9.4.2.1 Study drug code: ME2125 Chemical Name of ME2125

Generic name: safinamide mesylate

Chemical name: (S)-2- [[4-[(3-fluorophenyl) methoxy]phenyl]methyl]aminopropanamide methanesulfonate

Molecular formula: $C_{17}H_{19}FN_2O_2 \bullet CH_4O_3S$

Molecular weight: 398.45

9.4.2.2 Labeling for Study Drug

The label of study drug will include the following information as per local regulation:

- "For clinical trial use only" or similar wording

- Name/identifier of study drug including formulation, route of administration, quantity of dose units, strength, etc. as required.
- Lot number/batch number
- Name, address, and contact number of the sponsor
- Expiration date
- Storage conditions
- "Keep out of the reach of children" statement
- Reference code to identify the clinical trial
- Subject identification number and treatment number
- Special precautions for storage and handling according to the approved label

9.4.2.3 Storage Conditions

Study drug will be stored in accordance with the approved label as follow:

Storage conditions: tight container, store at room temperature (1°C to 30°C)

Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigators 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 Group

This is a multi-center, open-label, single-arm, interventional 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 the study drug daily for approximately 18 weeks as add-on therapy to levodopa. There is no randomization in this study.

9.4.4 Selection of Doses and Method of Administration in the Study

The dose of the study drug will start with 50 mg administered orally once daily for 2 weeks (14 days) starting from the next day after Visit 2 (Baseline) and will be increased to 100 mg once daily afterwards.

The study drug is provided in the form of a 50 mg tablet. If administering 50 mg/day, administer 1 tablet once daily. If administering 100 mg/day, administer 2 tablets once daily.

9.4.5 Timing of Study Drug Administration

The study drug will be taken at the same time each day without regard to meals.

The study drug will be administered at the dose prescribed at the regular visits from the next day after that visit until the day of the next regular visit.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Medications / Concomitant Therapy

Prior medication within 1 month and current medications (including levodopa) will be recorded at Visit 1 (Screening). The information on prior medication will include the name of the product or ingredient, dose and administration (daily dose and dose unit), administration period (start date and end date), and purpose of administration.

Any concomitant medications and concomitant therapy during this study (starting at the date of informed consent) will be recorded at each visit. The information on concomitant medications (including levodopa) will include the name of product or ingredient, dose and administration (daily dose and dose unit), administration period (start date and end date), and purpose of administration.

The information on concomitant therapy includes the name of concomitant therapy, period of concomitant therapy (start date and end date), and purpose of concomitant therapy. Any Adverse Events (AE) or medical status shall be recorded during the administration of concomitant medication or use of concomitant therapy.

- Addition and dose adjustment of anticholinergic and/or amantadine during the study period will be based on an investigator's judgment.

CCI [redacted]

9.4.7.1 Drug-Drug Interactions

The investigators should carefully evaluate the potential of interaction before prescribing any concomitant medication in consideration of the package insert of safinamide. Drugs with clinically significant interaction with safinamide are listed on Appendix 1.

9.4.7.2 Prohibited Concomitant Medications and Therapies

Prohibited concomitant medications and therapies are listed below.

Prohibited medications:

- Acetylcholinesterase inhibitors
- COMT inhibitor
- Any investigational drugs/biologics
- All the contraindicated medications listed on the approved label of study drug (Appendix 1)

Prohibited therapies:

- DBS(Deep brain stimulation)
- Surgical treatment
- LCIG(Levodopa-carbidopa intestinal gel) therapy

Concomitant medications and therapies listed above will be prohibited during the trial participation. Nevertheless, if continuous use of any prohibited medication/therapy is indicated for treatment of the subject during the trial, in the judgment of an investigator who treats the subject's other medical symptoms, the subject must discontinue the trial immediately, and the details should be recorded in the Case Report Form (CRF).

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical Research Associates (CRA) will review treatment compliance during site visits and at the completion of the study.

At 8 weeks and 18 weeks during the Treatment Period, and if applicable, at 19 weeks during the Tapering Period, at unscheduled visits, or at premature termination visit, unused study drugs received at last visit will be returned to the investigators or designee. The medication will be inventoried, and the percent compliance will be calculated by dividing the number of doses administered by subjects by the number of days of the treatment period.

9.4.9 Drug Supplies and Accountability

The investigators or the designee 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 requirements.

Under no circumstances will the investigators 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. 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 investigators or the designee 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 depot 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 depot. 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 depot must be boxed, sealed, and shipped back to the depot following all local regulatory requirements. 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/Baseline Assessments

9.5.1.1.1 Demography

Subject demographic information will be collected at Visit 1 (Screening). Demography information includes year and month of birth (or age) and sex.

9.5.1.1.2 Height

Height will be collected at Visit 1 (Screening).

9.5.1.1.3 Medical History

Medical and surgical history and current medical conditions will be recorded at Visit 1 (Screening). All medical history within 6 months and surgical history within 3 years must be recorded on the medical history CRF.

