12.1.9 Documentation of Statistical Methods

This section includes the following:

Statistical Analysis Plan Version 1.0, dated 25 Jan 2021

Zambon SpA

Z7219M01

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SAFINAMIDE 100 MG ONCE DAILY, AS ADD-ON THERAPY, IN IDIOPATHIC PARKINSON'S DISEASE (PD) PATIENTS WITH MOTOR FLUCTUATIONS AND PD RELATED CHRONIC PAIN

25-JAN-2021

Statistical Analysis Plan

Version 1.0

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Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

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Confidential

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic Case Report Form
EoT	End of Treatment
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	Gamma Glutamyl transpeptidase
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
IPD	Idiopathic Parkinson's Disease
IWRS	Interactive Web Response System
L-Dopa	Levodopa
LLT	Lower Level Term
LOCF	Last Observation Carried Forward
MAO-B	Monoamine Oxidase-B
MAR	Missing at Random
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MMRM	Mixed Model Repeated Measures
MMSE	Mini-mental State Examination
NRS	Numerical Rating Scale
od	Once Daily
PD	Parkinson's Disease
PGI	Patient Global Impression
PGI-C	Patient Global Impression of Change
PP	Per Protocol
PRN	Pro Re Nata (When Necessary)
PT	Preferred Term
RBC	Red Blood Cell
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SE	Standard Error
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase

SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
WHODDE	World Health Organization Drug Dictionary Enhanced
WBC	White Blood Cell

1. Introduction

Safinamide is an alpha-aminoamide derivative, structurally unrelated to any other drug for the treatment of Parkinson's Disease (PD).

Safinamide has both dopaminergic and non-dopaminergic activities. It is a potent, selective and reversible Monoamine oxidase-B (MAO-B) inhibitor, a mechanism associated with enhancement of dopaminergic transmission in the brain. Safinamide is also a state-dependent inhibitor of voltage-gated sodium channels and, at higher concentrations, inhibits calcium channels. These molecular mechanisms act in animal models of PD to increase brain dopamine, extend levodopa (L-Dopa) induced ON-time (dopaminergic actions) and reduce the severity of L-Dopa induced dyskinesia (non-dopaminergic action).

It is suggested that dopaminergic effects through selective and reversible inhibition of MAO-B, and non-dopaminergic effects through state dependent inhibition of voltage-gated sodium channels, are likely to be the principal relevant mechanisms for therapeutic activity in PD.

Safinamide (50mg and 100mg) has been approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) for the treatment of mid- to late-stage fluctuating PD subjects as add-on therapy to L-Dopa (alone or in combination with other anti-Parkinson drugs).

Pain is a frequent non-motor symptom of PD, often underestimated and inadequately treated, with a significant impact on patients' quality of life.

There is growing evidence that motor complications and pain may share common pathophysiologic mechanisms that include not only dopaminergic but also non-dopaminergic systems dysfunction, such as glutamatergic hyperactivity.

Results from a post-hoc analysis of the pooled data of two Phase III studies (016 and SETTLE) indicate that safinamide 100 mg/day significantly reduced in fluctuating PD patients the individual use of pain treatments by about 24% and improved two out of three items of the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) related to pain (Cattaneo et al. 2017).

Therefore, drugs that modulate glutamate release, such safinamide, may be a further option for the treatment of PD chronic pain.

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by the PPD Biostatistics department in the analysis and presentation of data for Zambon protocol number Z7219M01 entitled 'A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide 100 mg once daily, as add-on therapy, in idiopathic Parkinson's Disease (IPD) subjects with motor fluctuations and PD related chronic pain'.

This SAP has been written in accordance with International Conference on Harmonisation (ICH E9) and PPD Global Biostatistics and Programming standard operating procedures (SOPs) and using the final study protocol Version 3.0 (27 October 2020), electronic case report form (eCRF) Version 2.0 (10 January 2020).

2. Objectives

The primary objective is to evaluate the efficacy of safinamide 100 mg once daily (od), compared to placebo, as add-on therapy, for PD related chronic pain.

The secondary objectives include the following:

1) To assess the percentage of pain responders.
2) To assess the Clinical Global Impression.
3) To assess the Patient Global Impression.
4) To assess the reduction in use of pain drugs.
5) To assess the mood.
6) To assess motor and non-motor symptoms.
7) To evaluate of the safety and tolerability of safinamide 100mg compared to placebo in fluctuating PD patients with PD related pain.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase IV, international, multicentre, randomised, double-blind, placebo-controlled study in IPD male and female subjects 30 years of age or older, experiencing motor fluctuations and PD related chronic pain while on stable doses of L-Dopa. The duration of the study for each subject is 19 weeks (including the Screening period). Subjects will be randomised to receive either active or placebo in a 2:1 ratio, respectively. A telephone follow-up call will be performed 1 week after the end of treatment.

