Title Page

Protocol Title:

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

Protocol Number: **Z7219M01**

Amendment Number: **2 – AUS GER ITA ESP**

Compound: **Safinamide**

Short Title:

Effect of Safinamide on Parkinson's Disease Related Chronic Pain

Sponsor Name: **Zambon SpA**

Legal Registered Address: **Via Lillo del Duca 10, 20091 Bresso, Milan, Italy**

Regulatory Agency Identifying Number(s)-EUDRACT number :

2017-002426-20

Approval Date: **27th October 2020**

Sponsor Signatory:

17-11-2020

Charlotte Keywood
Open R&D Global Head

Date

Medical Monitor Name and Contact Information will be provided separately

Investigator Signature Page

I have read this protocol.

I agree to comply with the current International Council for Harmonization Guidelines for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved.

I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred or if any proceeding for debarment is pending or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the Health Authority/Ethics Committee/Institutional Review Board.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of the sponsor.

Investigator Signatory:

Name: Date:

Title:

Affiliation:

Protocol Amendment Summary of Change History

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Protocol Version	Key Changes
Version 1.0; 30 July 2018	Original protocol version
Version 2.0 Amendment 1.0, 10 October 2019	Eligibility criteria revised Screening failure allowed Reference Safety Information explicated Ambiguities in the text have been amended for clarification purposes For additional information, please refer to the Summary of Key Changes document associated with this protocol version.
Version 3.0 Amendment 2.0, 27 October2020	Sample size reassessed Statistical analyses better clarified Reference to the measures taken during COVID-19 outbreak added For additional information, please refer to the Summary of Key Changes document associated with this protocol version.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

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) patients with motor fluctuations and PD related chronic pain

Short Title:

Pain Study

Rationale:

To study the effect of safinamide on PD related chronic pain, a frequent non-motor symptom of IPD.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the potential efficacy of safinamide 100 mg once daily, compared to placebo, as add-on therapy, for PD related chronic pain.	• 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).
Secondary	
• The percentage of pain responders	• Participants with reduction in pain severity of ≥2 points ("average worst pain experienced in the last 7 days"), at week 16 as assessed by an 11-point NRS, compared to baseline.
• Clinical Global Impression for pain	• The CGI-S score for pain at week 16. • The change from baseline to week 16 in the CGI-C score for pain.
• Patient Global Impression for pain	• The change from baseline to week 16 in the PGI-C score for pain.

• Reduction of pain drugs	• The percentage of reduction in number of concomitant pain drugs from baseline to week 16. • The number of patients with at least one intake of PRN pain medication. • Amount of PRN pain medications.
• Mood	• The change from baseline to week 16 in the HADS score.
• Motor and non-motor Symptoms	• The change from baseline to week 16 in the MDS-UPDRS (total score and subscores) during the "ON" phase.
• Safety & Tolerability	• Descriptive

Overall Design:

This is a Phase IV, international, multicentre, randomised, double-blind, placebo controlled study in IPD patients, experiencing motor fluctuations and PD related chronic pain while on stable doses of levodopa (L-Dopa).

Participants will be randomized 2:1 to receive either active or placebo.

Number of Participants:

Up to 132 participants will be screened to achieve approximately 105 randomly assigned to study intervention and 84 evaluable participants for an estimated total of 56 and 28 evaluable participants in the active and placebo group respectively.

Intervention Groups and Duration:

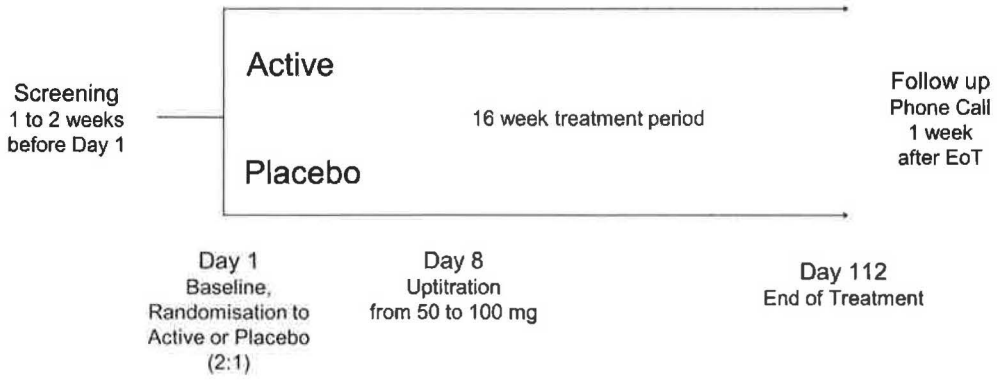
Study participation will be up to a maximum duration of 19 weeks and will comprise a screening period (1 to 2 weeks) and a treatment period (16 weeks). A telephone follow-up call will be performed 1 week after the end of treatment.

At baseline (Visit 2, Day 1), eligible participants 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 center. 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.

