# A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide, as add-on therapy, in idiopathic Chinese Parkinson's Disease (PD) patients with motor fluctuations treated with stable doses of levodopa

**ClinicalTrials.gov Identifier: NCT03881371**

**Protocol: Final 1.0, 10 Oct 2018**

**Protocol Amendment No.1: Final 2.0, 08 Oct 2019**

# CLINICAL TRIAL PROTOCOL

## A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SAFINAMIDE, AS ADD-ON THERAPY, IN IDIOPATHIC CHINESE PARKINSON'S DISEASE (PD) PATIENTS WITH MOTOR FLUCTUATIONS TREATED WITH STABLE DOSES OF LEVODOPA

Protocol Code: Z7219L05

Date: 10-October-2018

Version: Final 1.0

Zambon SpA
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# APPROVAL PAGE

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|---|---|
| **Clinical Trial Title:** | A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide, as add-on therapy, in idiopathic Chinese Parkinson's Disease (PD) patients with motor fluctuations treated with stable doses of levodopa. |
| **Protocol Code** | Z7219L05 |
| **Date:** | 10-October-2018 |
| **Authors:** | PPD |
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**Accepted for the Sponsor**

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## LIST OF COMMITTEES

Not applicable.

# 1.0 TABLE OF CONTENTS

# 2.0 ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of daily living |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| BUN | Blood Urea Nitrogen |
| CA | Competent Authority |
| 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 |
| CTP | Clinical trial protocol |
| CYP | Cytochrome P450 |
| 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 |
| GMP | Good Manufacturing Practice |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| 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 |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mL | Millilitres |
| NRS | Numerical Rating Scale |
| od | Once daily |
| PD | Parkinson's Disease |
| PDQ-39 | Parkinson's Disease Questionnaire-39 items |
| po | Per os (By mouth) |
| PP | Per protocol |
| PT | Preferred term |
| QA | Quality assurance |
| PR | Prolonged release |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SETTLE | SafinamidE Treatment as add-on To LEvodopa in idiopathic Parkinson's disease with motor fluctuations |
| SNRI | Serotonin-norepinephrine reuptake inhibitor |
| SOC | System organ class |
| SOP | Standard operating procedures |
| SmPC | Summary of Product Characteristics |
| SSRI | Selective serotonin reuptake inhibitor |
| TEAE | treatment-emergent adverse event |
| TMF | Trial Master file |
| WHO-DD | World Health Organization-Drug Dictionary |

# 3.0 SUMMARY

**Title:** A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide, as add-on therapy, in idiopathic Chinese Parkinson's Disease (PD) patients with motor fluctuations treated with stable doses of levodopa.

**Protocol Code:** Z7219L05

**Phase:** III

**Test Product:** Safinamide film-coated tablets.

**Control Product / Placebo:** Placebo-film coated tablets.

**Dosage:** Safinamide film-coated tablets for oral administration at an initial dose of 50 mg once daily (od) and increased the day after the Visit 3/week 2 (ideally at day 15) to the final dose of 100 mg od. Treatment will continue daily for a total of 16 weeks.

**Objectives:**

Efficacy:

To evaluate the efficacy of safinamide, compared with placebo, as add-on therapy in idiopathic Chinese PD patients with motor fluctuations treated with stable doses of levodopa (L-dopa).

Safety:

To evaluate the safety and tolerability of safinamide.

**Design:** This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study in idiopathic Chinese PD patients, experiencing motor fluctuations while on stable doses of levodopa (alone or in combination with other anti-Parkinson drugs). Study participation will be up to a maximum duration of 18 weeks and will comprise a screening period (up to 2 weeks) and a treatment period (16 weeks).

Screening Period

After providing written informed consent to participate in the study, patients will enter a screening period up to 2 weeks. During the screening period, patients will undergo all the evaluations necessary to establish their eligibility for the study. Patients considered non-eligible ("screening failures") due to clinically significant abnormalities in laboratory exams, ECG or vital signs, could be re-screened again only once during the study after a reasonable interval of time, based on the judgement of the Investigator that should be fully documented and explained in the clinical records and in the CRF. They would need to sign a new

consent form. Patients who will be confirmed to be non-eligible in this second screening visit should definitively be excluded from the study.
Patients and their caregivers will be trained on the completion of a 24-hour diary card and the last two days of recording prior to each study visit will be used for data analysis.

*The dose of L-dopa and of the other anti-Parkinson drugs (if any) must be kept constant during the screening period.*

Treatment Period

At baseline (day 1), eligible patients will enter the treatment period and will be randomised to receive either safinamide (initial 50 mg titrated to 100 mg the day after the Visit 3/week 2, ideally at day 15) or matching placebo, orally od in a 1:1 ratio. The investigational medicinal product (IMP) will be taken in the morning at breakfast time, in addition to the morning dose of L-dopa and other (if any) PD medications.
Following completion of all baseline assessments, they will receive the first dose of safinamide or placebo (50 mg) at the study centre. The day after the Visit 3/week 2 (ideally at day 15) the dose will be increased at home to 100 mg od. Each patient will receive treatment for 16 weeks, with visits at week 0/day 1 (baseline) and at weeks 2, 6, 10 and 16 (or early termination). A telephone follow-up will be performed 1 week after the end of treatment for safety reasons.
Patients who prematurely withdraw from the study while receiving study medication should complete the early termination visit assessments, when possible.
At the end of the study, the patients will be instructed to contact immediately the Investigator in case of appearance of any adverse reactions. Any ongoing adverse event or clinically abnormal laboratory parameter will be followed until resolution. In addition, all SAEs occurring within 30 days after a patient's last dose of study drug will be followed to their conclusion.

*The dose of L-dopa and/or of the concomitant anti-Parkinson treatments must be kept constant throughout the study.*

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

Efficacy will be assessed by the changes in "OFF" and "ON" time from the 24-hour patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Clinical Global Impression (CGI), the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the Numerical Rating Scale (NRS).
Safety will be assessed by clinical laboratory tests (haematology and serum chemistry), vital signs, 12-lead electrocardiogram, physical examination, adverse events and concomitant medications.
The visit procedures are summarised in the Study Flow Chart Section 29.0, Appendix 1.

**Sample Size:** Sample size was computed through a Monte Carlo study with 1000 runs and using a fixed sequence procedure to account for multiplicity over the study primary endpoint (change from baseline to week 16 in the mean total daily "OFF" time) and the key secondary endpoint (change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS). The fixed sequence procedure implies that the key secondary endpoint will be verifiable provided that the primary endpoint has achieved statistical significance (namely two-tailed p-value ≤ 0.05).
Based on the Monte Carlo simulation it was estimated that a total sample size of 260 patients (130 in the safinamide and 130 in the placebo groups) ensures 90% power to detect a mean difference in the 'off' time at least 0.9 h between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming standard deviations of 2.35 for safinamide and 2.06 for placebo.
Moreover, the same Monte Carlo study showed that the total sample size of 260 patients would also permit a marginal power equal to 88% to detect 1 point treatment difference in the NRS between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming a pooled standard deviations of 2.0.
Assuming an attrition rate equal to 15% a total of approximately **306 patients** will be **randomized** (153 in the safinamide and 153 in the placebo groups).

**Population:** **Inclusion criteria:**

1. Male or female patients aged ≥18 years old.
2. Chinese ethnicity.
3. Able to understand and willing to provide written informed consent.
4. Able to maintain an accurate and complete 24-hour diary with the help of a caregiver if needed.
5. Diagnosis of idiopathic Parkinson's Disease (IPD) using

the United Kingdom Parkinson's Disease Society Brain Bank criteria of more than 3 years duration.

6. Be levodopa responsive and receiving treatment with stable daily doses 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 dopamine agonists, anticholinergics and/or amantadine for at least 4 weeks prior to the screening visit.
7. A Hoehn and Yahr stage between 1-4 inclusive during the "ON" phase.
8. Experiencing motor fluctuations with a minimum of 1.5 hours/day of "OFF" time during the day (excluding morning akinesia), based on historical data.
9. If female, be post-menopausal for at least one year or have undergone hysterectomy or, if of child-bearing potential, must have a negative pregnancy test, must neither be breast-feeding nor become pregnant during the study and must use adequate contraception for 1 month prior to randomisation and for up to 1 month after the last dose of study drug. Adequate contraception is defined as:

a) Hormonal oral, implantable, transdermal, or injectable contraceptives or a non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit;
b) a male sexual partner who agrees to use a male condom with spermicide or a sterile sexual partner.

For all women of child-bearing potential, urine pregnancy test result at screening must be negative.

**Exclusion criteria:**

1. Any form of Parkinsonism other than IPD.
2. Diagnosis of chronic migraine (>15 days per month) or cancer pain.
3. L-dopa infusion.
4. Hoehn and Yahr stage 5 during the "ON" phase.
5. If female, pregnancy or breast-feeding.
6. Neurosurgical intervention of PD or stereotactic brain surgery.

7. Severe peak dose or biphasic dyskinesia, unpredictable or widely swinging fluctuations.
8. History of major depression or other clinically significant psychotic disorder which may compromise the ability to provide the informed consent or to participate to the study.
9. Drug and/or alcohol abuse within 12 months prior to the screening visit.
10. History of dementia or severe cognitive dysfunction.
11. Use of any investigational drug or device within 30 days prior to screening or 5 half-lives, whichever is the longest, or during the study.
12. Allergy/sensitivity or contraindications to the investigational medicinal products (IMPs) or their excipients, to anticonvulsants or to anti-Parkinson drugs.
13. Any clinically significant condition (including laboratory values) which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for patients while in the study.
14. Moderate or severe liver failure using the Child-Pugh classification score, or human immunodeficiency virus (HIV).
15. Treatment with monoamine oxidase inhibitors (MAOIs), pethidine, opiates, opioids, fluoxetine, fluvoxamine in the 4 weeks prior to the screening visit. These drugs are not allowed throughout the study and up 2 weeks after the last dose of study drug.
16. 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.