9.5.1.2 Efficacy Assessments

The procedure for the efficacy assessments consists of the subject diary and questionnaire examination. Each questionnaire test below (PDQ-39, MDS-UPDRS part 3 and part 4, KPPS, MMSE) is to be performed in the “on” state of the subject, and is tested in the “off” state only when it is difficult to evaluate it in the “on” state.

9.5.1.2.1 Subject Diary

Information on daily “off” time and “on” time will be collected by subject diary. Subjects and/or their caregivers will receive a subject diary, and investigator will train them how to complete the diary at Visit 1 (Screening).

Subjects will complete the diary for at least 3 consecutive days prior to each visit where completed diary review is conducted (Visit 2, Visit 4) and the diary will be maintained by the subject over a 24-hour period each day the diary is being completed. At 30-minute intervals throughout the period, the subject/caregiver will record whether the subject is currently 1) in an “on” phase, 2) in an “on” phase with dyskinesia, 3) in an “off” phase, or 4) asleep. Subjects will also check when they take their levodopa throughout the day.

An “off” phase will be defined as lack of mobility, bradykinesia, or akinesia whereas in an “on” phase, the subject will be functioning as well as can be expected for that subject, irrespective of whether or not he/she is having dyskinesia.

The daily “off” time is defined as the mean of the total daily “off” time during the last two 24-hour diary recording periods prior to the visit. The daily “on” time is defined as the mean of the total daily “on” time during the last two 24-hour diary recording periods prior to the visit.

Investigators will review the completed subject diary with subjects at Visit 2 (Baseline) and Visit 4 (EOT) and record the results of the subject diary in CRF. At Visit 4 (EOT), subjects will submit the subject diary to clinical trial staff or investigators.

9.5.1.2.2 PDQ-39

To assess the efficacy of non-motor symptoms and motor symptoms in subjects, Parkinson’s Disease Questionnaire (PDQ-39) will be used. The PDQ-39 consists of 39 questions measuring eight dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). A summary index score can also be calculated. The contents of the instrument were developed on the basis of exploratory in-depth interviews with subjects with Parkinson's Disease, and the reliability, validity and sensitivity to change of the instrument were then assessed in a number of large-scale surveys. The questionnaire will be provided in Korean to the subjects.

Once a subject completes PDQ-39, the investigators will record the result in CRF.

9.5.1.2.3 MDS-UPDRS Part 3

To assess the efficacy of motor symptoms in subjects, The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 will be used. The MDS-UPDRS is a rating tool used to follow the longitudinal course of Parkinson's Disease. It is made up of four parts that assess the following: Part 1 – Non-motor Aspects of Experiences of Daily Living; Part 2 – Motor Aspects of Experiences of Daily Living; Part 3 – Motor Examination; and Part 4 – Motor Complications. The information for these ratings is obtained through an interview with the subject and caregiver if available.

MDS-UPDRS Part 3 evaluates the motor function of the subject. This section of the scale consists of 18 items, with 33 separate ratings being performed on a scale from 0 (normal) to 4 (severe). Specific instructions are provided for the testing of each item, which should be followed in all instances. Raters demonstrate while describing tasks the subject is to perform and rate function immediately thereafter. The subject's speech, facial expressions, ability to arise from a chair, posture, gait, postural stability (retropulsion test), and body bradykinesia are assessed. In addition, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements (open/close), rapid alternating movements of hands (pronation/supination), and leg agility are assessed.

After completing MDS-UPDRS Part 3, the investigators will record the result in CRF.

9.5.1.2.4 MDS-UPDRS Part 4

In MDS-UPDRS Part 4, raters use historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Raters will use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. This section has instructions for the raters and also instructions to be read to the patient, and integrates patient-derived information with the rater's clinical observations and judgments. In Part A, the duration of, disability caused by, and functional impact of any dyskinesias experienced by the subject are rated on a scale from 0 to 4. Clinical fluctuations are assessed in Part B, which includes time spent in "off" state (estimation of the proportion of the waking day spent in the "off" state), functional impact of fluctuations, the predictability and timing of the subject's "off" periods, and proportion of the "off" state having painful dystonia.

After completing MDS-UPDRS Part 4, the investigators will record the result in CRF.

9.5.1.2.5 KPPS

To assess pain scale in subjects, King's Parkinson's Disease Pain Scale KPPS will be used. KPPS is Parkinson's Disease-specific pain scale. Its seven domains include 14 items; each item is scored by severity (0-3) multiplied by frequency (0-4), resulting in a subscore of 0 to 12 with a total possible score range from 0 to 168.

After completing KPPS, the investigators will record the result in CRF.