Data Monitoring Committee: No

1.2. Schema



1.3. Schedule of Activities (SoA)

For detailed description of assessments see Study Assessments and Procedures.

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, ethnicity, 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		
*= COVID- 19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, a Contingency Plan has been finalized (see Appendix 10) describing alternative procedures to be adopted in the study in order to mitigate the restrictions and keeping participants in the study trial (see Appendix 10 for details)							

2. Introduction

Safinamide is an alpha-aminoamide derivative, structurally unrelated to any other drug for the treatment of PD.

Safinamide has both dopaminergic and non-dopaminergic activities. It is a potent, selective and reversible 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 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 FDA for the treatment of mid- to late-stage fluctuating PD patients as add-on therapy to L-Dopa (alone or in combination with other anti-Parkinson drugs).

2.1. Study Rationale

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.

2.2. Background

IPD is a neurodegenerative condition characterized by the loss of neuromelanin containing neurons in the substantia nigra. Depletion of the dopaminergic neurons of the substantia nigra results in dopamine reduction, which is the main biochemical abnormality.

The main symptoms of IPD are resting tremor, bradykinesia and rigidity. The disease is also associated with non motor symptoms such as mood disorders and pain (Chaudhuri et al. 2009). The incidence of IPD increases with age, with incidence rates in the general population increasing from 0.3 per 1,000 person-years in participants aged 55 to 65 years, to 4.4 per 1,000 person-years for those aged ≥85 years (De Lau et al. 2004).

Levodopa (L-Dopa) remains the most effective therapy for IPD, but is associated with treatment complications such as motor fluctuations, wearing off phenomena and dyskinesia. As the disease progresses, the majority of participants will require therapies combining L-Dopa and with other agents which increase local dopamine concentrations or the efficacy of endogenous dopamine, such as adjunct dopamine agonists and/or MAO-B inhibitors. The demonstration of an anti-dyskinetic effect of the glutamate antagonist amantadine opened the door for novel non-dopaminergic approaches to PD therapy.

2.3. Benefit/Risk Assessment

The patient in active drug may benefit in reduction of pain medication's intake.

In terms of risk, safinamide is approved by both EMA and FDA.

When drawing blood samples, bruising might occur.

A detailed description of the chemistry, pharmacology, efficacy, and safety of safinamide is provided in the Summary of Product Characteristics (SmPC).

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the potential efficacy of safinamide 100 mg od, compared to placebo, as add-on therapy, for PD related chronic pain.	• 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).
Secondary	
• The percentage of pain responders	• Participants with reduction in pain severity of ≥2 points ("average worst pain experienced in the last 7 days"), at week 16 as assessed by an 11-point NRS, compared to baseline.
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• Mood	• The change from baseline to week 16 in the HADS score.
• Motor and non-motor symptoms	• The change from baseline to week 16 in the MDS-UPDRS (total score and subscores) during the "ON" phase.
• Safety & Tolerability	• Descriptive

4. Study Design

4.1. Overall Design

- International, multicentre, randomised, double-blind, placebo-controlled study.
- Two treatment groups, active & placebo, randomized 2:1.
- Up to 132 participants will be screened, of which approximately 105 will be enrolled, to have 84 evaluable participants (56 active: 28 placebo).
- 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, total duration 19 weeks.
- Study medication consists of active and matching placebo, presented in identical wallets, and during the first week of the treatment period participants will start with 50 mg dose for 1 week, before taking 100 mg which should contribute to maintaining the blind.
- Participants have a diagnosis of IPD (according to United Kingdom Parkinson's Disease Society Brain Bank criteria for at least 5 years), Hoehn and Yahr stage between 2-3 inclusive during the "ON" phase, experiencing motor fluctuations while on stable doses of L-Dopa (with or without benserazide/carbidopa, with or without addition of a catechol O-methyltransferase (COMT) inhibitor) and may be on stable doses of other PD medications (a dopamine agonist, an anticholinergic and/or amantadine), yet are experiencing chronic PD related pain.

4.2. Scientific Rationale for Study Design

The guideline on clinical investigation of medicinal products in the treatment of Parkinson's Disease (EMA/CHMP/330418/2012 rev. 2 dated 21 June 2012), paragraph "Symptomatic relief in patients with Parkinson's Disease on L-Dopa+", recommends performing placebo-controlled double-blind studies, in order to establish unequivocal safety and efficacy data in this patient population, as follows: "In patients with some form of advanced PD the test drug may be given as adjunctive to L-Dopa+. These patients may suffer from an insufficient control of motor symptoms despite treatment with L-Dopa+ or may suffer from dose dependent or non -dose dependent motor fluctuations.

The use of placebo in addition to background standard of care (SoC) therapy in this study is based on the ICH Topic E10 guideline on the "Choice of control group in clinical trials" (CPMP/ICH/364/96) and is in accordance with the EMA position for "Use of placebo in clinical trials with regard to the revised Declaration of Helsinki" (EMEA/17424/01).