**Endpoints**

Primary Endpoint:

- The change from baseline to week 16 in the mean total daily "OFF" time, as assessed by 24-hour patient diary cards.

Key Secondary Endpoint:

- The change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS).

Other Secondary Endpoints:

- The change from baseline to week 16 in the mean total daily "ON" time, as assessed by 24-hour patient diary

cards.

- The change from baseline to week 16 in the mean daily "ON" time with no/non-troublesome dyskinesia, as assessed by 24-hour patient diary cards.
- The change from baseline to week 16 in the UPDRS total score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part II (ADL) score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part III (motor function) score during the "ON" phase.
- The CGI-S score at week 16.
- The change from baseline to week 16 in the CGI-C.
- The change from baseline to week 16 in the PDQ-39 score.

Safety Endpoints:

- The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TSAEs).
- Physical examination findings (clinically significant).
- Vital signs (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities.
- 12-lead electrocardiogram (ECG) parameter measures, including occurrence of abnormalities.
- Clinical chemistry and haematology values, including shifts from baseline and occurrence of abnormalities.

**Statistical Analysis**

All efficacy analyses will be performed on the Full Analysis Set (FAS) population. Analysis of the primary and secondary efficacy variables will be also carried out on the Per Protocol (PP) population to assess the robustness of the findings. Safety outcomes will be analysed on the Safety population.

The primary objective of the study is to evaluate the change from baseline to week 16 in the mean "OFF" time, as assessed by the 24-hour patient diary, of safinamide 100 mg/day compared to placebo, given as add-on therapy in PD patients with motor fluctuations on stable doses of L-dopa. The analysis of primary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline mean "OFF" time measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-

tailed 95% confidence intervals and corresponding two-sided p-values.
The key secondary objective of the study is to evaluate the change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS), of safinamide 100 mg/day compared to placebo. Exactly as for the analysis of the primary endpoint, the analysis of key secondary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline NRS measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.

The overall type I family-wise error rate for testing the primary endpoint and key secondary endpoint will be controlled at the two-tailed 0.05 significance level using a fixed sequence procedure. This procedure will be fully described in the protocol.

The same statistical approach (ANCOVA) will be taken for the analysis of change from baseline to week 16 of all the other supportive secondary end-points listed above with the exclusion of CGI-S and CGI-C scores which will be analysed using the Wilcoxon-Mann-Whitney test stratified by centre. For the analyses of supportive secondary efficacy end-points no adjustment of significance level will be made to account for multiple comparisons.

The main time point for comparison between treatment groups is week 16, but other available measurements at other visits will be analysed as well.

Missing data on the primary and key secondary efficacy endpoints will be imputed using multiple imputation (MI) as the primary imputation method and last observation carried forward (LOCF) as sensitivity analysis. Missing data on all the other secondary efficacy endpoints will be imputed only using LOCF approach.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The analysis of adverse events will include summary tables displaying counts and percentages of patients experiencing adverse events by system organ class (SOC) and preferred term (PT). If a patient has more than one AE which codes to the same PT, the patient will be counted only once for that PT. The total number of events documented per SOC and PT will also be displayed. All other safety data will be analysed descriptively.

**Concomitant Treatments**

- 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.

Concomitant medications that are considered necessary for the safety and well-being of the patient are permitted during the study at the discretion of the Investigator, with the exception of the non-permitted drugs described here below.

**Non-permitted concomitant drugs are:**

- L-dopa infusion
- Opioids and opiates
- Fluoxetine or fluvoxamine
- Pethidine
- Any other investigational agent
- Traditional Chinese medicine

*The dose of L-dopa and of the other anti-Parkinson drugs (if any) must be kept constant throughout the study.*

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

In addition, patients must not participate in any other clinical study of an investigational product or device whilst participating in this study.

**Trial Duration:** First Patient In: 01 August 2019

Recruitment Period: Approximately 12 months.

Last Patient Out: 30 November 2020

Clinical Study Report: 31 March 2021

| | |
|---|---|
| **Treatment Duration:** | The study comprises a screening period of 1 to 2 weeks, a treatment period of 16 weeks, and a 1-week telephone follow-up. |
| **Participating Countries** | 1 country (China) |
| **Number of Sites** | Approximately 35 centres |

# 4.0 INTRODUCTION AND RATIONALE

## 4.1 Idiopathic Parkinson's Disease

Idiopathic Parkinson's Disease (IPD) is a neurodegenerative condition characterised 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 aetiology of IPD remains unknown but the involvement of genetic and environmental factors, such as exposures to different toxins, is most probable (1).

The main symptoms of IPD are resting tremor, bradykinesia and rigidity. The disease is also associated with non-motor symptoms such as depression, apathy, erectile dysfunction and gastrointestinal disturbances (2). The incidence of IPD increases with age, with incidence rates in the general population increasing from 0.3 per 1,000 person-years in patients aged 55 to 65 years, to 4.4 per 1,000 person-years for those aged ≥85 years (3).

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 patients will require therapies combining L-dopa and adjunct dopamine agonists, COMT inhibitors and/or MAO-B inhibitors.

Beyond dopamine, perturbations in neurotransmission in the basal ganglia of PD patients are known to involve glutamate and other transmitters and play important roles in the pathogenesis of primary symptoms, motor fluctuations, non-motor symptoms and possibly neuronal cell loss. Targeting non-dopaminergic systems may thus be an alternative approach to improve and control PD motor complications (4).

## 4.2 Background on Safinamide

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 a glutamate modulator. These molecular mechanisms increase brain dopamine, extend L-dopa induced "ON" time (dopaminergic actions) and reduce the severity of L-dopa induced dyskinesia and of some non-motor symptoms such as pain and depression (non-dopaminergic action) (5,6,7,8). By combining inhibition of both MAO-B and sodium channels, safinamide may represent a new strategy for the therapy of PD.

Safinamide has been approved by the European Medicines Agency (EMA) 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) and by the Food and Drug Administration (FDA) as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's Disease experiencing "OFF" episodes. At the current date safinamide is on the market in 11 European countries, in Switzerland and in US.

### *4.2.1 Pharmacokinetics*

Safinamide is almost completely absorbed after oral administration and is cleared from systemic circulation primarily by metabolism, with excretion of the formed metabolites mainly by the kidney and partly by the liver. The elimination half-life of safinamide is approximately 20-24 hours.

The potential for clinically relevant drug interaction due to cytochrome P450 (CYP) induction or inhibition is considered remote as demonstrated by in vitro studies and in a dedicated drug-drug interaction study performed with CYP1A2 and CYP3A4 substrates (caffeine and midazolam). Other drug-relevant CYPs, monoamine oxidase-A and L-dopa decarboxylase, as well as the most important drug transporters, are not inhibited by safinamide or its main human metabolites.

Safinamide does not require any restrictions related to dietary tyramine intake, as assessed by three Phase I trials in healthy volunteers specifically investigating the pressor effect of tyramine, given intravenously or orally (po), during safinamide administration up to 350 mg po (supratherapeutic dose).

### *4.2.2 Toxicology*

Safinamide did not exert pathophysiological relevant effects on the function of the cardiovascular, respiratory, renal and gastrointestinal system nor of the central nervous system.

Retinal degeneration was observed in repeated-dose studies in rat but not in monkey studies. However, these changes have not been noted in any human or non-human primate species despite detailed investigations having been performed for extended periods of time.

Treatment with safinamide was associated with effects on female fertility, embryo-foetal development and post-natal development in rats and rabbits. Fertile women have been excluded from clinical studies with safinamide unless practising adequate contraception.

### *4.2.3 Summary of Clinical Development Data*

More than 3,000 subjects have been enrolled in safinamide studies to date. Of these, >2,600 subjects were enrolled in therapeutic studies, including >2,500 with PD.

The clinical efficacy of safinamide 50 mg/day and 100 mg/day as add-on therapy to levodopa in mid- to late-stage PD patients experiencing motor fluctuations was evaluated in two 24-week, multicentre, double-blind, placebo-controlled trials: study 016 and the SETTLE study (9,10).

The long-term efficacy and safety of safinamide 50−100 mg/day in this patient population were evaluated in study 018, a 18-month, double-blind, placebo-controlled extension of the study 016 (11).

The primary efficacy variable in studies 016 and SETTLE was the change (increase) from baseline to endpoint (week 24) in the mean daily “ON” time (“ON” time without dyskinesia plus “ON” time with non-troublesome dyskinesia). In both trials there was a statistically significant result in the safinamide group compared with placebo, confirmed by a statistically significant reduction in the “OFF” time.

The benefits achieved in the “ON” and “OFF” time in the study 016 were maintained after 2-years treatment, as observed in extension study 018. There was no significant difference between the safinamide and placebo in the overall incidence of adverse events (AEs), serious adverse events (SAEs), laboratory tests, vital signs, ECGs, physical, neurological, dermatological or ophthalmological examinations. Safinamide treatment was not associated with an increase in daytime sleepiness or impulsive compulsive behaviour.

## 4.3 Evaluation of the anticipated risk/benefit ratio

Safinamide has both dopaminergic and non-dopaminergic activities. It is a MAO-B inhibitor (dopaminergic activity), and has also been shown to inhibit the stimulated release of glutamate through the sodium channels blockade (non-dopaminergic activity).

Altogether, these pharmacological properties indicate that safinamide may be beneficial in the treatment of patients with Parkinson’s Disease.

The existing clinical data on safinamide, derived from trials performed in >2,500 PD patients, supports an overall, favourable benefit/risk profile. Safinamide administration has been found to be generally well tolerated and may represent a new treatment strategy for PD, by offering better control of motor symptoms and motor complications with an acceptable safety profile.

Further information is available in the Summary of Product Characteristics (SmPC) (12) and in the Investigator’s Brochure (13).

## 4.4 Study Rationale

The efficacy of safinamide has been demonstrated in patients with motor fluctuations when administered as add-on therapy alongside standard of care therapy including L-dopa, dopamine agonists, catechol O-methyltransferase inhibitors, anticholinergics and amantadine, thus emphasizing the additional benefits it can offer when patients are no longer optimally controlled on their current treatment regimen. Importantly, a notable improvement in motor fluctuations is achieved without an increase in troublesome dyskinesia and the benefits are long lasting.