9.5.1.2.6 MMSE

To assess cognition in subjects, the Mini-Mental State Examination (MMSE) will be used. The MMSE is a brief practical screening test for cognitive dysfunction. The test consists of relevant sections (awareness of time, awareness of location, memory, attention, as well as ability to calculate, ability to recall, ability to name names, repetition, understanding, reading, writing, and drawing) and has a total possible score of 30. It is useful as a quick method to assess the severity of cognitive dysfunction.

After completing the MMSE, the investigators will record the result in CRF.

9.5.1.3 Safety Assessments

Safety assessment will consist of determining and recording all adverse events (AEs) and other events of special interests including pregnancy, breast feeding, overdose, abuse or misuse, lack of therapeutic efficacy, medication error, off label use, occupational exposure, and suspected transmission of an infectious agent; regular clinical laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and the performance of physical examinations as detailed in Table 3.

9.5.1.3.1 Adverse Events

Adverse Event (AE) refers to an unfavorable and unintended sign (e.g. abnormal laboratory finding) associated with administration/use of study drug, symptom, or disease, whether or not related to the medicinal (investigational) product. For this study, the study drug is safinamide mesilate.

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 (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.
- Recurrence of an intermittent medical condition (e.g., 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 after Visit 1 (Screening) through the last visit. 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 investigators 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 CRF.

All AEs must be followed until the end of the study (subject's last visit). All Serious Adverse Events (SAEs) must be followed to resolution or, if resolution is unlikely, to stabilization.

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

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 CRF. 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 from those used for seriousness (see Section 9.5.1.3.2 for the definition of an SAE).

Assessing Relationship to Study Drug

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

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable
- Whether the event is known to be associated with the study drug 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

In this study, the evaluation of the relationship between the drug and each adverse event according to the following evaluation criteria shall be recorded in the CRF.

Causality	Description
Certain	① The relationship before and after with the administration·use of the drug is reasonable, and it is not explained by other medicines, chemicals, or concomitant diseases. ② Showing a clinically reasonable response when the drug administration is discontinued.
Probable/likely	① The temporal relationship with the administration·use of the drug is reasonable, and it does not appear to be related to other medicines, chemicals, or concomitant diseases. ② Showing a clinically reasonable response when the drug administration is discontinued.
Possible	① The temporal relationship with the administration·use of the drug is reasonable, but it is also explained as depending on other drugs, chemicals, or concomitant diseases. ② In case information regarding discontinuation of the drug is insufficient or unclear
Unlikely	① Temporary cases that are unlikely to have a causal relationship with the administration·use of the drug. ② In case a reasonable explanation of the occurrence is possible with other drugs, chemicals, or potential diseases
Conditional/unclassified	① In case more data is needed for proper evaluation or when additional data is being reviewed
Unassessable/unclassifiable	① In case it cannot be determined as information is insufficient or conflicting, and it cannot be supplemented or verified

Outcome of Adverse Events

- Recovered
- Recovering
- Not recovered
- Recovered with side effects

- Death
- Unknown

9.5.1.3.2 Serious Adverse Events and Events Associated with Special Situations

SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE 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)
- Results in inpatient hospitalization
- Requires 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)
- Is a medically significant event

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 the study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; lack of efficacy. 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 CRF 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 “AE” (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

9.5.1.3.3 Laboratory Measurements

Laboratory tests to be performed according to the guideline of each site. In case that laboratory test is performed, laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.3.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Na, K, Ca, Cl, CPK, BUN, Creatinine, Uric acid, Total bilirubin, Albumin, Total protein, ALT, AST, γ-GTP, Alkaline phosphatase
Urinalysis	Specific gravity, pH, Protein, Glucose, Bilirubin, Ketones, RBC, WBC, Creatinine

9.5.1.3.4 Vital Signs and Weight Measurements

Vital sign measurements (i.e., systolic and diastolic blood pressure [mmHg], pulse [beats per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 3 by a validated method.

Vital signs will include blood pressure, pulse, and body temperature. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. All blood pressure measurements should be performed on the same arm, preferably by the same person.

Documentation of vital signs will be included in the source documentation at the site. Clinically significant abnormal findings at Visit 1 (Screening) will be recorded on the medical history CRF. Only changes from screening vital signs findings that meet the definition of an AE will be recorded on the Adverse Event CRF.

9.5.1.3.5 Physical Examinations

Physical examinations will be performed as designated in Table 3. Documentation of the physical examination will be included in the source documentation at the site. Clinically significant abnormal findings at Visit 1 (Screening) will be recorded on the medical history CRF. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Event CRF.

9.5.1.3.6 Electrocardiograms

ECG will be performed as designated in Table 3. An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.3.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Event CRF.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for this study.