As for participants who experience periodic worsening of their chronic pain during treatment or follow-up periods of the study, they may take PRN medications.

4.3. Justification for Dose

The dose of 100 mg/day (titrated from 50 mg/day after 1 week) was selected based on the results of the previous studies in PD patients and from the results of the post-hoc analysis on the effects of safinamide on pain.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the follow-up phone call after Visit 5 (End of Treatment) which is the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 30 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosed with IPD by using the United Kingdom Parkinson's Disease Society Brain Bank criteria for more than 5 years duration.
3. Receiving treatment with a stable dose of oral L-Dopa (including controlled release [CR], immediate release [IR] or a combination of CR/IR), with and without benserazide/carbidopa, with or without addition of a catechol O-methyltransferase (COMT) inhibitor and may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine for at least 4 weeks prior to the randomisation (baseline visit).
4. Hoehn and Yahr stage between 2-3 (inclusive) during the "ON" phase at the screening visit.
5. Experiencing motor fluctuations following optimum titration of treatment medications and within the 4 weeks immediately prior to randomisation.
6. Experiencing chronic pain (i.e. ongoing for ≥3 months prior to screening visit); the Investigator must consider chronic pain directly related to PD and not explained by any other health problem (e.g. peripheral neuropathy, organ disease or arthritis pain) OR consider the intensity of chronic pain specifically aggravated by PD.
7. If taking regular analgesics, the treatment regimen should be stable in the 4 weeks prior to the randomisation visit.
8. Able to maintain an accurate and complete electronic diary with the help of a caregiver.

Sex

9. Male or female

a. Female participants:

- A female participant is eligible to participate if she is not pregnant (see Appendix 4), not breastfeeding, and at least one of the following conditions applies:

    i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 4

OR

ii. A WOCBP who agrees to follow the contraceptive guidance in Appendix 4.

Informed Consent

10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any form of Parkinsonism other than IPD.
2. Diagnosis of chronic migraine (>15 days per month) or cancer pain.
3. History of bipolar disorder, depression, schizophrenia or other psychotic disorder requiring treatment with neuroleptics.
4. History of dementia or cognitive dysfunction.
5. Severe, peak dose or biphasic dyskinesia.
6. Unpredictable or widely swinging fluctuations.
7. Ophthalmologic history including any of the following conditions: albinism, uveitis, retinitis pigmentosa, retinal degeneration, active retinopathy, severe progressive diabetic retinopathy, inherited retinopathy or family history of hereditary retinal disease.
8. Moderate or severe liver failure using the Child-Pugh classification score.
9. History of drug and/or alcohol abuse within 12 months prior to screening as defined by the current edition of the Diagnostic and Statistical Manual of Mental Disorders.
10. Allergy/sensitivity, intolerance or contraindications to Safinamide.

Prior/Concomitant Therapy

11. Treatment with monoamine oxidase inhibitors (MAOIs), levodopa infusion, pethidine, fluoxetine, fluvoxamine less than 4 weeks prior to the randomisation visit.

Prior/Concurrent Clinical Study Experience

12. Use of any investigational drug or device within 30 days prior to screening or 5 half-lives, whichever is the longest.
13. Previous treatment with Safinamide in the 9 months before the screening visit

Diagnostic assessments

14. Mini-Mental State Exam (MMSE) total score <24 at screening.
15. NRS score $\leq$ 4 points at randomization visit.

Other Exclusions

16. Any clinically significant condition which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for participants while in the study.

5.3. Lifestyle Considerations

Not applicable, no dietary restrictions.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once within six weeks.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study Intervention Name:	Active	Placebo
Dosage formulation:	Safinamide methanesulfonate Excipients: microcrystalline cellulose, crospovidone, colloidal silicone dioxide, magnesium stearate, and for the coating: purified water, hypromellose and polyethylene glycol. Candurin® pigments are included for colour modification	microcrystalline cellulose, crospovidone, colloidal silicone dioxide, magnesium stearate, and for the coating: purified water, hypromellose and polyethylene glycol. Candurin® pigments are included for colour modification
Unit dose strength(s)/Dosage level(s):	50 mg, 100 mg safinamide (free base)	-
Route of Administration	Oral	
Dosing instructions:	Once daily, with or without food, at breakfast time when taking the morning dose of L-Dopa	

Packaging and Labeling	Study Intervention and placebo will be provided in PVC/PVDC60/Al blisters. Blister Wallets are used Each wallet will be labeled with a booklet label 3 wallets will be placed into a carton: 1x Wallet Visit 2, 1x Wallet Visit 3, 1x Wallet Visit 4 Each carton will be labeled with a booklet label Tamper seals applied.	
Manufacturer	Catalent, Schorndorf, Germany in alternative Zambon S.p.A., Vicenza, Italy	Zambon S.p.A., Vicenza, Italy
Primary Packaging	Catalent, Schorndorf, Germany in alternative Zambon S.p.A., Vicenza, Italy	
Secondary Packaging	Almac, Craigavon, United Kingdom	

6.2. Preparation/Handling/Storage/Accountability

Study medication will be stored on-site in a secure area with access limited to the Investigator and authorised study personnel.