This study is designed to collect data on the impact of safinamide on the motor complications of Chinese PD fluctuating patients over a treatment period of up to 16 weeks. Further information on the effect of safinamide on motor symptoms and quality of life in a clinical setting environment will also be gathered.

The study will be conducted in accordance with the Clinical Trial Protocol (CTP), any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.

## 4.5 Discussion of Study Design

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study to evaluate the effects of 100 mg safinamide, administered orally once daily (od), in Chinese PD patients, experiencing motor fluctuations while on stable doses of L-dopa (alone or in combination with other anti-Parkinson drugs). Eligible patients are required to meet the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria (14).

The double-blind design is adopted to minimize systematic bias in ratings resulting from the knowledge of the treatment received. Randomization helps achieve statistical balance across the two treatment groups. The principal efficacy measure, i.e., the increase in mean daily "OFF" time during the 24-hr diary recording period, was chosen based on regulatory guidance and prior use in other trials in similar populations. Other efficacy measures ("ON" time, UPDRS, CGI, PDQ-39 and NRS) were selected based on the domains of symptoms affected in patients with PD. Tolerability was assessed by changes in laboratory evaluations, vital signs, 12-lead ECG, physical and neurological examinations, and adverse events.

The dose of safinamide (100 mg/day titrated from 50 mg/day after 2 weeks) was selected based on the results of the previous pivotal trials (in particular the study SETTLE), and according to the recommendations of the SmPC. The modulation of glutamate is maximized with the dose of 100 mg. Moreover, this is the dose that has shown to improve significantly dyskinesia (in moderate-severe dyskinetic patients) and PD non-motor symptoms such as chronic pain and mood deterioration. In the SETTLE study, the same dose of 100 mg/day has been administered to a cohort of 168 Asian-Pacific patients, reaching significant positive improvement of fluctuations and motor symptoms.

The study involves a placebo group. Placebo will be added to the standard stabilized treatment as a control of the safinamide group, hence patients on placebo will have benefit from other ongoing anti-PD medication. In addition, patients will be observed during the study more frequently than in the normal clinical practice and in case of any safety issue or lack of efficacy can withdraw from the study at any time.

It is commonly accepted to use a placebo as a control group because a placebo effect can be observed in PD patients (15). A meta-analysis of 11 randomized, double-blind, placebo-controlled clinical trials in PD found an overall placebo response of 16% (16).

The use of placebo is also based on the ICH E10 Guidance for Industry "Choice of control groups and related issues in clinical trials" (CPMP/ICH/364/96), accepted by the FDA in May 2001, stating that (chapter 1.3.1) *"…the placebo control design, by allowing blinding and randomization and including a group that receives an inert treatment, controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug…"* (17), 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) (18).

Moreover, due to its unique mechanism of action (MoA), different from the other PD drugs, safinamide has not a direct comparator.

# 5.0 OBJECTIVES

## 5.1 Efficacy

The objective of the study is to evaluate the efficacy of safinamide compared with placebo, given as add-on therapy, in idiopathic Chinese PD patients with motor fluctuations treated with stable doses of levodopa (L-dopa).

## 5.2 Safety

The safety objective of the study is to evaluate the safety and tolerability of safinamide compared with placebo in Chinese PD patients with motor fluctuations.

# 6.0 ETHICS REQUIREMENTS

This study will be conducted in compliance with the last version of the Declaration of Helsinki (refer to the link https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/), with Good Clinical Practice (GCP), with the applicable regulatory requirements of the country where the study will be conducted and with Zambon and Parexel standard operating procedures (SOPs).

# 7.0 DESIGN AND DURATION OF CLINICAL TRIAL

## 7.1 Clinical Trial Design

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study in idiopathic Chinese PD patients, experiencing motor fluctuations while on stable doses of levodopa (alone or in combination with other anti-Parkinson drugs).

A total of 306 patients will be randomised into this study (153 in the safinamide and 153 in the placebo groups).

The visit procedures are summarised in the Study Flow Chart Section 29.0, Appendix 1.

**Screening Period**
After providing written informed consent to participate in the study, patients will enter a screening period up to 2 weeks. During the screening period, patients will undergo all the evaluations necessary to establish their eligibility for the study. Patients considered non-eligible (“screening failures”) due to clinically significant abnormalities in laboratory exams, ECG or vital signs, could be re-screened again only once during the study after a reasonable interval of time, based on the judgement of the Investigator that should be fully documented and explained in the clinical records and in the CRF. They would need to sign a new consent form. Patients who will be confirmed to be non-eligible in this second screening visit should be definitively excluded from the study.

Patients and their caregivers will be trained on the completion of a 24-hour diary card and the last two days of recording prior to each study visit will be used for data analysis.

*The dose of L-dopa and of the other anti-Parkinson drugs (if any) must be kept constant during the screening period.*

**Treatment Period**

At baseline (day 1), eligible patients will enter the treatment period and will be randomised to receive either safinamide (initial 50 mg titrated to 100 mg the day after the Visit 3/week 2, ideally at day 15) or matching placebo, orally od in a 1:1 ratio. The investigational medicinal product (IMP) will be taken in the morning at breakfast time, in addition to the morning dose of L-dopa and other (if any) PD medications.

Following completion of all baseline assessments, they will receive the first dose of safinamide or placebo (50 mg) at the study centre. The day after the Visit 3/week 2 (ideally at day 15) the dose will be increased at home to 100 mg od. Each patient will receive treatment for 16 weeks, with visits at week 0/day 1 (baseline) and at weeks 2, 6, 10 and 16 (or early termination). A telephone follow-up will be performed 1 week after the end of treatment for safety reasons.

Patients who prematurely withdraw from the study while receiving study medication should complete the early termination visit assessments, when possible.

At the end of the study, the patients will be instructed to contact immediately the Investigator in case of appearance of any adverse reactions. Any ongoing adverse event or clinically abnormal laboratory parameter will be followed until resolution. In addition, all SAEs occurring within 30 days after a patient's last dose of study drug will be followed to their conclusion.

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

**Efficacy** will be assessed by the changes in "OFF" and "ON" time from the 24-hour patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Clinical Global Impression (CGI), the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the Numerical Rating Scale (NRS).

**Safety** will be assessed by clinical laboratory tests (haematology and serum chemistry), vital signs, 12-lead electrocardiogram, physical examination, treatment emergent adverse events and concomitant medications.

## 7.2 Duration of Clinical Trial

Study participation will be up to a maximum duration of 18 weeks and will comprise a screening period (up to 2 weeks), a treatment period (16 weeks) and a 1-week telephone follow-up.

The start of the study is defined as the date of the first visit of the first patient participating in the study.

The end of the study is defined as the date of the last visit of the last patient participating in the study.

# 8.0 CLINICAL TRIAL POPULATION

## 8.1 Number of Patients

Assuming a screening failure rate of 10%, a total of approximately 340 patients will be screened. Assuming an attrition rate equal to 15% a total of approximately 306 patients will be randomized (153 in the safinamide and 153 in the placebo groups).

Approximately 35 study centres will participate in the study. The enrolment will be competitive among sites.

The sample size calculation is described in Section 20.3.

## 8.2 Selection of Patients

### *8.2.1 Inclusion Criteria*

Patients can be included in the study if they meet all inclusion criteria listed below:

1. Male or female patients aged ≥18 years old.
2. Chinese ethnicity.
3. Able to understand and willing to provide written informed consent.
4. Able to maintain an accurate and complete 24-hour diary with the help of a caregiver.
5. Diagnosis of idiopathic Parkinson's Disease (IPD) using the United Kingdom Parkinson's Disease Society Brain Bank criteria of more than 3 years duration.
6. Be levodopa responsive and receiving treatment with stable daily doses 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 dopamine agonists, anticholinergics and/or amantadine for at least 4 weeks prior to the screening visit.
7. A Hoehn and Yahr stage between 1-4 inclusive during the "ON" phase.
8. Experiencing motor fluctuations with a minimum of 1.5 hours/day of "OFF" time during the day (excluding morning akinesia), based on historical data.
9. If female, be post-menopausal for at least one year or have undergone hysterectomy or, if of child-bearing potential, must have a negative pregnancy test, must not be breast-feeding nor become pregnant during the study and must use adequate contraception for 1 month prior to randomisation and for up to 1 month after the last dose of study drug. Adequate contraception is defined as:

    a) Hormonal oral, implantable, transdermal, or injectable contraceptives or a non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 2 months before the screening visit;

    b) a male sexual partner who agrees to use a male condom with spermicide or a sterile sexual partner .

For all women of child-bearing potential, urine pregnancy test result at screening must be negative.

### *8.2.2 Exclusion Criteria*

Patients are not eligible for the study if they meet one or more of the exclusion criteria listed below:

1. Any form of Parkinsonism other than IPD.
2. Diagnosis of chronic migraine (>15 days per month) or cancer pain.
3. L-dopa infusion.
4. Hoehn and Yahr stage 5 during the “ON” phase.
5. If female, pregnancy or breast-feeding.
6. Neurosurgical intervention of PD or stereotactic brain surgery.
7. Severe peak dose or biphasic dyskinesia, unpredictable or widely swinging fluctuations.
8. History of major depression or other clinically significant psychotic disorder which compromise the ability to provide the informed consent or to participate to the study.
9. Drug and/or alcohol abuse within 12 months prior to the screening visit.
10. History of dementia or severe cognitive dysfunction.
11. Use of any investigational drug or device within 30 days prior to screening or 5 half-lives, whichever is the longest, or during the study.
12. Allergy/sensitivity or contraindications to the investigational medicinal products (IMPs) or their excipients, to anticonvulsants or to anti-Parkinson drugs.
13. Any clinically significant condition (including laboratory values) which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for patients while in the study.
14. Moderate or severe liver failure using the Child-Pugh classification score, or human immunodeficiency virus (HIV) infection.
15. Treatment with monoamine oxidase inhibitors (MAOIs), pethidine, opiates, opioids, fluoxetine, fluvoxamine in the 4 weeks prior to the screening visit. These drugs are not allowed throughout the study and up 2 weeks after the last dose of study drug.
16. 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.