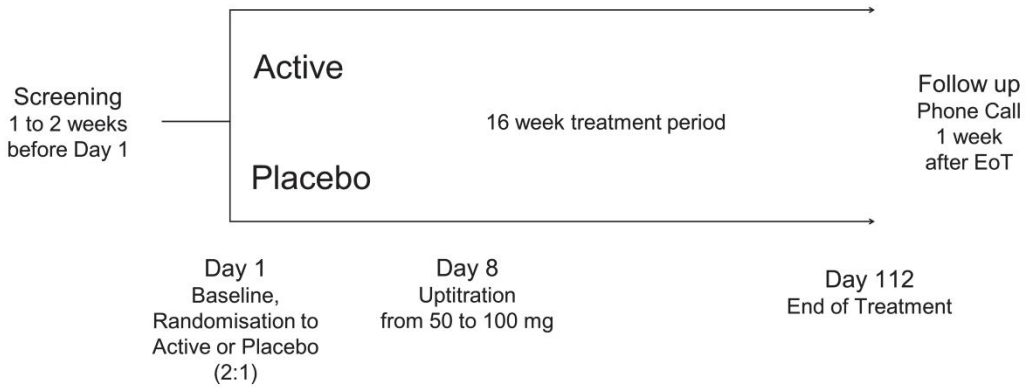
Study consists of two periods, screening (1-2 weeks) and a treatment period (16 weeks), with a follow-up call at 1 week after treatment, so total duration of 19 weeks.

The Screening visit (Visit 1) should occur up to 14 days before Day 1. At baseline (Visit 2, Day 1), eligible subjects will enter the treatment period and will receive study medication 50 mg (from Day 1 to Day 7) and then 100 mg (from Day 8 onwards), to be taken orally once daily (od). Following completion of all baseline assessments, they will receive the first dose of study medication at the study centre. Thereafter, study drug will be taken, at home, each morning along with their first morning dose of L-Dopa and other (if any) PD medications. On Day 8 the dose of study drug will be increased, at home, to 100 mg od. Each subject will receive treatment for 16 weeks, with visits at Week 0/Day 1 (baseline) and at Weeks 4, 8 and 16 (or early termination).

From day 1 onwards, participant will record the use of PRN medications along with indicating the worst pain experienced on a daily basis.

Diagram of Study Schedule:

Figure 1: Diagram of Study Schedule



Randomisation is in a 2:1 ratio of active:placebo; up to 132 participants will be screened to achieve up to 105 randomized, to have approximately 84 patients complete the study (56 in the active and 28 in the placebo group respectively). The detailed description is present in Section 4.1.

Subjects will take their allocated study drug in accordance with the assigned regimen:

Safinamide: 50 mg (from Day 1 to Day 7) and then 100 mg (from Day 8 onwards)
or
Placebo: 50 mg (from Day 1 to Day 7) and then 100 mg (from Day 8 onwards)

3.2. Study Endpoints

The primary endpoint measured in this study will be:

- The change from baseline to Week 16 in pain severity ("average worst pain experienced in the last 7 days"), as assessed by an 11-point Numerical Rating Scale (NRS).

The secondary endpoints measured in this study will be:

- The percentage of pain responders defined as the subjects with reduction in pain severity of ≥2 points ("average worst pain experienced in the last 7 days"), at weeks 4, 8 and 16 as assessed by an 11-point NRS, compared to baseline
- The pain severity score (average worst pain score using 11-point NRS Scale) at week 4, 8.

- The Clinical Global Impression of Severity (CGI-S) score at weeks 4, 8 and 16 (rated by Investigator),
- The change from baseline to Weeks 4 8 and 16 in the Clinical Global Impression of Change (CGI-C) score rated by Investigator,
- The change from baseline to Weeks 4, 8 and 16 in the Patient Global Impression of Change (PGI-C) score rated by the subject
- The percentage of subjects with a reduction in number of days using concomitant pain drugs in the 7 days before each visit at Weeks 4 8 and 16.
- The number of days with PRN pain medication in the 7 days before each visit at Week 4, 8 and 16 (by analysing 7-day intervals before each visit).
- The change from baseline to week 16 in the Hospital Anxiety and Depression Scale (HADS) score.
- The change from baseline to weeks 4, 8 and 16 in the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (total score and sub scores) during the "ON" phase.

Tolerability will be assessed by means of incidence of treatment emergent adverse events.

Safety variables include physical and neurological examinations, vital signs (blood pressure and heart rate) and clinical safety laboratory values (haematology, clinical chemistry).

4. General Statistical Considerations

Continuous data will be summarised using summary statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). For the summary statistics of all continuous data, minimum and maximum values will be displayed to the same level of precision as reported, unless otherwise specified. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

Categorical data will be described using the subject count and percentage in each category. When counts are presented, in cases where the count is zero, the percentage will not be displayed in order to draw attention to the non-zero counts. A row denoted 'Missing' will be included in count tabulations where specified on the shells to account for missing values. The denominator for all percentages will be the number of populated subjects in that treatment within the analysis set of interest, unless otherwise specified. Frequency statistics will be displayed using one decimal place except for the display of 100% frequency which will be displayed as 'XX (100)'.

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as '<0.001'. If a p-value is greater than 0.999 it will be reported as '>0.999'. Confidence intervals will be displayed to one level of precision greater than the data

collected. Data will be displayed in all listings sorted by treatment group, country, centre, and subject ID.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to or on the date that the first dose of treatment is taken. Study day is defined in relation to the date of first dose of study drug. Therefore, when an assessment date is before the first dose:

Study day = assessment date - first dose date of study drug

and when an assessment is on or after the first dose:

Study day = assessment date - first dose date of study drug + 1

All analyses will be conducted using SAS Version 9.4 or higher and all data will be summarised based on the visit name collected on the eCRF page.

4.1. Sample Size

On the basis of previous post-hoc analyses of pain (Cattaneo et al 2017) and of similar studies (Folstein et al, 1975), assuming a standard deviation of 2 it is anticipated that a sample size of 144 subjects would permit detection of a 1 point treatment difference in the NRS between safinamide and placebo at the 5% significance level with 80% power. A 1-point treatment difference is considered to be a clinically meaningful treatment effect (Rascol et al, 2016).