No special procedures for the storage or the safe handling of the study medication are required.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. *
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). *
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

5. The Sponsor and their authorized representatives such as study monitors or auditors as well as regulatory inspectors will be permitted, upon request, to audit the supplies, storage and dispensing procedures and records in accordance with applicable regulatory requirements

*= COVID- 19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, a Contingency Plan has been finalized describing alternative procedures to be adopted in the study in order to mitigate the restrictions and keeping participants in the trial (see Appendix 10 for details)

6.3. Measures to Minimize Bias: Randomization and Blinding

At screening, each participant who has signed an informed consent form and is screened will be allocated, by the IWRS, a screening number comprising the prefix 'xx' where xx is the unique site number and a 3-digit number representing the sequential order in which they are screened, e.g. 01-001, 01-002, 02-001 etc.

Participants who meet all criteria for enrolment will be randomised to double-blind treatment in a 2:1 ratio either to safinamide or placebo at visit 2 (day 1)

Investigators will be able to randomise participants using a web-based interactive web response system (IWRS) which is fully integrated within the eCRF.

The IWRS will allocate a unique medication kit number which will consist of a 4-digit number starting with 1001, 1002, etc.

Study using IWRS	All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System IWRS). Before the study is initiated, the log in information & directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in SoA. Returned study intervention should not be re-dispensed to the participants.

Blind Break (IVRS/IWRS)	The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant'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.

6.4. Study Intervention Compliance

The prescribed dosage, timing and mode of administration of study medication may not be changed.

Study medication accountability and subject compliance will be documented throughout the treatment period using study-specific study medication dispensing and return record forms.

Participants will be asked to return all unused medication. From Visits 3 to 5 (weeks 4 to 16), the study medication dispensed at the previous visit will be retrieved by the Investigator and compliance assessed by tablet count.

Non-compliance is defined as taking less than 80% of study medication during any visit-to-visit evaluation period.

Participants exhibiting non-compliance will be reminded about the importance of being compliant with the study dosing regimen.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study will be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

In particular, all pain medication taken on a PRN basis (e.g. paracetamol, up to a maximum of 4,000mg/day; NSAIDs) will be recorded in the dedicated section of eCRF.

In addition, patients will continue to use their regular non PRN pain medication, if taken, (e.g. oxycodone, codeine, botulinum toxin, gabapentin, nortriptyline, muscle relaxants, analgesics) which should remain stable from the 4 weeks prior to randomization visit and at least for the first 4 weeks of the study.

If the patient is using a combination analgesic that contains paracetamol, extreme caution must be exercised in the use of PRN medications containing paracetamol, so as not to exceed a paracetamol total daily dose of 4000 mg (see section 6.5.2)

Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Rescue Medicine

Not Applicable

6.5.2. Excluded Medicine

Treatment with the following drugs is not allowed 4 weeks before randomization, throughout the study and up 2 weeks after the last dose of study drug:

- Monoamine oxidase inhibitors (MAOIs),
- Levodopa infusion,
- Pethidine,
- Fluvoxamine,
- Fluoxetine,
- Combination analgesic products including paracetamol are permitted, but extreme caution must be exercised in the use of PRN medications containing paracetamol so as not to exceed a total daily dose of 4000mg paracetamol

The use of any prohibited concomitant medication is a protocol deviation and should be recorded.

6.5.3. Permitted Medication

Selective serotonin reuptake inhibitors (SSRIs) ,other than fluoxetine or fluvoxamine, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants can be administered provided they remain at the lowest effective dose and remain stable throughout the study

Dextromethorphan, sympathomimetics, nasal and oral decongestants or cold medicinal products containing ephedrine, pseudoephedrine, phenylephrine or phenylpropanolamine are permitted if used for treating cough but must be used with caution.

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

Phone call at one week after EoT.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Not applicable

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- Pregnant participants must be withdrawn from the study without delay

Participants who are withdrawn from the study will not be replaced.

In the event that a subject discontinues from the study prematurely due to an AE or SAE, they will be followed until the event has resolved (returns to normal or baseline values) or has stabilised.

The reason for withdrawal of a subject from the study must be fully documented in the eCRF as well in source documents.

Any major or critical deviation which may have an impact on study results and or safety of the participants should be immediately reported to Sponsor/CRO and notified to Regulatory Authorities (EC/CA) according to local regulations. A decision will be taken by the Sponsor, after consultation with the medical monitor as to whether or not the subject affected by the departure from the protocol, is to continue in the study. A deviation log will be maintained to track actual deviations and decisions taken, including all deviations occurred.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 20 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Local labs will be used in this study

Visit 1: Screening visit (7 to 14 days before Day1)

The screening visit (Visit 1) should take place at least 7 days prior to Visit 2 to allow sufficient time to receive lab results and for subject to complete 7 days' worth of diary data, to fully assess eligibility.