# 9.0 OVERALL CLINICAL TRIAL SCHEDULE

The current trial will include 4 planned clinical visits. A Study Flow Chart detailing all clinical study assessments and procedures is provided in Section 29.0, Appendix 1. The following sections outline the procedures to be performed at the individual visits.

## 9.1 Screening Period

Potential patients will be screened prior to entry into the study. Laboratory assessments may be repeated once for any laboratory parameter that falls outside the relevant exclusion criteria provided they are completed and reviewed within the screening period. Patients considered non-eligible ("screening failures") due to clinically significant abnormalities in laboratory exams, ECG or vital signs, could be re-screened again only once during the study after a reasonable interval of time, based on the judgement of the Investigator that should be fully documented and explained in the clinical records and in the CRF. They would need to sign a new consent form. Patients who will be confirmed to be non-eligible in this second screening visit should be definitively excluded from the study.

### *9.1.1 Visit 1 - Screening Visit (Day -14/-2)*

The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Obtain written informed consent (Section 21.0).
- Assignment of unique screening number; numbers will be allocated in sequence within each study center.
- Check of inclusion and exclusion criteria (Sections 8.2.1 and 8.2.2).
- Recording of demographic data, including age, sex, ethnicity, smoking and alcohol use (Section 10.1.1).
- Recording of medical history and PD diagnosis using the United Kingdom Parkinson's Disease Society Brain Bank (Section 29.0, Appendix 2), including Hoehn and Yahr (20) stage (Section 29.0, Appendix 3).
- Physical examination including height and body weight (Section 10.1.2).
- Neurological examination (Section 10.1.2).
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position) (Section 10.1.3).
- 12-lead ECG in the supine position (Section 10.1.4).
- Daily diary training (Section 10.1.6).
- Blood sampling for clinical laboratory assessments (haematology and clinical chemistry, including liver function tests) (Section 10.1.5).
- Urine sampling for urine (dipstick) pregnancy test for women of child-bearing potential (Section 10.1.5).

- Recording of prior medications, concomitant medications and therapies (Section 11.0).
- Issue daily diary with instructions to be completed two days before the baseline visit (visit 2).

## 9.2 Treatment Period

Following completion of all the screening assessments and procedures and review of the results, eligible patients will enter the treatment period. Details regarding the method of assignment to treatment are presented in Section 12.2.

### *9.2.1 Visit 2 - Baseline Visit (Week 0 / Day 1)*

The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Check of inclusion and exclusion criteria (note: inclusion and exclusion criteria must be fulfilled before patient is randomized).
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of UPDRS, PDQ-39 and CGI-S by the rater (Section 10.1.6).
- Completion of NRS by the patient (Section 10.1.6).
- Recording of prior medications, concomitant medications and therapies.
- Recording of AEs (Section 17.0).
- Review and evaluate daily diary (Section 10.1.6).
- Provide additional daily diary training, as required.
- Issue daily diary with instructions to be completed two days before the visit at week 2 (visit 3).
- Randomisation to study treatment.
- Following completion of the relevant assessments and procedures, patients will take their first 50 mg dose of oral safinamide or placebo at the study center.
- Dispense study medication (safinamide or placebo 50 mg od) for the next 14 days. Patients will take 50 mg/day safinamide at home in the morning for 2 weeks, then the dose will be increased at home to 100 mg/day the day after the Visit 3/week2, ideally at day 15. Safinamide can be taken with or without food.

### *9.2.2 Visit 3 (Week 2 / Day 14 ± 3 days), Visit 4 (Week 6 / Day 42 ± 3 days) and Visit 5 (Week 10 / Day 70 ± 3 days)*

At weeks 2, 6 and 8 (visits 3, 4 and 5), the following assessments and procedures will be performed as indicated in the Study Flow Chart (Section 29.0, Appendix 1):

- Completion of UPDRS, PDQ-39, CGI-S and GCI-C by the rater.

- Completion of NRS by the patient.
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Review and evaluate daily diary.
- Provide additional daily diary training, as required.
- Issue daily diary at weeks 2, 6 and 10, with instructions to be completed two days before the next visit (visit 4, 5 and 6).
- Drug accountability.
- Dispense study medication (safinamide or placebo 50 and 100 mg od). Patients will take 100 mg/day safinamide at home in the morning for 14 weeks. In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.

#### *9.2.3 Visit 6 (Week 16 / Day 112 ± 3 days) / End of Treatment (EOT) / Early Termination (ET)*

Following completion of 16 weeks treatment with safinamide or in the event of premature discontinuation, the following EOT/ET assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Physical examination including body weight.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- 12-lead ECG in the supine position.
- Completion of UPDRS, PDQ-39, CGI-S and GCI-C by the rater.
- Completion of NRS by the patient.
- Blood sampling for clinical laboratory assessments (haematology and clinical chemistry).
- Urine sampling for urine (dipstick) pregnancy test for women of child-bearing potential.
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Review and evaluate daily diary.

- Drug accountability.

### 9.3 Telephone Follow-up

A telephone follow-up call will be performed 1 week after the end of treatment for safety reasons. The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 129.0):

- Recording of concomitant medications and therapies.
- Recording of AEs.

### 9.4 Unscheduled Visit

An unscheduled visit should be performed in case of down-titration of safinamide or placebo from 100 to 50 mg for safety reasons. The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 129.0):

- Physical examination including body weight.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- 12-lead ECG in the supine position.
- Recording of concomitant medications and therapies.
- Drug accountability and drug dispensing.
- Recording of AEs.

## 10.0 METHODOLOGY

### 10.1 Methods of Assessment

#### *10.1.1 Demography and Medical History*

Age, sex and ethnicity will be recorded at screening (visit 1) as well as other baseline characteristics (smoking and alcohol use), including the patient's Hoehn and Yahr stage (Section 29.0, Appendix 3) and duration of PD.

Medical history will be recorded at screening (visit 1). Any significant and relevant past conditions and any current medical conditions prior to screening will be recorded.

#### *10.1.2 Physical and Neurological Examination*

A physical examination will be performed by a physician at the screening (visit 1) and at week 16 (visit 6/EOT/ET) and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system.

Height will be recorded at screening (visit 1) only. Body weight will be measured at screening (visit 1) and week 16 (visit 6/EOT/ET) only.

A neurological examination will be performed by a physician at the screening visit (visit 1) only.

#### *10.1.3 Vital Signs*

Systolic and diastolic blood pressure (measured after at least 5 minutes in the supine position) and pulse rate (measured after at least 5 minutes in the supine position) will be recorded at each study visit Automatic or manual devices may be used, but the same device should be used for any given patient throughout the study. The same arm should be used for all measurements.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant', or 'abnormal not clinically significant'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements may be performed to confirm values if needed.

#### *10.1.4 12-lead Electrocardiogram*

Computerised 12-lead ECG recordings will be obtained locally at each study centre at screening (visit 1) and at week 16 (visits 6/EOT/ET), after the patient has rested for at least 5 minutes in the supine position.

The Investigator should document the occurrence of any clinically significant 12-lead ECG abnormalities within the electronic case report form (eCRF). Repeat measurements will be performed if needed.

#### *10.1.5 Laboratory Evaluation*

Routine laboratory evaluations will be performed at screening (visit 1) and at week 16 (visit 6/EOT/ET). The haematology and clinical chemistry parameters detailed in Table 1 will be analysed at each local clinical laboratory, using standard, validated laboratory methods.

Urine (dipstick) pregnancy tests will be performed at the study centre at screening (visit 1) and week 16 (visit 6/EOT/ET) using commercially-sourced kits. If a positive pregnancy test is recorded at any time, the instructions detailed in Section 17.10 should be followed.

Clinical laboratory tests will be reviewed for results of potential clinical significance. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

**TABLE 1 CLINICAL LABORATORY EVALUATIONS**

| | | |
|---|---|---|
| **Haematology:** | | |
| Haemoglobin | Platelet count | |
| Haematocrit | Red blood cell count | |
| White blood cell count and absolute differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) | | |
| **Clinical Chemistry:** | | |
| Urea or BUN | Alkaline phosphatase (ALP) | Chloride |
| Creatinine | Alanine aminotransferase (ALT) | Sodium |
| Bilirubin (direct and total) | Aspartate aminotransferase (AST) | Calcium |
| Uric acid | Gamma-glutamyltranspeptidase (GGT) | Potassium |
| **Pregnancy Tests:** | | |
| Dipstick - urine pregnancy test at visit 1 (screening) and visit 6 (week 16/EOT/ET) | | |

An estimate of the total blood volume to be taken from each patient during scheduled study visits (visits 1 and 6) is summarized in Table 2.

**TABLE 2 ESTIMATE OF TOTAL PER PATIENT BLOOD SAMPLING VOLUME (VISITS 1 AND 6)**

| Sampling For: | Sample Volume (mL) | No of Samples | Total Volume (mL) |
|---|---|---|---|
| Haematology and clinical chemistry | 5 | 2 | 10 |

The maximum volume of blood to be drawn from each patient for routine safety monitoring across all scheduled visits is estimated to be approximately 10 mL; however, this figure may vary according to local clinical laboratory practices. Additional or repeat safety laboratory samples may also be taken during the study if required by the Investigator.

### *10.1.6 Efficacy Evaluations*

The efficacy will be assessed by the changes in "OFF" and "ON" time from the 24-hour patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Clinical Global Impression (CGI), the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the Numerical Rating Scale (NRS).

The following parameters are to be completed by the rater: UPDRS, PDQ-39, CGI-S and CGI-C.

Site personnel who are to be involved in performing the efficacy assessments must be expert in the use of the various scales and questionnaires. At least two raters (the primary and a back-up) must be available to perform the required key efficacy evaluations at each study centre. To ensure consistency of ratings on each efficacy measure for each patient throughout their participation in the study, the same rater should perform the assessments where possible.