Table 3. Schedule of Procedures/Assessments in Study ME2125-M082-401

Visit	Visit 1	Visit 2	Visit 3	Visit 4 (EOT)	Visit 5	Premature Discontinuation Visit[C]
Period	Screening Period	Baseline	Treatment Period[a]		Taper Period[b]	
Week	–3 weeks to –1 day	0	8 weeks	18 weeks	19 weeks	
Visit window	0	0	- 4 weeks / + 2 weeks	± 2 weeks	±1 week	
Informed Consent	x					
Eligibility Assessment	x	x				
Demography[d]	x					
Height	x					
Weight	x	(x)	(x)	x	(x)	x
Medical History[e]	x					
Prior and Concomitant Medications/ Concomitant Therapies[f]	x	x	x	x	x	x
Clinical Laboratory Tests[g]	x		(x)	x	(x)	x
12-lead ECG[h]	(x)		(x)	(x)	(x)	(x)
Vital Signs[i]	x	x	x	x	x	x
Urine Pregnancy Test[j]	x			x		x
Physical Examinations	x	x	x	x	x	x
Dispense study drug[k]		x	x	x*		x*
Study drug administration[l]		→			x	

Visit	Visit 1	Visit 2	Visit 3	Visit 4 (EOT)	Visit 5	Premature Discontinuation Visit[c]
Period	Screening Period	Baseline	Treatment Period[a]		Taper Period[b]	
Week	–3 weeks to –1 day	0	8 weeks	18 weeks	19 weeks	
Visit window	0	0	- 4 weeks / + 2 weeks	± 2 weeks	±1 week	
Retrieve unused study drug			x	x	x	x
Check study drug compliance			x	x	x	x
AE assessment[m]	→				x	x
Efficacy assessment						
Review of Subject diary Card[n]: Daily "off" time and "on" time	x*	x		x		x
PDQ-39		x		x		x
MDS-UPDRS Part 3		x		x		x
MDS-UPDRS Part 4		x		x		x
KPPS		x		x		x
MMSE	x[o]			x		x

12-lead ECG, Electrocardiogram; EOT, End of Treatment; KPPS, King's Parkinson's disease Pain Scale; MMSE, Mini-Mental State Examination; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire-39

a Regular site visits will be determined by the treating investigators according to standard clinical practice as long as visits are made within the visit window

b Subjects who complete 18 weeks of treatment may undergo a Taper Period for 1 week if necessary The Taper Period may be omitted if the subject's daily dose of study drug at the end of treatment is 50mg, if subjects will continue to take the study drug after the completion of the trial, or if it is considered not required by an investigator

For the subjects who do not require the Taper Period, their participation in the study will be completed after the completion of Visit 4 (EOT)

c A subject who prematurely discontinues taking the study drug should return to the site as soon as practicable after discontinuing study drug (preferably within 7 days) to complete Premature Discontinuation Visit Following the completion of Premature Discontinuation Visit, the subjects who require taper will undergo a Taper Period for 1 week

d Demography information includes year and month of birth (age) and sex

e All medical history within 6 months and surgical history within 3 years will be recorded in the medical history CRF

f Prior medication within 1 month and current medications (including levodopa) will be recorded at Visit 1 (Screening)
The information on prior medication will include the name of the product or ingredient, dose and administration (daily dose and dose unit), administration period (start date and end date), and purpose of administration

Any concomitant medications and therapies during this study (starting at the date of informed consent) will be recorded at each visit The information on concomitant medications (including levodopa) will include the name of product or ingredient, dose and administration (daily dose and dose unit), administration period (start date and end date), and purpose of administration The information on concomitant therapies should include the name of therapy, therapy period (start date and end date), and purpose of therapy Any Adverse Events or medical status shall be recorded during the administration of concomitant medication or use of concomitant therapy

g Clinical laboratory tests to be performed according to the guideline of each site

At Visit 3 and Visit 5, clinical laboratory tests will only be performed if considered necessary by an investigator based on the subject's symptoms
In case of tests related to liver function, a re-test or re-screening is allowed once during the Screening period

h ECG will only be performed if considered necessary by an investigator based on the subject's symptoms

i Vital signs will include blood pressure, pulse, and body temperature Vital signs will be measured preferably after the subject has rested comfortably for 5 minutes at each visit

j Females of childbearing potential only A dipstick will be used for urine pregnancy testing

k Subjects will administer the study drug at the dose prescribed at regular visits from the next day after that visit to the day of the next regular visit
*It is not necessary to distribute the study drug at Visit 4 (EOT) or Premature Discontinuation Visit to subjects who do not proceed with the tapering period

l Study drug will be distributed to subjects who continue to meet the eligibility criteria at Visit 2 (baseline), and they are instructed to take the study drug daily for the next 18 weeks from the next day after Visit 2 (baseline) The dose of the study drug is started at 50 mg once a day for 2 weeks (14 days) starting from the next day after Visit 2 (Baseline) and is increased to 100 mg once a day afterwards Subjects who need to increase the dose at the discretion of an investigator shall visit the site (unscheduled) prior to the dose increase If an Adverse Event occurs following the increase in dose, the investigator may reduce the dose back to 50 mg/day through unscheduled site visit or phone visit After reduction from 100mg/day to 50mg/day, the dose may be increased back to 100 mg/day at the discretion of the investigator

m All adverse events (AEs) should be recorded after Visit 1 (Screening) to the last visit, regardless of relevance to the study drug or the procedure, and all AEs should be followed up until the end of the study (subject's last visit) During the AE evaluation, events associated with special situations listed in Section 9 5 4 2 are also evaluated