Approximately 220 subjects will be screened to achieve approximately 177 randomly assigned to study treatment and of which approximately 144 subjects completing the study (n= 96 and n= 48 evaluable subjects in the active and placebo group respectively).

Since March 2020, the COVID-19 emergency has impacted the feasibility of the trial, which is being conducted in a vulnerable group of patients. Upon receipt of the guidance “Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency” issued by FDA on June 2020, released with the aim of helping sponsors ensure that trials conducted during the Covid-19 emergency could continue, where appropriate, to provide interpretable findings with correct statistical quantification of uncertainty, the Sponsor performed a Blind Data Review Analysis of the primary endpoint data (pain severity) for the 26 patients who had completed the study as of June 2020.

The results of the analysis show that the standard deviation used in the original sample size estimation (SD = 2) was a conservative overestimate of the observed SD from the actual trial data, which was 1.43 at the time of the blinded data review.

Based on this, the Standard Deviation, for the estimation of sample size has now been amended to 1.50, and the power has been maintained as 80%. New sample size estimates have been performed considering different magnitudes of Treatment Difference but keeping

the same assumptions of screen failure rates and dropout rates. These are summarized below in Table 4.1.

Table 4.1 Sample Size Estimations

SCENARIO	SAMPLE SIZE
Power = 80% Standard deviation = 1.5 Treatment Difference = 1 point	Pts to screen= 132 Pts to randomize= 105 Pts completing study= 84
Power = 80% Standard deviation = 1.5 Treatment Difference = 1.5 points	Pts to screen= 66 Pts to randomize= 51 Pts completing study= 39
Power = 80% Standard deviation = 1.5 Treatment Difference = 2 points	Pts to screen= 39 Pts to randomize= 30 Pts completing study= 24

Currently, it is planned to keep the initial conservative estimate of treatment difference as 1 and change the SD to 1.5 in line with what was observed with the Blind Data Review Analysis. Using these parameters, up to 132 participants will be screened to achieve up to 105 randomized, to have approximately 84 patients complete the study (56 in the active and 28 in the placebo group respectively).

However, given the continuous and uncertain impact that COVID-19 outbreak is having in the countries participating in the trial, any of other scenarios might be adopted if at the end of December 2020, the above enrollment goal will not be achieved. From the table above it can be seen that if the treatment difference is greater than 1, statistical significance can be achieved with a substantially lower sample size. Thus, the study maintains its robustness.

4.2. Randomisation, Stratification, and Blinding

Subjects will be randomised to double-blinded treatment in a 2:1 ratio to receive either safinamide or placebo at Visit 2 (day 1). An interactive web response system (IWRS) will be used for the randomisation. PPD Biostatistics will generate the randomisation schedule for IWRS, which links sequential subject randomisation numbers to treatment codes.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted and should make every effort to contact the sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded,

the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

4.3. Analysis Set

The analysis sets that will be used in this study are detailed below in Table 4.2. Membership to each analysis set will be reviewed and confirmed prior to database lock.

The number and percentage of subjects in each analysis population will be summarised by the treatment they were randomised to as well as for the total number of subjects. A listing will also be produced displaying subjects excluded from each population.

Table 4.2 Analysis Populations Definition

Population	Description
Full analysis set	The FAS is defined as all randomized subjects in the study, with at least one measurement of the primary efficacy variable following at least one dose of study medication. Summaries on the FAS will be performed for all efficacy endpoints. Subjects in this analysis set will be summarized according to the treatment they were randomly assigned to.
Per Protocol	The PP Set will be a subset of subjects in the FAS who completed the study and for whom no relevant protocol deviations were documented. Identification of relevant protocol deviations will occur on a blinded review meeting preceding database lock. A second analysis of the primary efficacy endpoint will be based on the PP Set. All subjects in the PP Set will be summarized according to the treatment they were assigned to.
Safety	The Safety Set will include all randomized subjects assigned to study intervention and who take at least 1 dose of study medication. The Safety Set will be used for the analysis of all safety endpoints. All subjects in the Safety Set will be summarized according to the treatment they actually received (according to the Drug Accountability eCRF page).

The Screened Population will include all subjects who sign the informed consent form (ICF). This population will be listed but not used for statistical analyses. The data from this population will be summarized and used for presenting subject study disposition

All Enrolled population includes all subjects who signed the informed consent form (ICF) and enrolled into the study. The data from this population will be summarized and used for presenting subject study disposition.

The decision whether a protocol deviation is relevant or not for the exclusion of subjects from the per protocol (PP) set will be made case-by-case in a blind data review meeting.

The primary analysis of the primary efficacy variable will be based on the FAS data set. A secondary analysis of the primary efficacy parameter will be based on the PP set.

All other secondary efficacy analyses will be based on the FAS.

Safety analyses will be based on the safety analysis (SA) set.

5. Visit Attendance

The number and percentage of subjects who attended a visit or received a safety call will be presented for the following visits:

- Visit 2 (Baseline or Day 1)
- Visit 3 (Day 28)
- Visit 4 (Day 56)
- Visit 5 (EoT or Day 112)
- Follow-up Call

For Subjects with on-going site visits, wherever possible all efforts will be made to have the patient attend the hospital for their on-site study visits accordingly to schedule in the protocol. Assessment will be performed via phone call for Adverse event, Concomitant medication and e-questionnaires MDS-UPDRS, CGI-s and CGI-c if site visit is not possible. Anticipated data which will be missing due to COVID-19 outbreak is mostly LAB and ECG which requires on-site attendance.