- Obtain written informed consent.
- Record details in IWRS (Section 6.3) for screening number allocation.
- Record demographic data, including age, sex, ethnicity, smoking and alcohol use.
- Record of medical history and PD diagnosis, including Hoehn and Yahr stage.
- Recording of prior medications, concomitant medications (including PRN medication for pain) and therapies (Section 6.5).
- Neurological examination.
- MMSE (Section 8.2.3).
- Physical examination (Section 8.2.1).
- Vital signs (heart rate, systolic and diastolic blood pressure) measured after at least 5 minutes in the supine position (Section 8.2.2).
- Blood sampling for clinical laboratory assessments (haematology and clinical chemistry, including liver function tests) (Section 8.2.4 & 10.2).
- Show the subject how to use the electronic diary (Section 8.1.1).
- Check of inclusion and exclusion criteria (Sections 5.1 and 5.2).

- Issue electronic diary with instructions for the NRS pain assessment and PRN pain medication intake to be completed daily over the seven consecutive days immediately prior to the baseline visit (Visit 2).
- When agreeing the visit schedule with the subject, bear in mind that scales & questionnaires should be done at approximately the same time of day, preferably at least one hour after the usual morning L-Dopa dose (and study medication), when participant is in an optimal ON state.

Visit 2: Baseline visit (Day 1)

At Visit 2, if subject is eligible, the baseline values will be established, and the first dose of study medication will be administered under supervision at the site.

- NRS score of pain intensity > 4 for eligibility, as recorded in the electronic diary. (Section 8.1.1).
- Check of inclusion and exclusion criteria. If participant is eligible, upon completing the data entry in the EDC system the randomization form will appear to randomise subject.
- Vital signs (heart rate, systolic and diastolic blood pressure) measured after at least 5 minutes in the supine position.
- Urine sampling for urine (dipstick) pregnancy test for women of child-bearing potential (WOCB).
- Completion of MDS-UPDRS (part IB and II) and HADS by the subject (Section 8.1).
- Completion of MDS-UPDRS (part IA, III and IV) and CGI-S by the rater (Section 8.1).
- Administer subject's first dose of study medication (50 mg) at the study centre.
- Instruct participants to take the study medication, once daily, in the morning, along with their usual dose of L-Dopa. During Week 1 subject will take 50 mg, which will be increased up 100 mg at home on Day 8.
- Dispense study medication for the next 28 days.
- Re-issue electronic diary with instructions for the NRS pain assessment to be completed daily over the 7 consecutive days immediately prior to the visit at week 4 (Visit 3) and the intake of PRN pain medication to be recorded daily according to use.
- Recording of prior medications, of concomitant medications and therapies.
- Recording of AEs (Section 8.3).

When scheduling Visits 3, 4 and 5, bear in mind that:

- where possible, the subject should be in an optimal ON state, i.e. at least 1 hour after the morning dose L-Dopa and study medication.

- the questionnaires should be completed at the approximately on the same time of the day as at the baseline visit.

COVID- 19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, a Contingency

Plan has been finalized describing alternative procedures to be adopted in the study in order to mitigate the restrictions and keeping participants in the trial (see Appendix 10 for details).

Visit 3 & Visit 4: interim visits (Day 28 & Day 56)

- Completion of MDS-UPDRS (part IB and II), and PGI-C by the subject.
- Completion of MDS-UPDRS (part IA, III and IV), CGI-S and CGI-C by the rater.
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Drug accountability.
- Review and evaluate daily diary (provide additional daily diary training, as required).
- Re-issue electronic diary at weeks 4 and 8, with instructions for the NRS pain assessment and the intake of PRN pain medication to be completed daily over the 7 consecutive days immediately prior to the next visit (Visits 4 & 5).
- Dispense study medication for next period.

COVID- 19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, a Contingency Plan has been finalized describing alternative procedures to be adopted in the study in order to mitigate the restrictions and keeping participants in the trial (see Appendix 10 for details).

Visit 5: End of Treatment (Day 112)

Following completion of 16 weeks' of treatment or in the event of premature discontinuation, the following End of Treatment (EOT) assessments and procedures should be performed.

- Neurological & Physical examination.
- Vital signs (heart rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- MDS-UPDRS (part IB and II), HADS and PGI-C completed by the participant.
- MDS-UPDRS (part IA, III and IV), CGI-S and CGI-C completed by the rater.
- Obtain blood sample for clinical laboratory assessments (haematology and clinical chemistry).
- Obtain urine sample only for WOCBP for urine (dipstick) pregnancy test.
- Record any changes or new concomitant medications and therapies.
- Record any AEs.
- Review and evaluate daily e-diary.
- Drug (all used & unused study medication) and final accountability.
- Collect e-diary.
- Agree on day & time for the follow up call in one weeks' time.