All serious adverse events (SAEs) should be followed up until resolution or, if no resolution is possible, until stabilization

n At Visit 2 (Baseline) and Visit 4 (EOT), the investigators will review the completed subject diary with subjects Subjects must completed the diary at least three consecutive days prior to each visit where completed diary review is conducted (Visit 2, Visit 4) At Visit 4 (EOT), subjects shall submit the diary to the investigators or other clinical trial staff

* Subjects and/or their caregivers will receive a subject diary and investigator will train them how to complete the diary at Visit 1 (Screening) Subjects who meet the eligibility criteria of the study will be instructed to complete the diary for 3 consecutive days prior to Visit 2 (Baseline)

o The result from MMSE conducted at Visit 1 (Screening) will be the baseline result If MMSE was not conducted at Visit 1 (Screening), it can be performed at Visit 2 (Baseline) and then the MMSE result from Visit 2 (Baseline) will be considered as baseline result In other words, if MMSE is conducted at either Visit 1 (Screening) or Visit 2 (Baseline), the subject will be considered to have completed the MMSE

9.5.2.2 Description of Procedures/Assessments Schedule

9.5.2.2.1 Visit 1 (Screening, -3 weeks ~ -1 day)

All procedures will be conducted after obtaining informed consent from subjects who want to participate in this clinical trial. After obtaining informed consent, the following procedures will be performed to establish eligibility for the trial:

- Demography
- Height
- Weight
- Medical history
- Prior and concomitant medications
- Concomitant therapies
- Clinical laboratory tests
- 12-lead ECG: if deemed necessary by an investigator based on subject's symptoms
- Vital signs
- Urine pregnancy test
- Physical examinations
- AE assessment
- Subjects and/or their caregivers receive a subject diary and investigator will train them how to complete a diary.
- Conduct the MMSE among the efficacy assessments.

During Screening Period, if subjects have previously taken medication such as COMT inhibitor and/or MAO-B inhibitor, they have to undergo an appropriate wash-out period for each medication.

Subjects who meet the eligibility criteria of the study will be instructed to complete the diary for 3 consecutive days prior to Visit 2 (Baseline).

9.5.2.2.2 Visit 2 (Baseline, 0 week)

At Visit 2 (Baseline), the following procedures will be performed:

- Reconfirmation of eligibility assessment
- Weight: if deemed necessary by an investigator
- Concomitant medications
- Concomitant therapies
- Vital signs
- Physical examinations
- Study drug dispensation
- AE assessment
- Efficacy assessments including PDQ-39, MDS-UPDRS Part 3 and Part 4, and KPPS, are performed. The completed subject diary will be reviewed by an investigator together with a subject.

If MMSE was not conducted at Visit 1 (Screening), it can be performed at Visit 2 (Baseline). If MMSE is conducted at either Visit 1 (Screening) or Visit 2 (Baseline), the subject will be considered to have completed the MMSE.

9.5.2.2.3 Visit 3 (8 weeks, -4/+2 weeks)

At Visit 3, the following procedures will be performed:

- Weight: if deemed necessary by an investigator
- Concomitant medications
- Concomitant therapies
- Clinical laboratory tests
- 12-lead ECG: if deemed necessary by an investigator based on subject's symptoms
- Vital signs
- Physical examinations

- Study drug dispensation
- Unused study drug return
- Study drug compliance check
- AE assessment

9.5.2.2.4 Visit 4 (EOT; 18 weeks, +/-2 weeks)

At Visit 4 (EOT), the following procedures will be performed:

- Weight
- Concomitant medications
- Concomitant therapies
- Clinical laboratory tests
- 12-lead ECG: if deemed necessary by an investigator based on subject's symptoms
- Vital signs
- Urine pregnancy test
- Physical examinations
- Dispensation of study drug(only if tapering period is conducted)
- Return of unused study drug
- Check compliance of the study drug
- AE assessment
- Efficacy assessments including PDQ-39, MDS-UPDRS Part 3 and Part 4, KPPS, and MMSE are performed. The completed subject diary will be reviewed by an investigator with a subject.

Of the subjects who have completed Visit 4(EOT), those who require tapering will enter a Taper Period for 1 week. After the completion of the Taper Period, subjects will return to the site for Visit 5.

The Taper Period may be omitted if the subject's daily dose of study drug at the end of treatment is 50mg, if subjects will continue to take the study drug after the completion of the trial, or if it is considered not required by an investigator. For the subjects who do not require

the Taper Period, their participation in the study will be completed after Visit 4, the End of Treatment Visit.