To minimise intra-patient variability, e.g. due to holidays or changes in personnel, etc., it is recommended that the two raters (the primary and a back-up) perform a co-rating of a patient prior to any change in the rater (either permanent or temporary), and arrive at a consensus on the patient's scores. For scales that require assessing the change in the patient's condition since baseline, it is recommended that both raters are present for the

baseline interview, and/or that the primary rater's notes on the patient's baseline status and other background information are provided to the back-up rater.

**At the baseline visit (visit 2/day 1), all baseline assessments should be completed before the patient receives the first dose of study medication.**

Wherever possible the 24-hours diary and the NRS should be completed by the patient. However, in the case of the patient's incapacity, for example due to dyskinesia, tremor, etc., the patient's caregiver may complete the 24-hours diary and the NRS based on information reported by the patient.

Efficacy assessments will be undertaken as outlined in the Study Flow Chart (Section 29.0, Appendix 1), using the methodologies described here below:

**Daily Diary**

A 24-hour diary will be completed daily by each patient the two days before the baseline (visit 2/day 1) and weeks 2, 6, 10 and 16 visits (visits 3, 4, 5 and 6/EOT/ET).

A home diary was developed and published by Hauser et al (19) to assess functional status in patients with PD with motor fluctuations and dyskinesia. The diary requires patients to indicate their predominant status during 30-minute intervals over a 24-hour period.

*Daily Diary Training*

At the screening visit, patients and their caregivers will be trained on the completion of the daily diary card. The Investigator will review with the patients the definition of "ON", "OFF" and dyskinesia symptoms and agree a consistent interpretation of when "ON" and "OFF" symptoms begin and end, and when dyskinesia occurs. The patients will be given a daily diary to fill out at home two days before the baseline visit (visit 2/day 1).

At the baseline visit, the patient will receive a new daily diary and will be instructed to maintain the diary the day before the visit 3 (week 2). This process will be repeated prior to visits 4, 5 and 6 (weeks 6. 10 and 16). On each occasion, the patient will be instructed to complete the diary two days before the next visit.

*Daily Diary Completion and Assessment*

Patients will complete the daily diary by selecting one of the following five options for each 30-minute time period:

- "OFF".
- "ON" without dyskinesia.
- "ON" with non-troublesome dyskinesia.
- "ON" with troublesome dyskinesia.
- Asleep.

If the patients do not know what category applied during a specific 30-minute period, they should be instructed to enter "not done" rather than leaving the time point value blank. During the study visit, the Investigator will review the daily diary with the patient, and the data recorded for each 30-minute period will be transcribed into the eCRF at study centre.

### Hoehn and Yahr staging

Hoehn and Yahr Staging (20) is a rating system used to classify the severity of PD. Originally, 5 stages were defined, based upon PD symptoms; recently, 2 intermediate stages have been included. The following stages were used:

- Stage 1: Mild symptoms on only 1 side of the body, which were not disabling, e.g. mild tremor of 1 limb. If there was axial involvement, a rating of stage 1.5 was given.
- Stage 2: Bilateral involvement and posture and gait were affected; however, symptoms caused minimal disability. If balance was also affected (i.e. recovery on pull test), a rating of stage 2.5 was given.
- Stage 3: Moderately severe bilateral disease, significant slowing of body movements, and impairment of equilibrium, although the patient was still physically independent.
- Stage 4: Severe disability, including rigidity and bradykinesia; however, the patient was still able to walk or stand unassisted. At this stage, the patient was no longer able to live alone.
- Stage 5: Unable to walk or stand unaided, and wheelchair-bound or bedridden. At this stage, patients were generally cachectic and required constant nursing care.

### Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS (21) will be completed by the Investigator at baseline (visit 2/day 1) and weeks 2, 6, 10 and 16 (visits 3, 4, 5 and 6/EOT/ET).

The UPDRS is the most commonly used scale in clinical studies to follow the longitudinal course of PD It comprises three parts that are used to evaluate the following key areas of disability, plus a fourth part that evaluates any complication of treatment:

- Part I: Evaluation of mentation or cognition, behavior and mood.
- Part II: Evaluation of the activities of daily life.
- Part III: Evaluation of motor function.
- Part IV: Evaluation of complications of therapy.

The UPDRS should be performed by the Investigator with points assigned to each item in the scale based on the patient's response as well as observation and physical examination.

Together Parts I-III contain 44 items, with each item scored on a 5-point scale. Part IV contains 11 questions with a scale ranging from 0 to 23. Thus, the final total score may range from 0 (no disability) to 199 (total disability).

### Clinical Global Impression (CGI)

The CGI (22) is the general name for 2 scales, the CGI-Severity scale (CGI-S) and the CGI-Change scale (CGI-C). The CGI-S scale measures global severity of illness at a given point in time. It will be rated on a 7-point Likert-type scale ranging from 1 (normal, not ill at all) to 7 (extremely severe). The CGI-S will be assessed at all visits, starting at baseline. The CGI-C scale will measure the change in the patient's clinical status from baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. The change from the patient's baseline condition will be assessed by the Investigator at all post-baseline visits. In completing the CGI-C, the rater will review all efficacy-related data, and assess its clinical meaningfulness.

**Parkinson's Disease Questionnaire-39 items (PDQ-39)**

The PDQ-39 (23) comprises 39 questions measuring eight dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily pain. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). A summary index score could also be calculated. The contents of the instrument were developed on the basis of exploratory in-depth interviews with patients with Parkinson's disease, and the reliability, validity, and sensitivity to change of the instrument were then assessed in a number of large scale surveys.

**Numerical Rating Scale (NRS)**

The NRS (24) is a segmented numeric version of the visual analogue scale (VAS) in which a patient selects a whole number that best reflects the intensity of his/her pain, ranging from '0' ("no pain") to '10' ("worst possible pain").

Patients should record the intensity of their PD-associated pain, as the worst pain experienced over the past 24 hours (at any time during the day), in the evening before going to sleep.

If the patient suffered from more than one PD-associated pain, the more severe pain will be documented.

#### *10.1.7 Safety Evaluations*

Safety will be assessed throughout the study, i.e. from the provision of informed consent until the last patient visit. In addition, any AE that, in the opinion of the Investigator, requires the patient to withdraw from treatment or from the study, will be followed until the event has subsided or the condition has stabilised. All SAEs that are spontaneously reported within 30 days of a patient's last dose of study drug will also be reported and followed.

Individual safety assessments will be performed using the parameters and time points for collection listed below:

- Physical examination, clinical chemistry and haematology and 12-lead ECG at screening (visit 1) and week 16 (visit 6/EOT/ET).
- Neurological examination at screening (visit 1).
- Vital signs at each study visit AEs at every post-screening visit.

Further details are provided in Section 10.1 and in the Study Flow Chart (Section 29.0, Appendix 1).

Further information regarding AE definitions and reporting is provided in Section 17.0.

## 10.2 Compliance

The prescribed dosage, timing and mode of administration of study medication may not be changed. Study medication accountability and patient compliance will be documented

throughout the treatment period using study-specific study medication dispensing and return record forms.

The evaluation of compliance will be done using the following formula:

$$\% \text{ of administered drug} = 100 \times \frac{\text{Total number of administered doses}}{\text{Total number of scheduled doses*}}$$

**1 dose x number of days between visits*

Patients will be asked to return all unused medication. From visits 3 to 6 (weeks 2 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% or more than 120% of study medication during any visit-to-visit evaluation period.

Patients exhibiting non-compliance as assessed by tablet counts should be counselled on the importance of good compliance to the study dosing regimen.

### 10.3 Pharmacodynamics

Not applicable.

### 10.4 Pharmacokinetics

Not applicable.

## 11.0 CONCOMITANT TREATMENTS

Concomitant medication is defined as any medication, other than the study medication, which is taken during the study from the time the patient provides informed consent until the last study visit for the patient, including prescription and over-the-counter medicines. All concomitant medications taken should be recorded on the eCRF.

### 11.1 Excluded Medications

Medications that are excluded prior to the study are listed in the exclusion criteria (Section 8.2.2).

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.

Concomitant medications that are considered necessary for the safety and well-being of the patient are permitted during the study at the discretion of the Investigator, with the following exceptions:

- Opioids and opiates
- L-dopa infusion and MAOIs
- Fluoxetine or fluvoxamine
- Pethidine
- Any other investigational agent
- Traditional Chinese medicine

The use of any prohibited concomitant medication is a protocol deviation and should be recorded as such within the eCRF.

In addition, patients must not participate in any other clinical study of an investigational product or device whilst participating in this study.

### 11.2 Permitted Medications

Prior and concomitant medications which are considered necessary for the safety and well-being of the patient are permitted during the study at the discretion of the Investigator provided the medication is not listed within the Exclusion Criteria (Section 8.2.2) or in the Excluded Medications (Section 11.1).

The dose of L-dopa and/or of the concomitant anti-Parkinson treatments must be kept constant throughout the study.

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. They would need to sign a new consent form. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

## 12.0 INVESTIGATIONAL MEDICINAL PRODUCT

### 12.1 Investigational Medicinal Product Supplies and Packaging

Safinamide will be manufactured according to current Good Manufacturing Practice (GMP) compliance standards and supplied as film-coated tablets containing 50 mg or 100 mg of active substance for oral administration. A description of safinamide is given in Table 3.

**TABLE 3 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT (SAFINAMIDE)**

| Characteristic | Investigational Product |
|---|---|
| Product name | Safinamide |
| Active ingredient | Safinamide methanesulfonate |
| Physical appearance | Orange to copper, round, biconcave film-coated tablets |
| Dosage | Once daily |
| Unit dose strength | 50 mg, 100 mg safinamide (free base) |
| Route of administration | Oral |
| Treatment duration | 16 weeks |
| Manufacturer[1] | Zambon S.p.A. Vicenza |
| Company performing primary packaging | Zambon S.p.A. Vicenza |
| Company performing secondary packaging/labelling[2] | Parexel |

[1] Manufactured according to current Good Manufacturing Practice.
[2] Labelling will conform to applicable regulatory requirements.