COVID- 19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, a Contingency Plan has been finalized describing alternative procedures to be adopted in the study in order to to mitigate the restriction sand keeping participants in the trial (see Appendix 10 for details)

8.1. Efficacy Assessments

Site personnel who are to be involved in performing the efficacy assessments must be experienced in the use of the various scales and questionnaires.

To ensure consistency of ratings on each efficacy measure for each participant during the study, the same rater should perform the assessments where possible.

Wherever possible the NRS, part IB and II of the MDS-UPDRS, the HADS and the PGI-C should be completed by the participant. However, in the case of the participant's incapacity, for example due to dyskinesia, tremor, etc., the participant's caregiver may complete the NRS, part IB and II of the MDS-UPDRS, the HADS and the PGI-C based on information reported by the participant.

The following parameters are to be completed by the rater:

- MDS-UPDRS (part IA, III and IV).
- CGI-S.
- CGI-C.

8.1.1. Pain Assessments

The primary efficacy endpoint for the study is the mean change in pain severity ("average pain experienced in the last 7 days"), as assessed by an 11-point NRS, from baseline to week 16.

Pain severity data will be derived from the daily diary.

Daily Diary

An electronic diary will be completed daily by each participant as follows:

- to record the PD pain score at screening (Visit 1), by completion of an 11-point NRS, to confirm eligibility
- the NRS score is calculated over 7 consecutive days immediately prior to baseline (Visit 2/Day 1) and Visits 3, 4 and 5-/EOT/ET (Weeks 4, 8 and 16), completion of an 11-point NRS, to allow for the assessment of the average pain experienced in the last 7 days during which patient records on a daily basis the most severe pain using an 11-point NRS.
- on a daily basis from baseline onwards, an accurate record of the use of PRN pain medication for PD-associated pain (Section 10.1.6.2).

Daily Diary Training

At the screening visit, the Investigator (or other trained, qualified personnel) will reinforce recognition of PD-related chronic pain, as well as the use of the daily diary.

On each visit, the Investigator will instruct the participant to complete the daily diary at home for the 7 consecutive days immediately prior to the next visit.

Participants will record the intensity of their PD-associated pain, as the worst pain experienced over the past 24 hours, (from 0 [no pain] to 10 [worst possible pain]) using an 11-point NRS. Pain intensity should be recorded if possible, in the evening before going to sleep. If the subject suffered from more than 1 PD-associated pain, the more severe pain will be documented.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system and nervous system.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Blood pressure and heart rate will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Measurement should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.3. Cognitive Impairment

Participants will be evaluated for cognitive impairment using the MMSE. The MMSE (Folstein et al, 1975) is a brief practical screening test for cognitive dysfunction. The test consists of 5 sections (orientation, registration, attention and calculation, recall, and language) and has a total possible score of 30. It will be used as a quick method to assess the severity of cognitive dysfunction. The MMSE will be used for screening participants (a total score < 24 is exclusionary).

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study both in the appropriate section of eCRF study's visit and in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 2 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Suicidal Risk Monitoring

Not applicable.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7)

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All (S)AEs will be collected from the signing of the informed consent form (ICF) until the follow-up call at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it in the Investigator Study File and will notify the IRB/IEC, if appropriate according to local requirements.
- The reference safety information for this study is the Summary of Product Characteristics of Safinamide

8.3.5. Pregnancy

- Details of all pregnancies in female will be collected after the start of study intervention and until 1 month after the last dose of study drug
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.4. Treatment of 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.

There is no known antidote to safinamide or any specific treatment for a safinamide overdose. If a significant overdose should occur, safinamide treatment should be discontinued and supportive treatment should be administered as clinically indicated.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE or laboratory abnormalities
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health Economics are not evaluated

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis is that safinamide is not able to reduce pain severity compared to placebo.

9.2. Sample Size Determination

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

Approximately 220 participants will be screened to achieve 177 randomly assigned to study intervention and of which approximately 144 participants complete the study (96 and 48 evaluable participants 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 is 1.43.

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 drop out rates. These are summarized below in Table below

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

It is now 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.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

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 decision whether a protocol deviation is relevant or not for the exclusion of participants 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.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

- Primary efficacy endpoint

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.

The primary efficacy endpoint, change from baseline to Week 16 in pain severity score, will be analyzed using a mixed model repeated measures (MMRM) using visit on subject ID as the repeated factor with unstructured covariance term.

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.

- Secondary efficacy endpoint

Percentage of pain responders defined as 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 weeks 4 and 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 the 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 weeks 4, 8 and 16;

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 subscores) during the "ON" phase;

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.

The analysis of amount of concomitant PRN PD pain medication (as reported in the Patient Diary) and concomitant pain drugs (as reported on the "Concomitant Medication" eCRF page) will be done in the same way at weeks 4, 8 and 16

PGI-C, CGI-C, CGI-S, and MDS-UPDRS will be analysed at weeks 4, 8 and 16 using the same statistical method as for the primary efficacy parameter.