6. Subject Disposition

6.1. Disposition

A listing of randomisation information (including randomisation and kit number) for all randomised subjects will be produced.

Subject disposition will be summarised for the following categories: subjects in the All Enrolled, FAS, PP Set and Safety Set. A disposition of subjects includes the number and percentage of subjects who were enrolled, subjects that were screening failures, subjects randomised and subjects who completed the study, subjects who discontinued from the study, and subjects that were unblinded during the study. The number of subjects will be displayed by treatment group and overall, except screening failures where counts will only be displayed in the overall group. The reasons for study discontinuation may include any of

the following: Lost to Follow-up, Subject withdraws consent, Death, Adverse event, Physician decision, Pregnancy, Protocol violation, Study terminated by the Sponsor, and Other. The reasons for study discontinuation will also be summarised in this table. The percentages will be based on the number of subjects randomised.

Disposition data, displaying both randomised and actual treatment in case of randomised/treated subjects, will be listed, for all enrolled set.

6.2. Protocol Deviations

Major (relevant) protocol deviations will be identified and confirmed prior to database lock and summarised by the deviation categories shown in study deviation rules document.

The major protocol deviations will be summarised for the FAS and includes the number and percentage of subjects who had each major deviation. Subjects can have more than one type of major deviation. Percentages will be based on the total number of subjects in the FAS.

Protocol deviations (including minor deviations) will also be presented in a listing. A flag (Y/N) will be added to the listing to denote whether a subject is included or excluded from the PP Set.

7. Demographics and Baseline Characteristics

7.1. Demographics

A summary of demographics and baseline information will be presented for the Safety and Full Analysis Sets. The demographic characteristics consist of age (years), sex (Female, or male), race (Caucasian, Asian, African, Indian, or Mixed/Other), smoking and alcohol use.

Age (years) will be summarised using descriptive statistics. The number and percentage of subjects by sex, race, smoking and alcohol consumption will also be reported. Percentages will be based on the total number of subjects in the specific analysis set being summarised (Safety Set or Full Analysis Set as applicable).

7.2. Baseline Disease Characteristics

The following baseline disease characteristics of PD history, Mini-mental State Examination (MMSE), and duration of PD, will be summarised for the Safety and Full Analysis Sets (FAS), as recorded on the “Demography” and “Mini-mental State Examination (MMSE)” eCRF pages. MMSE score and duration of PD will be summarised using descriptive statistics. The number and percentage of subjects by PD history by Hoehn and Yahr stage and MMSE score category: abnormal (severe (≤9 points), moderate (10-18 points), mild (19-23 points)) and normal (≥24 points), and the number and percentage of duration of PD category (<5 years, 5-10 years, and >10 years), will also be reported. Percentages will be based on the total number of subjects in the specific analysis set being summarised).

Subject demographic and baseline characteristics will be listed for all patients enrolled in the study, including screen failures

7.3. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. The primary system organ class (SOC) and preferred term (PT) will be coded according to the Lower Level Term (LLT). The number and percentage of subjects with any medical history will be summarised overall and for each SOC and PT. Percentages will be calculated based on number of subjects in the Safety Set.

This summary will be presented in alphabetical order for the SOC. Within each SOC, the PTs will be presented by descending order of frequency.

Subject medical history data will be presented for the Safety Set in a listing.

7.4. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria for eligibility for participation in the study are listed in sections 5.1 and 5.2 of the study Protocol. Subjects including screen failure subjects along with the inclusion/exclusion criteria will be listed for all subjects enrolled.

8. Prior and Concomitant Medications

All medications or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study, will be will be collected on the eCRF. All medications will be coded according to the World Health Organization Drug Dictionary Enhanced (WHODDE, March 2018). In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code for Anti-Parkinson Treatment Prior and Concomitant Medication, and Level 4 of the ATC coding and PT is required.

For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time on and after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started on and after the first dose of study drug).

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start dates and end dates will be imputed as follows:

- If year and month are present and day is missing, then set day to first day of month for start date, and set day to last day of month for end date
- If year and day are present and month is missing, then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing, then set month and day to January 1 for start date, and set month and day to December 31 for end date

- Completely missing dates will not be imputed

If start date is completely missing and end date is not prior to the first dose, then the medication will be classified as concomitant. If the start date is completely missing and end date is prior to the first dose of study drug, then the medication will be classified as prior. If the end date is missing, then the medication will be classified as ongoing.

8.1. Prior Medications

The total number of prior and concomitant medications, as reported on the "Concomitant Medications" eCRF page (identified based on start date in relation to first dose date), the number and percentages of subjects using each type of prior and concomitant medication, and the number and percentages of subjects with at least one prior and concomitant medication,), will be summarised by treatment group and listed by ATC level 4 category, and PTs.

Anti-Parkisonian Prior and Concomitant medication as reported on "Anti-Parkinsonian Prior and Concomitant" eCRF page will be defined in a similar way as for Prior and Concomitant Medication.

These will be presented in a single summary table.

These summaries will be presented in descending order of frequency, by ATC level 4 category. Likewise, within each ATC level 4 category, preferred terms will be presented by descending order of frequency.

All summaries and listings will be performed using the Safety Set.