If a subject is withdrawn from the study before Visit 4 (EOT), Premature Discontinuation Visit should be completed as soon as practicable after discontinuing study drug (preferably within 7 days). Following the completion of Premature Discontinuation Visit, subjects who require taper will undergo a Taper Period for 1 week. Then the subjects will return to the site for Visit 5. For the subjects who do not require a Taper Period, Premature Discontinuation Visit would be their last visit in the study.

9.5.2.2.5 Visit 5 (19 weeks, +1 week)

After the completion of Taper Period, subjects will undergo the following examinations at Visit 5:

- Weight: if deemed necessary by an investigator
- Concomitant medications
- Concomitant therapies
- Clinical laboratory tests: if deemed necessary by an investigator based on subject's symptoms
- 12-lead ECG: if deemed necessary by an investigator based on subject's symptoms
- Vital signs
- Physical examinations
- Unused study drug return
- Study drug compliance check
- AE assessment

9.5.2.2.6 Unscheduled Visit

Subjects can additionally visit separately from a scheduled visit if medical treatment is needed in case of abnormal test result or AE occurs, or follow-up is needed after the occurrence of AE.

Subjects may conduct an unscheduled visit after Visit 2 (Baseline) if examination is required prior to increasing the dose of study drug (from 50 mg/day to 100 mg/day).

If the dose reduction (from 100mg/day to 50mg/day) is required due to events such as AE, the dose may be reduced back to 50mg/day at the discretion of an investigator through

unscheduled site visit or phone visit. In the case of a phone visit, the information such as date of study drug dose change (start date of dose reduction) and relevant Adverse Events shall be collected.

If subjects need to increase the dose back to 100mg/day after the reduction to 50mg/day, they may conduct an unscheduled site visit and the dose may be increased back to 100mg/day at the discretion of an investigator.

9.5.3 Appropriateness of Measurements

All clinical assessments performed in this study are standard measurements commonly used in studies of Parkinson's Disease.

9.5.4 Reporting of Serious Adverse Events 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 drug, must be reported on a completed SAE form as soon as possible but no later than 24 hours from the date an investigator becomes aware of the event.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigators to be related to the study drug 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 an 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 site case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Events Associated with Special Situations

The following special situations must be collected and reported in the same manner as SAEs regardless of occurrence of adverse events.

- Pregnancy: paternal/maternal exposure
- Breastfeeding
- Lack of therapeutic efficacy
- Drug interactions
- Suspected transmission of infectious agents
- Overdose, abuse, off-label use, misuse, mediation error, and occupational exposure
- Suspected or confirmed falsified medicinal product

9.5.4.2.1 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 from the last day of administration of the study drug, or any exposure to study drug through breastfeeding during study treatment or within 28 days from the last day of administration of the study drug, 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 (refer to Section 9.5.4.1).

Pregnancies or exposure to the study drug through breastfeeding must be reported as soon as possible but no later than 24 hours from the date an investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to the 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. A subject who becomes pregnant may remain in the study if an investigator judges that the potential benefit to the subject outweighs any potential risk to the subject or the fetus, and the subject gives informed consent for further participation.

9.5.4.2.2 Reporting of Lack of Efficacy

"Efficacy" is defined as:

- The ability of an intervention to produce desired beneficial effect in expert hands and under ideal circumstances
- In pharmacology, the ability of a drug, biologic, or device to produce desired therapeutic effect independent of potency (amount of the product needed for desired effect).

"Effect" is defined as the result produced by an action. Lack of efficacy/effect is, therefore evidence of less than the expected effect of a product. There might be subpopulations that have a higher risk for lack of efficacy/effect; in order to identify such cases, one needs to consider the types of events that may be reported in such situations for the specific product and indication.

All AEs associated with lack of efficacy should be collected on the Adverse Event CRF and reported in an expedited manner using the SAE form regardless of seriousness.

9.5.4.2.3 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. Intentional and inappropriate use of study drug not in accordance with the prescribed or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
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 CRF 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 CRF.

9.5.4.3 Expedited Reporting

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

9.5.4.4 Regulatory Reporting of Adverse Events

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

9.5.5 Completion/Discontinuation of Subjects

In this study, subjects are assumed to have completed the clinical trial upon their completion of Visit 4 (EOT).

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 Table 3.

An 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 the following reasons: AE, lost to follow-up, withdrawal of consent by subject, lack of efficacy, noncompliance with study procedure, impossibility to increase study drug dose, pregnancy, study terminated by sponsor, or other.

A subject removed from the study for any reason may not be replaced.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may 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 CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF 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 CRF must follow the instructions described in the CRF Completion Guidelines. The investigators have ultimate responsibility for the collection and reporting of all clinical data entered on the CRF.

The investigators must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai Korea Inc. and should not be made available in any form to third parties without written permission from Eisai Korea Inc., except for authorized representatives of Eisai Korea Inc. 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 CRF and external data (e.g., 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 statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of this study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

The descriptive statistics for continuous variables are the numbers of subjects, mean, standard deviation, median, minimum, maximum, and for categorical variables are the numbers of subjects and percentage. The statistical testing for efficacy endpoints is conducted using the two-sided test at a 2.5% significance level.