Each tablet consists of safinamide methanesulfonate combined with the following inactive ingredients: 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.

Safinamide film-coated tablets, 50 and 100 mg, will be supplied in PVC/PVDC60/Al blisters.

A sufficient quantity of safinamide film-coated tablets (50 mg and 100 mg) will be supplied by the Sponsor, together with certificates of analysis, material safety data sheets, expiry dates and a statement that the study medication has been manufactured in accordance with GMP.

Placebo film-coated tablets are composed of the inactive ingredients used in the safinamide tablets (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. A description of placebo is given in Table 4.

Placebo film-coated tablets, 50 and 100 mg, will be supplied in PVC/PVDC60/Al blisters.

A sufficient quantity of placebo film-coated tablets (50 mg and 100 mg) will be supplied by the Sponsor, together with certificates of analysis, material safety data sheets, expiry dates and a statement that the study medication has been manufactured in accordance with GMP.

**TABLE 4 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT (PLACEBO)**

| Characteristic | Investigational Product |
|---|---|
| Product name | Placebo |
| Physical appearance | Orange to copper, round, biconcave film-coated tablets |
| Dosage | Once daily |
| Unit dose strength | 50 mg, 100 mg |
| Route of administration | Oral |
| Treatment duration | 16 weeks |
| Manufacturer[1] | Zambon S.p.A. Vicenza |
| Company performing primary packaging | Zambon S.p.A. Vicenza |
| Company performing secondary packaging/labelling[2] | Parexel |

[1] Manufactured according to current Good Manufacturing Practice.
[2] Labelling will conform to applicable regulatory requirements.

Study medication will be labelled in accordance with GMP and country-specific regulations as required by the regulatory bodies in the country where the study is conducted. Labels will be printed in the local language.

As part of the drug packaging and distribution process, emergency unblinding envelopes will be produced and distributed to the Sponsor's pharmacovigilance unit. These sealed individual patient unblinding envelopes will bear the medication kit number on the outside and also include the relevant unblinded study treatment on the inside of the security envelope.

## 12.2 Investigational Medicinal Product Dispensing and Administration

The first dose of safinamide or placebo (50 mg) will be administered at the study centre following completion of all baseline assessments and based on randomization list. Patients will take subsequently 50 mg od safinamide (or placebo) at home (i.e. either unsupervised or with the assistance of a caregiver) in the morning (at breakfast time, in addition to the morning dose of L-dopa and other, if any, PD medications) for 2 weeks and increase then the dose to 100 mg/day the day after the Visit 3/week 2, ideally at day 15 (at home).

Treatment with oral safinamide (or placebo) 100 mg od will continue up to week 16 and will be self-administered (i.e. either unsupervised at home or with the assistance of a caregiver) at approximately the same time each day. On study visits after visit 2, patients should take their dose of safinamide/placebo in the morning prior to attending the study centre.

Patients will be asked to return all unused medication to the study centre for compliance calculation (Section 10.2).

*Throughout the study, patients will continue to take their standard, prescribed anti-Parkinsonian treatment; doses must be kept constant.*

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and*

*maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

The patients will be provided at each visit with sufficient IMP for the treatment until the following visit, including additional spare tablets.

Study medication will be stored on-site in accordance with the label requirements 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. The Sponsor and their authorised 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.

Once medication has been dispensed to study patients, it should be stored in accordance with the instructions on the label.

## 12.3 Randomisation

Patients who meet all criteria for enrolment will be randomised to double-blind treatment in a 1:1 ratio either to safinamide or placebo at visit 2 (day 1) and will be allocated a medication kit number according to the randomised treatment group. The randomisation will be done with blocks sized of unequal length to guarantee a good balance between safinamide and placebo at any stage of the enrolment minimizing the procedure selection bias.

**Patient identification:**

Each patient who has signed an informed consent form and is screened will be allocated to a 3-digit 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.

The number will be assigned by the eCRF/IWRS upon entry in the system.

**Kit number**

At randomisation, the eCRF/IWRS will allocate a unique medication kit number.

## 12.4 Investigational Medicinal Product Accountability

IMP inventory and accountability records will be kept by the Investigator or Pharmacy. The following rules are to be followed:

a) the Investigator will keep IMP in a pharmacy, or a locked and secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the IMP.

b) the inventory will be maintained by the Investigator or pharmacist or other nominated individual. The inventory will be done by means of a specific "Subject/Study Investigational Product Accountability Record & Investigational Product Reconciliation Log" provided by the CRO/IWRS and will include details of IMP received and a clear record of when they were dispensed and to which patient. The log shall indicate the

quantity and description of all IMPs on hand at any time during the course of the clinical trial.

c) at the conclusion or termination of the clinical trial, the Investigator agrees to conduct a final IMP inventory and to record the results of the inventory on an appropriate form provided by the CRO/IWRS (Investigational Product Return Form). The monitor will check that IMP accountability was correctly performed. According to instructions, the Investigator will return all original IMP containers, whether empty or containing test preparations, to local depot delegated by the CRO for final reconciliation and destruction. Sites can also handle destruction.

d) the IMP can be dispensed to patients only by Investigator/pharmacist who agrees not to supply IMP to any person except those named as Investigators/Co-Investigators as detailed in the Site Signature/Delegation Log, and to patients in this trial.

### 12.5 Treatment of Overdose

Reports of overdose with safinamide have been rare. 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.

## 13.0 CLINICAL TRIAL AMENDMENTS

Changes to the Clinical Trial Protocol (CTP) can be made by preparing written amendments to be agreed and signed by the Investigator and Sponsor. A substantial amendment may not be implemented without a favourable opinion of the Ethics Committee (EC) and Competent Authority (CA), unless the changes consist of urgent safety measures to protect trial patients.

Amendments which are non-substantial amendments as defined by present regulations can be sent to EC/CA for notification and may be implemented at the site before EC/CA notification according to local rules.

## 14.0 DEVIATIONS FROM THE CLINICAL TRIAL PROTOCOL

Any major or critical deviation which may have an impact on study results and safety of the patients should be immediately reported to Sponsor/CRO and notified to Regulatory Authorities (EC/CA) according to local regulations. A decision will be taken together with the Sponsor whether or not the patient affected by the deviation from the CTP is to continue in the study. The eCRF will describe the deviation from the CTP. A deviation log will be maintained to track actual deviations and decisions taken, including all deviations occurred.

In case of an emergency deviation from the CTP applicable only when an emergency situation has to be faced for a patient, this deviation will be only applied to that individual.

In such an emergency the Investigator must contact the CRO by telephone as soon as possible.

### 14.1 Code Breaking

The code for any individual patient will not be broken by the Investigator during course of the trial except in the circumstance of an SAE of life-threatening significance.

In case of emergency, unblinding of the treatment code will be done through IWRS. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IWRS will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the site users. Site users will be provided with usernames and passwords to access the IWRS.

Unblinding of the study treatment must be done in case of an emergency situation, where the Investigator considers it essential to know what treatment the patient was taking. Access to the unblinding option will be granted only to the Investigators and sub-Investigators at the sites. If the treatment code has been opened, this must be recorded in the eCRF.

**The IWRS will immediately notify the Sponsor/CRO pharmacovigilance and the Clinical Trial Monitor whenever a treatment code is unblinded.**

Users from CRO and Sponsor Pharmacovigilance will have their own passwords to unblind patients in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the CA and ECs as applicable.

## 15.0 CLINICAL TRIAL WITHDRAWALS/ DROP-OUTS

Patients may be withdrawn from the study at their own request or at the discretion of the Investigator for one of the following reasons:

- Patient withdraws consent to participate.
- 
- Pregnant female patients must be withdrawn from the study without delay. Follow-up should be performed in accordance with Section 17.10.
- Patient has an AE that, in the opinion of the Investigator, requires the patient's discontinuation. Follow-up should be in accordance with Section 17.9.
- Any clinically significant abnormal findings in physical examination, ECG, vital signs, haematology, chemical chemistry which, in the opinion of the Investigator may compromise the safety of the patient in the study or interfere with evaluation of the IMP or reduce the patient's ability to participate in the study.
- Intercurrent illness requiring pharmacological treatment with a non-permitted drug or a drug which interacts in any way with the test treatment or with study evaluations.
- Patient is non-compliant with the protocol.

- Continuation in the study would be detrimental to the patient's safety in the opinion of the Investigator.
- The Investigator or the Sponsor, for any reason, stops the study.
- Sponsor, CA, or EC terminate the trial at an individual site.

Patients who prematurely withdraw from the study while receiving study medication should complete the EOT Visit assessments, when possible. Patients must return the medications and details regarding AEs and concomitant medications will be collected.

Patients who are withdrawn from the study will not be replaced. In the event that a patient 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 patient from the study or premature discontinuation of the treatment must be fully documented in the eCRF as well in source documents. Follow-up for withdrawn patients follows the procedures described in Section 17.8 and Section 17.9.

# 16.0 STOPPING AND DISCONTINUATION CRITERIA FOR THE TRIAL

The study may be prematurely terminated for one of the following reasons:

- The Sponsor feels that the number and/or severity of AEs justify discontinuation of the study.
- The Sponsor considers the applied doses of the IMP to no longer be relevant.
- Data not previously known become available and raise concern about the safety of the IMP so that continuation would pose potential risks to the patients.
- Difficulties in enrolment that would compromise reasonable timing for study conclusion or would delay study beyond reasonable timing and results.

Premature termination of the study must be reported to the EC and CA according to applicable laws generally within 15 days. A detailed written explanation of the reason should be given and alternative procedures for patients under treatment specified. However, study results have to be reported according to the requirements outlined in this protocol as far as applicable.

If after the termination of the trial, the risk/benefit analyses have changed, the new evaluation should be provided for the best interest of the patients who have participated in the study.

The Sponsor reserves the right to discontinue the study at a particular site or at multiple sites for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all documentation and investigational product pertaining to the study must be returned to the sponsor or its representative.

# 17.0 REPORTING SAFETY INFORMATION

## 17.1 Definition of Adverse Event (AE)

An Adverse Event (AE) is "*any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*".