8.2. PRN Medications

The total number of PRN PD pain medications, the number and percentages of subjects using each type of PRN PD pain medication, and the number and percentages of subjects with at least one intake of PRN PD pain medication as reported on the "PRN Parkinson's Disease Pain Medication" eCRF page, will be summarised by treatment group and listed by ATC4 category, and PT. All summaries and listings will be performed using the Safety Set.

9. Exposure and Compliance

9.1. Exposure to study treatment

In case an additional kit is obtained to replace the Randomization Kit that might have been lost or damaged, Investigator shall initiate an unscheduled dispensation. A listing of subjects'

unscheduled dispensing, as recorded in "Unscheduled Dispensation" eCRF page will be produced for the Safety Set.

9.2. Study compliance

Study medication accountability and subject compliance will be documented throughout the treatment period, using study-specific study medication dispensing and return record forms, and will be reported in 'Drug Accountability' eCRF page. The eCRF does not collect exposure data in a fashion that enables to calculate compliance, only investigator's assessment result for compliance is collected by visit as Yes or No. Compliance categories of "Yes" or "No" indicate that the patients took at least 80% of the study medication during any visit- to- visit evaluation Period "Yes" and non-compliance is defined as taking less than 80 % of study medication "No".

Complete data about study medication accountability and subject compliance will be presented in a listing.

10. Efficacy Analysis

The primary analysis of the efficacy endpoint will be performed for the FAS and in case there is a difference of more than 10% between FAS & PP, will be repeated on the PP Set as a sensitivity analysis.

Secondary efficacy endpoints will be analysed for the FAS population at Week 4,8 and 16.

Data listings will be provided for all endpoints. An additional listing of diary collection status by visit, as reported in "Questionnaire Collection Status -Baseline", "Questionnaire Collection Status", and "Questionnaire Collection Status – V5 EoT WK16" eCRF pages, will be presented.

10.1. Primary Efficacy Endpoint

Pain severity data will be derived from the daily diary.

The primary endpoint evaluated in this study is the mean change in pain severity ("average worst pain experienced in the last 7 days", i.e. average of the worst pain score on each of the 7 days preceding the site visit), as assessed by an 11-point NRS, from baseline to Week 16. For efficacy analysis, at least 4 out of 7 daily pain scores are needed to calculate a valid average over 7 days.

The null hypothesis for the primary endpoint is that safinamide is no better than placebo in managing pain; thus $\mu(\text{Safinamide}) > \mu(\text{Placebo})$, where μ represents the population mean change in pain severity score from baseline at Week 16 and a negative change would indicate improvement.

The primary efficacy endpoint, change from baseline to Week 16 in pain severity score, will be analysed using a mixed model repeated measures (MMRM) using visit on subject ID as

the repeated factor with unstructured covariance term (REPEATED VISIT/SUBJECT=SUBJID TYPE=UN). If convergence is not achieved, then other covariance structures will be investigated such as compound symmetric (TYPE=CS). The model will include fixed effects terms for treatment, country, visit and regular pain medication use at baseline (yes or no) and covariate term for pain severity score at baseline. The method above (e.g. MMRM) is unbiased under the MAR assumption and can be thought of as aiming to estimate the treatment effect assuming that after withdrawal, subjects would have continued on a similar trajectory to their peers in the same arm who have the same covariates.

The likelihood-based mixed-effect model repeated measure will be performed using a SAS PROC MIXED procedure, and the Kenward-Roger method for degrees of freedom will be applied. The restricted maximum likelihood (REML) method will be used for estimation. The least square (LS) means of change from baseline in pain severity along with the associated SE and 95% CIs will be calculated from the model at each time point. The LS mean difference between the treatment groups at Week 16 will also be reported, along with the corresponding SE, 95% CIs, and the p-value derived for the difference between treatment arms (safinamide – placebo). No adjustment is being made for multiple comparisons.

Results for time points other than Week 16 (Weeks 4 and 8) will be presented in both the above discussed model-adjusted and descriptive forms.

10.2. Sensitivity of Primary Endpoint

The following two sensitivity analyses will be performed:

a) This sensitivity analysis will be based on the PP Set, and the primary endpoint (mean change pain severity as assessed by an 11-point NRS, from baseline to Week 16), will be analysed using similar MMRM approach as specified in Section 10.1. No imputation will be performed in this analysis.

b) This sensitivity analysis will be based on the FAS population. Missing records of subjects who prematurely discontinued the randomly assigned study drug, will be imputed with the worst value from baseline before drop out within each subject. Intermittent missing data will not be imputed and all missing values after discontinuation will be imputed. The worst value is the highest pain score from baseline to before drop out. Change from baseline for the imputed Week 16 value will then be calculated as imputed Week 16 - baseline. For example in the following case:

   3 1 x 2 3 y y

   where x and y are missing data, the imputation will complete y values but not x as it is the intermittent missing data.
   The primary endpoint (mean change in pain severity as assessed by an 11-point NRS, from baseline to Week 16), will be analysed by using a repeated measures analysis

of covariance (ANCOVA) for the imputed population, using visit on subject ID as the repeated factor with unstructured covariance term (REPEATED VISIT/SUBJECT=SUBJID TYPE=UN). If convergence is not achieved then other covariance structures will be investigated such as compound symmetric (TYPE=CS). The model will include fixed effects terms for treatment, country, and visit, and covariate term for pain severity score at baseline.