9.7.1.1 Study Endpoints

9.7.1.1.1 Primary Endpoints

- Change at the 18th week from baseline in daily “off” time

- Change at the 18th week from baselines in PDQ-39 score

9.7.1.1.2 Secondary Endpoints

- Change at the 18th week from baseline in below assessments:
  - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 3
  - Movement Disorder Society-Unified Parkinson's Disease Rating (MDS-UPDRS) Part 4
  - King's Parkinson's disease Pain Scale (KPPS)
  - Mini-Mental State Examination (MMSE)
- Safety of safinamide mesilate
- Change at the 18th week from baseline in daily "on" time without dyskinesia

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set (SAS) is the group of subjects who received at least 1 dose of study drug and completed at least 1 post-dose safety assessment. The Full Analysis Set (FAS) is the group of subjects who received at least 1 dose of study drug and had at least 1 post-dose daily "off" time or PDQ-39. The Per Protocol Set (PPS) is for subjects who have fully complied with the study protocol. The details of the evaluability criteria will be determined prior to database lock and will be specified in the statistical analysis plan.

9.7.1.3 Subject Disposition

The disposition of subjects will be tabulated as follows:

- Number of screened subjects
- Number of screening failed subjects and reasons for screening failure
- Number of discontinued subjects and reasons for discontinuation
- Number of subjects who completed the study

The analysis set of subjects will be tabulated as follows:

- Number of subjects for the SAS
- Number of subjects who were excluded from the SAS and reasons
- Number of subjects for the FAS
- Number of subjects who were excluded from the FAS and reasons

- Number of subjects for the PPS
- Number of subjects who were excluded from the PPS and reasons

9.7.1.4 Demography

Demography for the SAS and FAS will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, height, weight; categorical variables include sex, age group.

9.7.1.5 Medical History

All investigator terms for medical history recorded in the CRF will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number (percentage) of subjects who have medical history will be summarized using descriptive statistics on the SAS. The medical history will be classified by SOC and PT.

Surgical history will be performed on the SAS. The number (percentage) of subjects with surgical history will be summarized. The history of surgical operation will be classified according to SOC and PT.

9.7.1.6 Prior and Concomitant Medications

All investigator terms for medications recorded in the CRF will be coded to the Anatomical Therapeutic Chemical (ATC) code. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the SAS by ATC class. If the SAS and FAS differ substantially, then the prior and concomitant medications summaries will be repeated on the FAS.

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 are 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 Visit 4 (EOT) Visit. All medications will be presented in subject data listings.

9.7.1.7 Efficacy Analyses

All efficacy analysis will use FAS as the primary population and PPS as the secondary population. Efficacy data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Each variable and the difference from baseline will be used for summary statistics.

9.7.1.7.1 Primary Efficacy Analyses

Two primary efficacy parameters, which are daily "off" time and PDQ-39, will be analyzed.

The daily "off" time will be analyzed using a paired t-test on the change at the 18th week from baseline. The descriptive statistics for the daily "off" time will be summarized by each visit.

The PDQ-39 will be analyzed using a paired t-test on the change at the 18th week from baseline. The descriptive statistics for the PDQ-39 will be summarized by each visit.

9.7.1.7.2 Secondary Efficacy Analyses

For the following items, the descriptive statistics will be summarized by each visit, and it will be analyzed using a paired t-test on the change at the 18th week from baseline.

- MDS-UPDRS Part 3
- MDS-UPDRS Part 4
- KPPS
- MMSE
- Daily "on" time without dyskinesia

9.7.1.8 SAFETY ANALYSES

All safety analyses will be performed on the SAS. Safety data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include Treatment-Emergent Adverse Events (TEAEs), clinical laboratory parameters, and vital signs.

9.7.1.8.1 Extent of Exposure

Descriptive statistics for the extent of exposure during the study period will be summarized.

The extent of exposure to the study drug should be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed.

Compliance for the study drug will be calculated on the basis of the number of tablets dispensed, lost and returned. Summaries will provide descriptive summary statistics and number (percentage) of subjects below 80%, between 80% and 120%, and greater than 120%.

9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). AEs will be coded to the MedDRA (Version 23.0 or higher) Lower Level Term (LLT) closest to the verbatim term. The linked MedDRA PT and primary 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 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 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 will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigators to be related to the study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized using the SAS. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by dose level and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and PT will be calculated. Incidence (%) by causal relationship with study drug and by severity will also be calculated. For clinically significant events, time of onset, and recovery will be reported.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent Serious Adverse Events (SAEs) will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from the study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from the study drug will be provided.