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.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Descriptive statistics analysis will be applied to safety variables and the summaries will be presented in descending order of frequency by SOC. Likewise, within each SOC, the PTs will be presented by descending order of frequency.

9.4.3. Baseline Descriptive Analyses

Data collected at screening visit (i.e. age, sex, ethnicity, smoking and alcohol use, MMSE score, Hoehn and Yahr stage, duration of PD, as well as the participant's Medical History, Prior and Concomitant medication) will be tabulated with descriptive statistics or counts/percentages depending on the variable and where appropriate.

9.5. Interim Analyses

No interim analysis planned.

9.5.1. Data Monitoring Committee (DMC)

No Data Monitoring Committee planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent

that meets the requirements of ICH E6 (R2) Good clinical practice, local regulations, Regulation (EU) 2016/679 (GDPR) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Internal approval process involves protocol reviewed by the Protocol Review Committee, Pharmacovigilance & Quality Assurance.

10.1.6. Dissemination of Clinical Study Data

A Clinical Trial Report of the study will be prepared and written by the CRO according to ICH topic E3 (CPMP/ICH/137/95). A summary of the report will be sent to Investigators / ECs / Regulatory Authorities, according to current regulations.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- As per ICH E6 document, section 1.52, source documents are defined as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report, by signing and dating it.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count			White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
		Calcium	Alkaline phosphatase	Gamma-glutamyltranspeptidase
Pregnancy Tests:	Dipstick - urine pregnancy test			

NOTES :

[1] All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: 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.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to CRO's Pharmacovigilance in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Medical Monitor or Pharmacovigilance. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the requestor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Summary of Product Characteristics of Safinamide in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Pharmacovigilance. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pharmacovigilance.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide CRO's Pharmacovigilance with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to pharmacovigilance within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Pharmacovigilance via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pharmacovigilance will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the Investigator Study File.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categ**ories are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 2.

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information:

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.5. Appendix 9: Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
CA	Competent Authority
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
COMT	Catechol-O-methyltransferase
CR	Controlled release
CRF	Case report form
CRO	Contract research organization
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
EMA	European Medicines Agency
EOT	End of treatment
ePRO	Electronic patient reported outcomes
ET	Early termination
FAS	Full analysis set
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale

HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization (now International Council on Harmonization)
IMP	Investigational medicinal product
IPD	Idiopathic Parkinson's Disease
IR	Immediate release
IWRS	Interactive web response system
L-Dopa	Levodopa
LOCF	Last observation carried forward
MAO-B	Monoamine oxidase-B
MAOI	Monoamine oxidase inhibitor
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
MMSE	Mini-mental State Examination
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
od	Once daily
PD	Parkinson's Disease
PGI	Patient Global Impression
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PP	Per protocol

PT	Preferred term
SA	Safety analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SETTLE	SafinamidE Treatment as add-on To LEvodopa in idiopathic Parkinson's disease with motor fluctuations
SOC	System organ class
SOP	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction

10.6. Appendix 10: Contingency Plan

Zambon PAIN study Coronavirus (2019-nCoV)

Contingency Plan - V7 – 07 April 2020

Study Code: Z7219M01

EUDRACT number : 2017-002426-20

Background and Rationale

CDC is closely monitoring an outbreak of respiratory illness caused by a novel (new) coronavirus (named "2019-nCoV") that was first detected in Wuhan City, Hubei Province, China and which continues to expand. On January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization declared the outbreak a "public health emergency of international concern" and subsequently on March 11, 2020 the pandemic status has been declared. Coronaviruses are a large family of viruses that are common in many different species of animals, including camels, cattle, cats, and bats. Rarely, animal coronaviruses can infect people and then spread between people such as with MERS, SARS, and now with 2019-nCoV.

In response to this outbreak, many restrictions have been implementing by government and health departments in the affected countries. These restrictions include but are not limited to the establishment of quarantine zones, recommended self-quarantine periods, and travel restrictions. To mitigate the impact of such restrictions on the conduct of these studies and ensure the safety and wellbeing of participating patients and investigator sites, as well support patient retention and maintain data integrity, the following plan has been created.

1. Close monitoring of the contingency and monitoring activities

In the agenda of the study regular calls between Zambon and CRO, a specific item for discussion should be added aimed at sharing for each of the countries involved in the study the current status of the coronavirus emergency (government recommendations, any specific restriction in the areas of the study sites) covering:

- impacts on the study enrolment/patients' visit at site: for this topic please refers to sections 2 and 3)

- impacts on monitoring activities: for this topic, on top of what is reported in section 2, please note that Zambon should be informed about any CRO's restrictions in performing visit activities at site; all the efforts should be spent to respect the monitoring visit frequency as per Monitoring Plan; deviations should be documented and approved by Sponsor. The Monitoring plan will be updated and will reflect the new conditions for the micro-management. The updated monitoring Plan will be approved by Zambon.