10.3. Secondary Efficacy Endpoints

The PGI-C, CGI-C, CGI-S, and MDS-UPDRS will be analysed at weeks 4, 8 and 16 using the same statistical methods i.e. MMRM as for the primary efficacy parameter defined in Section 10.1 by replacing covariate of pain severity at baseline with respective efficacy parameter

Pain severity score at Weeks 4 and 8 will also be analysed by the same MMRM method used for Pain severity score at Week 16 as defined in Section 10.1

Change from baseline in HADS at Week 16 will be analysed using an ANCOVA. The model will include treatment, baseline HADS and country as fixed effects. The Least Square (LS) means of the change from baseline in HADS score along with the associated SE and 95% CIs will be calculated, and the p-value derived for the difference between treatment groups at Week 16 will be presented.

Percentage of pain responders defined as subjects with reduction in pain severity of ≥2 points ("average worst pain experienced in the last 7 days") as assessed by an 11-point NRS, compared to baseline), will be analysed at weeks 4, 8 and 16 using a Cochran-Mantel-Haenszel adjusted test of the difference in proportions between the two treatment groups. Country will be used as the stratification factor. A 95% confidence interval of the difference in proportions and p-value will be reported. For percentage of pain responders, a missing value at each visit will be imputed to indicate that a subject was a non-responder i.e. a Worst-Case imputation. It will be summarized for both Observed data and Imputed data.

The analysis of amount of concomitant PRN PD pain medications (as reported in the Patient Diary) and concomitant pain drugs (as reported on the 'Concomitant Medications' eCRF page) will be summarized in two ways i.e. the number of days on which pain medication was taken in the 7 days preceding Visits at Weeks 4, 8 and 16 and the number of patients taking pain medication in the 7 days preceding Visits at Weeks 4, 8 and 16.

The number of days that pain medication was taken will be analysed using a two-sided Mann Whitney test at the 5% level of significance level to test the null hypothesis of no difference between the two treatments. In case if the patient has not taken any pain medication in the 7

days preceding Visits at Weeks 4, 8 and 16, then the number of days will be considered as zero for that particular patient for that particular visit.

The percentage of patients using pain medication will be analysed using a Cochran-Mantel-Haenszel (CMH) adjusted test of the difference in proportions between the two treatment groups. Country will be used as the stratification factor. A 95% confidence interval of the difference in proportions and p-value will be reported.

11. Safety Analysis

All analyses of safety will be conducted using the Safety Set.

11.1. Adverse Events

An AE is any untoward medical occurrence in a subject or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- begins on or after the first dose of study drug and before the end of study drug + 30 days;
- begins before the first dose of study drug and worsens in severity on or after the first dose of study drug and before the end of study drug + 30 days;
- is completely missing an onset date and end date;
- is completely missing an onset date and the end date is on or after the first dose of study drug.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where UN and UNK indicate unknown or missing day and month respectively):

- UN-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- DD-UKN-YYYY/UN-UNK-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the year the data was collected. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first

dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UN-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume DD-DEC-YYYY or 31-DEC-YYYY respectively.

All adverse events will be classified by SOC and PT according to MedDRA (Version 21.0). Percentages will be calculated based on the number of subjects in the Safety Set, unless otherwise specified.

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, study drug-related TEAE, study drug-related serious TEAE, TEAE leading to study discontinuation/ early withdrawal, TEAE leading to treatment discontinuation, and AE leading to death will be provided by treatment group.

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided by treatment group and overall. TEAEs will be presented in descending order of frequency by SOC. Likewise, within each SOC, the PTs will be presented by descending order of frequency.

11.1.1. Incidence of Adverse Events

Summaries of the number and percentage of subjects with at least one TEAE will be provided for each treatment group by SOC and PT. Subjects that report more than one event will only be counted once for each level of SOC and PT summary.

This summary will be presented in descending order of frequency by SOC. Likewise, within each SOC, the PTs will be presented by descending order of frequency.

All AEs will be presented in a listing on the Safety Set.

11.1.2. Severity of Adverse Event to Study Drug

A summary of TEAEs by severity will be presented in a table. The possible severities are ‘Mild,’ ‘Moderate,’ and ‘Severe.’ In this table, if a subject reported multiple occurrence of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are

missing severity will be presented in tables as 'Severe' but will be presented in the data listing with a missing severity.

This summary will be presented in descending order of frequency by SOC. Likewise, within each SOC, the PTs will be presented by descending order of frequency.

11.1.3. Relationship of Adverse Events to Study Drug

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are 'Not Related', and 'Related'. If a subject reports multiple occurrence of the same TEAE and any of those are 'Related', the subject will be counted as 'Related' for that TEAE. Treatment-emergent AEs that are missing a relationship will be presented in the summary table as 'Related' but will be presented in the data listing with a missing relationship.

This summary will be presented in descending order of frequency by SOC. Likewise, within each SOC, the PTs will be presented by descending order of frequency.

The TEAE data will be categorized and presented by SOC, PT, and severity, for 'Related' and 'Not Related' separately.

11.1.4. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A serious AE (SAE) is defined as any untoward medical occurrence that at any dose results in death, is considered life-threatening, is a congenital anomaly/birth defect, requires in-subject hospitalization or prolongation of existing hospitalization, or results in significant disability.

A summary of the total number of treatment-emergent SAEs and the number and percentage of subjects with at least one treatment-emergent SAE will be provided for each treatment group and presented by SOC and PT in a manner similar to that described in Section 11.1.1.