Adverse events include:

- Worsening (change in nature, severity or frequency) of conditions present at the onset of the study.
- Patient deterioration due to the primary illness.
- Intercurrent illnesses.
- Drug interactions.
- Events related or possibly related to concomitant medications.
- Abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

The following medical conditions will not be documented as AEs and will be documented as medical history (or other as applicable):

- Symptoms or laboratory or instrumental abnormalities of a pre-existing (i.e. before patient entered the study) condition which have not worsened since enrolment;
- Surgical interventions or hospitalizations planned before patient entered the study.

## 17.2 Definition of Adverse Event of special interest

No AEs of special interest are defined for this trial.

## 17.3 Definition of Adverse Drug Reaction (ADR)

An Adverse Drug Reaction (ADR) is *"any untoward and unintended response to an IMP related to any dose administered and which implies an AE with at least a reasonable possibility of a causal relationship with the use of the product (i.e. a causal relationship cannot be ruled out, meaning that there is evidence or arguments to suggest a causal relationship). The definition covers also medication error and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP* ".

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

### *17.3.1 Definition of Unexpected Adverse Drug Reaction*

An unexpected ADR is "*an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure [IB] for an*

*unapproved investigational product or Summary of Product Characteristics [SmPC], for approved product)*".

The Reference Safety Information for evaluation of AE expectedness in this trial will be the IB (13).

## 17.4 Definition of Serious Adverse Events or Serious Adverse Drug Reaction

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is: "*any untoward medical occurrence or effect that at any dose"*:

- Results in death.
- Is life-threatening (i.e. the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation but, according to appropriate medical judgment, it may jeopardise the patient and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

A non-serious adverse event (non-SAE) is any AE that does not meet the criteria listed above for an SAE.

### *17.4.1 Definition of Suspected Unexpected Serious Adverse Reactions*

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs/SARs that, although foreseeable, are potentially related to the IMP and not identified in the reference safety information and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

## 17.5 Definition of Severity of Adverse Events

The term "severe" is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the patient may experience slight discomfort.
- Moderate: causing some limitation of usual activities; the patient may experience annoying discomfort.
- Severe: causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

## 17.6 Definition of Adverse Event Causality

Causality shall be determined according to the definition of ADR as given in Section 17.3.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as ADRs. The causality assessment given by the Investigator should not be downgraded by the Sponsor.

The following binary decision for causality will be used:

- Reasonable possibility that the IMP caused the event.
- No reasonable possibility that the IMP caused the event.

Features supportive of an association include:

- Temporal plausibility.
- Pharmacological properties of the drug or of the substance class.
- Course of the AE after dechallenge and, if applicable, after rechallenge.
- Specific tests indicating involvement of the drug in the occurrence/worsening of the AE.
- Alternative explanations.

## 17.7 Adverse Event Recording

Each AE occurring to a patient, either spontaneously revealed by the patient or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the IMP, must be recorded on the AE information page of the eCRF. Also for SAEs, information must be recorded in the eCRF (Section 19.1).

The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF.

## 17.8 Adverse Event Reporting

The Investigator must report to the CRO all AEs which occur during the study following written informed consent, regardless of their relationship to IMP. All AEs are to be recorded by the Investigator on the AE information page of the eCRF. For SAEs information must be recorded also on the “Adverse Event Form for immediate reporting”.

In addition, an SAE will have to be reported according to the following detailed procedure.

### *17.8.1 Reporting Serious Adverse Events*

Investigators must report SAEs **within 24 hours of first awareness of the event**.

The SAE must be reported through the eCRF to the CRO's Pharmacovigilance group as per contact details provided in the "List of Zambon/CRO personnel" at the beginning of this CTP.
If there is any issue with the electronic reporting process, such as internet failure or database issues, this must not delay SAE reporting. The back-up procedure is to send the back-up paper Serious Adverse Event Form to the CRO's Pharmacovigilance group by email or fax using the contact details specified in the SAE guidelines and SAE report form.

Note: Any reports submitted on paper must be retrospectively added to the eCRF as soon as possible.
The national and local standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.
SAEs are reportable from the time a patient signs the informed consent to the follow-up phone call or visit occurring 2 weeks (± 3 days) after the last dose of IMP.
If the Investigator becomes aware of any SAE occurring to a subject within the follow-up window established in this CTP, he/she will report the SAE as above. The SAE will be also reported in the eCRF.

If the Investigator becomes aware of any SAE outside the follow-up window established in this CTP, it is the Investigator's responsibility to report the SAE to the CRO. The Investigator might use the eCRF, as described above. However, the SAE is not an event occurred within the trial period.

#### *17.8.2 Reporting Adverse Events of Special Interest*

Not applicable.

## 17.9 Follow-up for Adverse Events

All AEs resulting in the patient's discontinuation and SAEs will be followed up until they are resolved or closed.

Resolution of an AE is defined as the return to pre-treatment status or stabilisation of the condition with the expectation that it will remain chronic.

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) and answer any question that Sponsor or designee may have regarding the AE.

Regarding SAEs, the timelines and procedure for follow-up reports are the same as those for the initial reports for SAEs.

This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

If follow-up information on SAEs is available, a follow-up e_CRF form will be completed by the Investigator and sent to the CRO as above-described, under Section 17.8.1.

## 17.10 Pregnancy

Patients must be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator, who must then withdraw the patient

from the study without delay. The Investigator should also be notified in case the partner of a male study subject becomes pregnant at any time during the course of the study (in this event a specific ICF for the subject's partner will be obtained).

In the event that a patient is subsequently found to be pregnant after inclusion in the study, then pregnancy will be actively followed up to the term and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the CRO.

The Investigator will send pregnancy reports to the CRO according to the timeframes stated for SAEs (Section 17.8.1), with follow-up information to be actively sought for the outcome of pregnancy.

If pregnancy results in abnormal outcome that the investigator and/or the Sponsor considers to be due to the IMP, this will be treated as an expedited ADR report.

# 18.0 RESPONSIBILITIES

The clinical conduct of this study will be overseen by the CRO. The CRO Medical Monitor will be responsible for daily medical monitoring, including safety monitoring. The specific responsibilities of the CRO are detailed in the relevant study agreement.

## 18.1 Responsibilities of the Sponsor (or delegated CRO)

Responsibilities of the Sponsor include the following:

- Select qualified Investigators.
- Provide each Investigator with the last approved SmPC for the authorised product.
- Submit clinical trial application/notification to the concerned Competent Authorities (CA) involved in the clinical trial.
- Prepare and submit to the EC/CA all the pertinent documentation needed for approvals.
- Implement and maintain quality assurance (QA) and quality control (QC) system with written SOPs to ensure the studies are conducted and data are generated, documented (recorded), and reported in compliance with the CTP, GCPs, and the applicable regulatory requirements.
- Promptly act in case of non-compliance by an Investigator or by members of the Sponsor or CRO.
- Ensure that the IMP is manufactured in accordance with any applicable GMP, is coded and labelled in a manner that protects blinding, if applicable, and labelling complies with applicable regulatory requirements.
- Supply the Investigators/Institutions with the IMP(s).
- Appoint appropriate trained Clinical Trial Monitor(s).
- Ensure the ongoing safety evaluation of the IMP.
- Promptly submit all Suspected Unexpected Serious Adverse Reactions (SUSARs) or other safety issues requiring expedited reporting to ECs and CAs in accordance with

local or international regulations and take appropriate measures necessary to safeguard study patients.

- Promptly notify all concerned Investigators, the ECs and the CAs of findings that could adversely affect the health of patients, impact on the conduct of the study, or alter the EC/CA authorisation to continue the study.
- When the study is completed or prematurely terminated, prepare or ensure preparation of a comprehensive Clinical Trial Report (CTR) for regulatory purposes.
- Prepare and submit to ECs and CAs safety updates and Development Safety Update Reports, as applicable.
- Secure agreement from all involved parties to ensure direct access to all study related centres, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.
- Provide adequate treatment/compensation for patients in the event of trial-related injury in accordance with the applicable regulatory requirements.
- Provide indemnity for the Investigator in accordance with Section 25.0 of this CTP.
- Terminate the Investigator's/Institution's participation in case of non-compliance.
- Promptly inform the Investigators/Institutions, the CAs and the ECs of premature termination or suspension of a study and the reason(s) for the termination or suspension.
- Designate appropriately qualified medical personnel who will be readily available to advise on study-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

## 18.2 Responsibilities of the Clinical Trial Monitor

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. CRO's monitors will work in accordance with CRO's SOPs, with the exception of the use of the "Adverse Event Form for immediate reporting" provided by the Sponsor.

The Clinical Trial Monitor is the principal communication link between the Sponsor/CRO and the Investigator. Responsibilities of the Clinical Trial Monitor include to:

- Train the Investigator(s) on all applicable SOPs, guidelines and regulations concerning the clinical evaluation of an IMP, including the safety reporting, and ensure a deep understanding of the CTP, the reporting requirements and responsibilities.
- Act according to predetermined SOPs, visit the Investigator periodically to verify adherence to the CTP and assure that all data are correctly and completely recorded. In order to perform his/her role effectively.
- Ensure that the trial site has adequate space, facilities, equipment, lab and staff.
- Ensure that all staff assisting the Investigator in the trial have been adequately informed about the details of the trial, verifying that the Investigator follows the approved CTP and all amendment(s), if any, and that they are performing the specified

activities and procedures and have not delegated these functions to unauthorised individuals.

- Verify that informed consent has been obtained and recorded from all the patients prior to their participation to the trial.
- Aid the Investigator and at the same time the Sponsor/CRO, in the maintenance of complete, legible, well-organised and easily retrievable data.
- Inform the Investigator of any eCRF entry error, omission or illegibility. The Clinical Trial Monitor should also ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the Investigator;
- Check that the storage, dispensing, administering, returning of IMPs are safe, handled in accordance with local regulations as well as study requirements and Sponsor/CRO SOPs. All those activities have to be adequately documented.
- Assist the Investigator in any notification procedure of SAE within 24h and verify the seriousness of the AEs.
- Submit promptly to the Sponsor/CRO a written monitoring report after each site visit and written documentation of all relevant telephone calls, letters and other contacts with the Investigator.
- Verify that the Investigator is maintaining the essential documents (Investigator's file) up to end of study and for the required period.