2. Communication with site

Ongoing communication with the PI/site should happen according to the study specific frequency agreed with Zambon until the concerned site continues activity under standard working conditions. The frequency of the communications should be increased after agreement with the Zambon if the status at site changes.

Topics to be discussed during the calls (on top of the standard ones):

a) Investigate any potential issue related to coronavirus outbreak

b) Health status of patients (AE/SAE recording)

c) Inform the PI/site of any delay to planned SIV or MV.

d) Confirm with the PI/sites whether or not they plan to continue enrolling new patients.

e) Perform remote motoring (details will be in the MP)

f) For sites with ongoing patients, please see next section.

3. Sites with ongoing patients:

Wherever possible, every effort should be made to have the patient attend the hospital for their on site study visits according to the schedule in the protocol.

During the contact with sites please consider the following options that should be discussed case by case and approved by Zambon prior to implementation:

a) If the patient does not want to go the hospital for the visit or they are not allowed by local authorities, the following can be explored with the site in order to maintain patient retention and then feedback to Sponsor for approval:

- Recommend patients to use private car/driver or to pay a taxi for the on site visits. Costs will be reimbursed upon the evidence of receipts;

- Decide whether assessment might be performed via phone call like for example interviewing patients about general health conditions (Adverse Event, Concomitant Medication) and collection of vital signs using patient's domestic equipment (if feasible). The study's e-questionnaires MDS-UPDRS, CGI-s and CGI-c to be completed by the site staff at specific study visits through the study device might be compiled during the phone call. In case of site inability in using the site-based device, the site staff might make use of the paper version of the e-questionnaires which will be provided by the Sponsor.

  The data collected through the paper form will then be transferred into the specific study database via data correction form. This will also be documented in medical charts and paper forms retained as source document.

- Patient verbal consent to continuing in the study and to being contacted by site staff via phone call will be documented in medical charts as well as the details of which assessment have been done via phone call and with which equipment and method

b) If the clinic location where study visits are routinely performed is not available due to the Coronavirus outbreak (e.g. closed, being utilized for non-study purposes, etc.), sites may conduct study visits at a suitable alternative location and lab samples can be taken and analysed from the local lab of the alternative site (every effort should be spent to collect normal ranges). In such case, it should first be checked if there is any regulatory or ethical implication for involving an alternative location.

c) Confirm with the site if it is permitted by the EC/GCP/local authorities to send study drug directly to the patient's home. If the study drug is to be sent to patient's home, the patient must also confirm their agreement for the courier to be provided with their name and address for shipping purposes. This confirmation will be documented in the patient's source notes. The patient's name and address will not be provided to any other parties (e.g. Sponsor, CRO, vendor, etc.). Upon receipt of study drug, the patient should promptly inform the site staff if the drug has been received in good condition. Site staff need to document the entire process from site to home in the patient chart.

Site can also explore if a patient's care-giver is willing to go at site to pick up the IMP.

Details will be given at sites case by case according to the recommendation coming from regulatory/local authorities.

d) Where required, patient visits may be changed beyond the maximum visit window permitted in the current approved protocol. The permissible duration of any delay will be assessed on a case by case basis and supported by a phone call between PI/study staff and

patient in order to assess any potential adverse events (AEs), whether the patient has sufficient study supplies and to confirm the patient's status and wellbeing. Patients will continue on study treatment at home during this extension and the site is authorised to allow subjects to administer the additional tablets present in the wallet that are in the 'grey colored slots' and that are marked as Do Not Take in the IP label. As confirmed by Almac (CMO responsible for IP secondary packaging) the tablets in those slots can be dispensed in the same manner as for the other tablets in the wallet and there are no blinding concerns

- Patient verbal consent to continuing in the study and to being contacted by site staff via phone call will be documented in medical charts.
- All decisions regarding patient re-scheduling and follow-up must be clearly documented in the patient's source notes.
- The CRA will document all patient visits performed outside of the protocol defined visit window as protocol deviations, referencing this contingency plan.
- In cases where approval is given to extend home-treatment for a patient, and they do not have sufficient IMP to enable continued treatment until the rescheduled visit date, the site will ship additional IMP to the patient (please refer to paragraph 3c). If not feasible, Zambon may consider with ALMAC the IMP delivery at patient home. Details will be given at sites case by case according to the recommendation coming from regulatory/local authorities. For IMP shipping from site to patient home, a dedicated courier appointed by the Sponsor/CRO/site will be involved and a data privacy infographic for the subject will be included in the shipping packaging either by site pharmacist or directly by the appointed courier

e) At the end of the 2019-nCoV emergency and when it will be possible to reach the site, the subject or caregiver/familiar will return the IP and eDiaries to site at the earliest opportunity. The site staff will ensure it and will document it in the patient's source document

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