A summary of treatment-emergent SAEs by relationship to study drug will be presented in a table in a manner similar to that described in Section 11.1.1.
All SAEs will be presented in a listing on the Safety Set.

11.1.5. Adverse Events Leading to Treatment Discontinuation

A summary of TEAEs which leading tostudy drug discontinuation, as reported in Adverse Events CRF page (where action taken with study treatment will be "Drug Permanently

Withdrawn") will be presented in a table. Subjects that report more than one event will only be counted once for each level of SOC and PT summary.

This summary will be presented by SOC, PT in a manner similar to that described in Section 11.1.1.

All AEs leading to treatment discontinuation will be presented in a listing on the Safety Set.

11.1.6. Adverse Events Leading to Study Discontinuation

A summary of TEAEs leading to study discontinuation, as reported in 'Study Completion/Termination' CRF page (early withdrawals where primary reason for termination is 'Adverse Event'), will be presented in a table. Subjects that report more than one event will only be counted once for each level of SOC and PT summarisation.

This summary will be presented by SOC, PT in a manner similar to that described in Section 11.1.1.

All AEs leading to study discontinuation will be presented in a listing on the Safety Set.

11.1.7. Overdose

The anticipated pattern of events or symptoms following intentional or accidental overdose with safinamide is that related to its pharmacodynamic profile (MAO-B inhibition with activity dependent inhibition of sodium channels). The symptoms of excessive MAO-B inhibition (increase in dopamine level) could include hypertension, postural hypotension, hallucinations, agitation, nausea, vomiting and dyskinesia.

If the investigator identifies a subject has taken an accidental overdose but none of the symptoms of overdose were reported, then the accidental overdose will not be recorded as an AE. If the investigator identifies an intentional overdose with suicidal intent, then this will be recorded as an SAE.

The number and percentage of subjects with any overdose will be displayed, as reported on the "Drug Accountability" eCRF page.

A listing will be provided for intentional overdose events. Intentional overdose will be reported as AE/SAE and will be identified based on MedDRA codes.

The listing will be based on the Safety Set.

11.1.8. Death

All subjects who have an AE with an outcome of 'Death' will be presented in a listing using the Safety Set.

11.2. Telephone Contact

All data will be presented in a listing on the Safety Set.

11.3. Clinical Laboratory Evaluations

Summary tables presenting numbers and percentages at Screening and Week 16 visits will be presented for clinical laboratory tests, by treatment group for subjects in the Safety Set. The following laboratory test results will be included: Normal; Abnormal (Clinically Significant), Abnormal (Not Clinically Significant).

All data will be presented in a listing on the Safety Set.

11.3.1. Haematology

The following laboratory tests will be included: Platelet Count, Red Blood Cell (RBC) Count, Hemoglobin, Hematocrit, White Blood Cell (WBC) Count, Absolute Neutrophils, Neutrophils %, Absolute Lymphocytes, Lymphocytes %, Absolute Monocytes, Monocytes %, Absolute Eosinophils, Eosinophils %, Absolute Basophils, and Basophils %.

11.3.2. Clinical Chemistry

The following laboratory tests will be included: Blood Urea Nitrogen (BUN), Potassium, Sodium, Creatinine, Calcium, Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT), Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT), Alkaline phosphatase, Total bilirubin, Direct bilirubin, Urea, Total Protein, and Gamma Glutamyl transpeptidase (GGT).

11.3.3. Urinalysis

Urine pregnancy test results will be listed (where applicable).

11.4. Vital Sign Measurements

A summary table presenting observed values of vital signs data at Screening, Baseline and Week 16 visits, and changes from baseline for Week 16 visit assessed in the supine position,

including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm), by treatment group for subjects in the Safety Set.

All vital sign data will be presented in a listing on the Safety Set.

11.5. Physical Examination

A table will summarise physical examination results at Screening and Week 16 visits by treatment group for the Safety Set. Each visit captures the status of multiple body systems and any finding associated with the body system as not assessed, normal, abnormal (clinically significant), abnormal (not clinically significant), or not done. The summary will include the number and percentage of subjects with each physical examination outcome for the following: general appearance; head, ears, eyes, nose, throat; neck; skin; cardiovascular system; respiratory system; abdominal system; nervous system; other.

Physical examination results for all subjects will be presented in a listing on the Safety Set.

11.6. Neurological Examination

A table will summarise neurological examination results at Screening and Week 16 visits, by treatment group for the Safety Set. Each visit captures the status of the neurological system and any finding associated with the body system as normal, abnormal (clinically significant), abnormal (not clinically significant), or not done. The summary will include the number and percentage of subjects by neurological examination outcome for the following: Gait, Balance, Coordination, Cranial nerves, Motor examination, Sensory examination, and Other.

Neurological examination results for all subjects will be presented in a listing on the Safety Set.

12. Changes in the Planned Analysis

Section 3 of the protocol states about the objective and endpoint of the study. The secondary objective and endpoint i.e. “Clinical Global Impression for pain” and “Patient Global Impression for pain” signifies “Clinical Global Impression” and “Patient Global Impression”.

13. References

1. ICH Harmonized Tripartite Guideline – Statistical Principals for Clinical Trials, E9.
2. ICH Harmonized Tripartite Guideline – Clinical Trial Reports: Structure and Content, E3.
3. Cattaneo C, Barone P, Bonizzoni E, Sardina M. Effects of safinamide on pain in fluctuating Parkinson’s Disease patients: a post-hoc analysis. J Parkinsons Dis 2017; 7(1): 95-101.

4. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12(3): 189 98.
5. Handling missing items in the Hospital Anxiety and Depression Scale (HADS): a simulation study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5075158/)
6. Handling Missing Values in the MDS-UPDRS (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5072275/)
7. Rascol O, Zesiewicz T, Chaudhuri KR, Asgharnejad M, Surmann E, Dohin E et al. A randomised controlled exploratory pilot study to evaluate the effect of rotigotine transdermal patch on Parkinson’s Disease-associated chronic pain. J Clin Pharmacol 2016; 56(7): 852-861

14. Appendices

14.1. Schedule of Activities (SoA)

Visit	1 Screening	2 Baseline	3 Interim Week 4	4 Interim Week 8	5 EoT Week 16	6 Call	
Day / Procedure	(up to 14 days before Day 1)	1	28 ± 3	56 ± 3	112 ± 3	119 ± 3	Notes
Informed consent	X						After informed consent signing, enter details in IWRS to obtain screening number.
Eligibility criteria	X	X					Check prior to randomisation/ 1st dose of study medication
Randomisation		X					Use IWRS to randomise
Demographics	X						Age, sex, race, smoking and alcohol use
Medical history	X						PD diagnosis, Hoehn & Yahr staging, etc.
Vital signs	X	X			X		Heart rate, systolic and diastolic blood pressure

Visit	**1 Screening**	**2 Baseline**	**3 Interim Week 4**	**4 Interim Week 8**	**5 EoT Week 16**	**6 Call**	
Day / Procedure	**(up to 14 days before Day 1)**	**1**	**28 ± 3**	**56 ± 3**	**112 ± 3**	**119 ± 3**	**Notes**
Physical examination and neurological examination	X				X		
MMSE	X						
eDiary Issue, Training and return	X	X			X		
eDiary Review		X	X	X	X		Participant to complete diary for 7 days prior to each visit.
NRS Review		X					For eligibility: PI checks NRS score to confim eligibility
MDS-UPDRS		X	X	X	X		
CGI-S		X	X	X	X		
CGI-C			X	X	X		
PGI-C			X	X	X		
HADS		X			X		

Visit	**1 Screening**	**2 Baseline**	**3 Interim Week 4**	**4 Interim Week 8**	**5 EoT Week 16**	**6 Call**	
Day / Procedure	**(up to 14 days before Day 1)**	**1**	**28 ± 3**	**56 ± 3**	**112 ± 3**	**119 ± 3**	**Notes**
Blood draw	X				X		For Haematology & Clinical chemistry
Pregnancy test		X			X		Urine dipstick test for WOCBP only
Prior and concomitant medications	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	
Drug Dispense		X	X	X			
Drug accountability			X	X	X		

14.2. HADS scores and MDS-UPDRS scores

The method for HADS questionnaires for missing items is to replace the missing items with the mean of the answered items in the subscale, if at least half of that subscale has been answered. The rationale behind this rule is that an individual's score would not have enough information to be valid if fewer items than half were answered (see *Handling missing items in the Hospital Anxiety and Depression Scale (HADS): a simulation study*, for reference).

The MDS-UPDRS is designed as four separate parts, with summary scores for each to provide an overall severity measure of a given aspect of Parkinson's disease (part I, non-motor experiences of daily living; part II, motor experiences of daily living; part III, motor examination; part IV, motor complications). The Hoehn and Yahr Scale is used to measure how Parkinson's symptoms progress and the level of disability, including stages 1 to 5.

- Stage 1 - Unilateral involvement only
- Stage 2 - Bilateral involvement without impairment of balance
- Stage 3 - Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test
- Stage 4 - Severe disability; still able to walk or stand unassisted
- Stage 5 - Wheelchair bound or bedridden unless aided

To provide valid part scores applicable across all Hoehn and Yahr (H&Y) stages when the same items are consistently missing, one missing item from Part I, one from Part II, three from Part III, but none from Part IV can be allowed (Table 1) (see *Handling Missing Values in the MDS-UPDRS* for reference). To provide valid part scores applicable across all H&Y stages when random item entries are missing, one missing item from Part I, two from Part II, seven from Part III, but none from Part IV can be allowed (Table 1). These analyses are useful for constructing valid surrogate part scores for MDS-UPDRS when missing items fall within the identified threshold and give scientific justification for rejecting partially completed ratings that fall below the threshold.

Table 1

Maximal number of allowable missing items to calculate MDS-UPDRS total part scores

	Same Item(s) Consistently Missing	Across All Patients	Different Item(s) Randomly	Missing Across Patients
Part I: Across all HY	**1**		**1**	
HY 1–2 only		1		2
HY 3 only		1		2
HY 4–5 only		1		1
Part II: Across all HY	**1**		**2**	
HY 1–2 only		1		3
HY 3 only		1		2
HY 4–5 only		1		2
Part III: Across all HY	**3**		**7**	
HY 1–2 only		4		
HY 3 only		3		9
HY 4–5 only		3		9
				7
Part IV: Across all HY	**0**		**0**	
HY 1–2 only		0		1
HY 3 only		0		0
HY 4–5 only		0		0

The standard score for each patient's MDS-UPDRS (Part I, II, III, IV) score is used as the gold standard, and standard scores are calculated for each permutation with missing values. The threshold of a minimum CCC >0.95 is used to indicate the number of missing values allowable to provide a valid standard score even with missing data. HY, Hoehn and Yahr stages.