9.7.1.8.3 Laboratory Values

For all quantitative parameters listed in Section 9.5.1.3.3, the actual value and the change at the 18th week from baseline will be summarized using descriptive statistics. Qualitative parameters listed in Section 9.5.1.3.3 will be summarized using frequencies (number and percentage of subjects), and changes at the 18th week from baseline will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and 18 weeks results.

9.7.1.8.4 Vital Signs and Weight

Descriptive statistics for the vital sign parameters (systolic and diastolic blood pressure, pulse, body temperature) and weight will be presented by each visit.

9.7.1.9 Other Analyses

Levodopa dose administered during the study will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Efficacy analyses will be performed in subgroups based on levodopa dose, and details will be described in the SAP.

9.7.2 Determination of Sample Size

The sample size is calculated under assumption the efficacy of this study at 18 weeks is comparable to the efficacy of phase 3 clinical study at 24 weeks.[7]

The sample size is calculated using each 2 primary endpoints, and a larger sample size is selected conservatively. The sample size for each evaluation variable is as follows.

1) Endpoint 1: Paired t-test for “off” time

Based on the above assumptions, to calculate the number of subjects for the comparison of the “off” time mean change 24 weeks after Baseline, the sample size was calculated assuming average change (-1.56) and standard deviation (2.35).

The results were performed through PASS (version 2020), the sample sizes of 31 achieve 90% power and the significance level (alpha) is 0.025.

2) Endpoint 2: Paired t-test for PDQ-39 score

Based on the above assumptions, to calculate the number of subjects for the comparison of the PDQ-39 score mean change 24 weeks after Baseline, the sample size was calculated assuming average change (-3.17) and standard deviation (10.86).

The results were performed through PASS (version 2020), the sample sizes of 149 achieve 90% power, and the significance level (alpha) is 0.025.

According to the above two endpoints, the sample sizes are 31, 149 at each assumption. The sample size of endpoint 2 is larger than endpoint 1. Therefore, the final sample size obtained, considering the drop-out rate of 25% during the study period is 199.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

10 REFERENCE LIST

1. Cattaneo C, Sardina M, Bonizzoni E. Safinamide as Add-On Therapy to Levodopa in Mid- to Late-Stage Parkinson's Disease Fluctuating Patients: Post hoc Analyses of Studies 016 and SETTLE. J Parkinsons Dis. 2016;6(1):165-73.

2. Hattori N, Tsuboi Y, Yamamoto A, Sasagawa Y, Nomoto M, Nomoto M. Efficacy and safety of safinamide as an add-on therapy to L-DOPA for patients with Parkinson's Disease: A randomized, double-blind, placebo-controlled, phase II/III study. Parkinsonism Relat Disord. 2020;75:17-23.

3. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's Disease with motor fluctuations. Mov Disord. 2014;29(2):229-37.

4. XADAGO (safinamide) tablets, for oral use Initial U.S. Approval: 2017

5. National Institute for Health and Care Excellence. Parkinson's disease in adults. Published: 19 July 2017.

6. Equfina Tab. 50 mg (safinamide mesilate), for oral use South Korea. Approval: 2020

7. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, et al. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol. 2017 Feb 1;74(2):216-224.

8. Guidelines for Clinical Trials Targeting Patients with Hepatopathy. National Institute of Food and Drug Safety Evaluation. Digestive Medicine Department, Drug Evaluation Division. December 2015.

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. These requirements should in no way prevent any immediate action from being taken by the investigators, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigators determine 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 representative or appropriate study team member and the IRB/IEC for the site must be notified immediately.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

The CRO's CRA will maintain contact with the investigators 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 investigators will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs 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 may 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 IxRS, x-rays, and other imaging reports regardless of how these images are stored, including microfiche and photographic negatives
- Subject diary, PDQ-39, MMSE, MDS-UPDRS Part 3 and Part 4, and KPPS completed by the subjects or investigators
- Records of telephone contacts
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs

- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correction 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 investigators must sign each CRF. The investigators will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigators are responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, Investigator and Site Information Form, ICFs, and IRB/IEC correspondence. The site should plan to retain study documents, as directed by the sponsor, for at least 5 years following the completion of the study.

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

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department may conduct audits of clinical research activities in accordance with the sponsor's SOPs 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 (e.g., locked cabinet) and stored according to the conditions specified on the drug label. 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 label 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 among the sponsor, CRO, and the institution/investigators. 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 Clinical Trial Agreement among the sponsor, CRO, and the institution/investigators.

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 investigators, the investigators' 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 among the sponsor, CRO, and the institution/investigators.

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 among the sponsor, CRO, and the institution/investigators.

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 of the termination or suspension and the reasons for the

termination or suspension. The IRB/IEC will also be informed promptly and provided the reasons for the termination or suspension by the sponsor or by the investigators/institution, as specified by the applicable regulatory requirements.

The investigators reserve the right to discontinue the study should his/her judgment dictate. If the investigators terminate or suspend a study without prior agreement of the sponsor, the investigators should inform the institution where applicable, and the investigators/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.