## 18.3 Responsibilities of the Investigator

Responsibilities of the Investigator include to:

- Ensure that he/she has sufficient time to conduct and complete the trial; nominate adequate staff and has appropriate facilities.
- Submit an up-to-date curriculum vitae and GCP trainings and awareness of GCPs to the Sponsor/CRO and to EC/CA.
- Agree and sign the CTP with the Sponsor confirming that he/she will work according to the CTP and GCPs and procedures as stated in the paragraph 18.2; assist monitoring and permit auditing.
- Follow the submission of notification/application to EC jointly with the Sponsor/CRO, where appropriate.
- Provide information to all staff members involved with the trial.
- Be thoroughly familiar with the appropriate use of the IMP(s) as described in the SmPC, protocol and any other information sources provided.
- Fully inform trial patients about the clinical trial and obtain their informed consent.
- Certify that all IMP(s) have been correctly delivered, stored, and safely handled, and that reconciliation of IMPs will be done at the end, after any discrepancies are justified.
- Follow the trial randomisation procedure and ensure that the code is broken only in accordance with the CTP.

- Collect, record, and report data properly.
- Notify the Sponsor/CRO within 24h in the case of SAE and take appropriate measures to safeguard patients.
- Promptly report to EC and Sponsor changes increasing the risk to patients and/or affecting significantly the conduct of the trial and new information that may affect adversely the safety of the patients or the conduct of the trial.
- Agree with and sign the Clinical Study Report of the trial, if requested.
- Ensure that the confidentiality of study patients personal data is respected by all persons involved as per laws in force.
- Keep the information supplied by the Sponsor as strictly confidential.
- Make all data available for direct access to the Sponsor/CRO personnel (e.g.: Clinical Trial Monitor, Auditor), EC or CAs for validation/audit/review/inspection purposes.
- Ensure that in the patient medical records it is clearly evident that the patient is participating in the clinical trial.
- Inform the family doctor, with patient's consent, about patient's participation in the trial.
- Provide a list of appropriately qualified persons (Site Signature/Delegation Log) to whom the Investigator has delegated some duties relevant to the conduct of the trial, together with their signatures and initials.
- Provide patients enrolled in the study with a card bearing information that he/she is participating in a clinical study, and where contact addresses/telephone numbers are reported.
- Submit, during the trial, on regular basis, written summaries of the trial status to the EC, when requested.

# 19.0 RECORDS

## 19.1 Case Report Forms (CRFs)

Electronic case report forms will be used in this study. The Investigator must ensure that the clinical data required by the study protocol are carefully reported in English in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the official files (source documentation).

Before the start of clinical activities an agreement will be completed and signed by the Investigator and the Sponsor/CRO, to summarise the source of data captured in the eCRF, specifying those data that will be recorded directly into the eCRF (i.e. for which there will be no prior written or electronic record of data).

ECG measurement results must be printed and signed by the Investigator and kept as source data on site after entering into the eCRF. The investigator will receive the results from the local laboratory by means of a laboratory report: this report should be signed by the investigator, stored as source and a copy should be present in the patient's file.

All other data has to be documented in the patient file as source data first and then entered into the eCRF.

Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a patient visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by trial monitors for completeness and acceptability during monitoring visits. Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

## 19.2 Records Maintained by the Investigator

A copy of all trial records (any documents sent or received from the Sponsor/CRO, correspondence with EC and any other institution or authority and relevant approvals, patients' source data and patients' identification documentation) must be maintained by the Investigator for at least 5 years, or for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the Investigator.

## 19.3 Trial Master File

The Trial Master File (TMF) will be maintained electronically by the CRO according to the respective CRO SOPs with direct access for all study participants.

At the end of the trial, the TMF will be transferred to the Sponsor, where it will be archived according to specific Sponsor SOPs. A copy of the Investigator files will be left on site after trial end.

## 19.4 Trial Monitoring

The trial will be monitored by means of regular visits and telephone calls according to specific and pre-defined SOPs and trial specific monitoring guidelines. Details of the visits will be recorded in appropriate Monitoring Report forms to be submitted regularly to Sponsor. Any relevant protocol deviation must be promptly communicated to designated Sponsor’s personnel.

Monitoring will be performed by personnel of the CRO.

## 19.5 Confidentiality of Subject’s Information

The Investigator has the responsibility to maintain the pseudonymity of patients in compliance with the applicable data protection law. In all study documents, patients are associated to a code which does not reveal the patient’s identity. Only at the site, the Investigator will hold the patient’s identity on a Subject Identification Form under his/her responsibility.

The site and the Sponsor shall process personal data of patients involved in the clinical study

as Data Controllers and in compliance with the applicable data protection laws, each of them in its area of competence and in accordance with the responsibilities provided by GCP, only in relation to the study performance and for pharmacovigilance purposes. The Investigator will maintain this for the longest period allowed by his/her own institution and, in any case, until further communication from the Sponsor.

Any contracted organisation either as Data Processor including the CRO, the local laboratory and IWRS provider, will act in compliance with the term and conditions agreed with the Sponsor.

# 20.0 BIOMETRICS

## 20.1 Data Handling

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at PAREXEL.

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- eCRF and Electronic Data Capture (EDC) system – data capture
- Statistical Analysis System (SAS®) – statistical review and analysis
- Pharmacovigilance safety database

Subject data will be captured in an eCRF system and reviewed by the Clinical Research Associate in order to check CTP adherence and to detect any data inconsistency or discrepancy (data validation step).
Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version current at trial start and which will be updated at each release of a new version during the trial.
Previous and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Actual versions of coding dictionaries used will be stated in the CTR.
The final data file will be transferred to the Sponsor in the agreed format as soon as possible after the trial is completed.

## 20.2 Endpoints

### *20.2.1 Primary Endpoint*

The primary efficacy endpoint of this study is the change from baseline to week 16 in the mean total daily “OFF” time, as assessed by 24-hour patient diary cards, of safinamide 100 mg/day compared to placebo, given as add-on therapy in PD patients with motor fluctuations on stable doses of L-dopa.

### *20.2.2 Secondary Endpoints*

The key secondary efficacy endpoint of this study is:

- The change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS).

Other secondary efficacy endpoints of this study are:

- The change from baseline to week 16 in the mean total daily "ON" time, as assessed by 24-hour patient diary cards.
- The change from baseline to week 16 in the mean daily "ON" time with no/non-troublesome dyskinesia, as assessed by 24-hour patient diary cards.
- The change from baseline to week 16 in the UPDRS total score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part II (ADL) score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part III (motor function) score during the "ON" phase.
- The CGI-S score at week 16.
- The change from baseline to week 16 in the CGI-C.
- The change from baseline to week 16 in the PDQ-39 score.

### *20.2.3 Safety Endpoints*

The safety endpoints for this study are:

- The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TSAEs).
- Physical examination findings (clinically significant).
- Vital sign (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities.
- 12-lead electrocardiogram (ECG) parameter measures, including occurrence of abnormalities
- Clinical chemistry and haematology values, including shifts from baseline and occurrence of abnormalities.

## 20.3 Sample Size

Sample size was computed through a Monte Carlo study with 1000 runs and using a Fixed Sequence Procedure (25) to account for multiplicity over the study primary endpoint (change from baseline to week 16 in the mean total daily "OFF" time) and the key secondary endpoint (change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale - NRS). The Fixed Sequence Procedure implies that the key secondary endpoint will be testable provided that the primary endpoint has achieved statistical significance with a two-tailed p-value ≤ 0.05.
Based on the Monte Carlo simulation it was estimated that a total sample size of 260 patients (130 in the safinamide and 130 in the placebo groups) ensures 90% power to

detect a mean difference in the 'off' time at least 0.9 h between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming standard deviations of 2.35 for safinamide and 2.06 for placebo. Effect size and standard deviation estimates used in sample size computations are gathered from the Settle Statistical Report (Table 15.2.13).
Moreover, the same Monte Carlo study showed that the total sample size of 260 patients would also permit a marginal power equal to 88% to detect 1 point treatment difference in the NRS between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming a pooled standard deviations of 2.0. Standard deviation was estimated on the basis of previous post-hoc analyses of pain (25) whilst a 1 point treatment difference is considered to be a clinically meaningful treatment effect (26).
Assuming an attrition rate equal to 15% a total of approximately 306 patients will be randomized (153 in the safinamide and 153 in the placebo groups). The sample size calculations were performed using the Mediana package (27).

## 20.4 Statistical Analyses

### *20.4.1 General Statistical Considerations*

All data captured on eCRFs will be available as listings.

The statistical analysis will be performed by the CRO. If not otherwise stated all statistical analyses and data tabulations will be produced using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA).

Unless stated otherwise, all available data from withdrawn subjects will be included in the analysis up to the time of withdrawal.
The primary study objective will be assessed by testing the superiority of Safinamide compared to placebo and will be achieved if the analysis on primary end-point will be found statistically significant. The key secondary objective will be always assessed through a superiority analysis of Safinamide compared to placebo and, similarly, will be reached if the analysis on key secondary end-point will be found statistically significant. Conversely, the analyses on the remaining secondary efficacy endpoints will be treated as non-key secondary objectives since they will be performed only to support primary endpoints findings.

All tests will be two-sided and performed at the significance nominal level of $\alpha = 0.05$. Details are reported in Section 20.4.5.

### *20.4.2 Trial Populations*

There will be 4 analysis populations defined for the trial analyses:

<u>Randomized Population</u>

The Randomized Population will include all subjects who provided informed consent and received a patient number (randomisation number) whether or not they receive IMP.

Full Analysis Set

The Full Analysis Set (FAS) will comprise all patients who provided informed consent, were randomized and received at least 1 dose or partial dose of the IMP.

Primary analyses will be performed on the FAS population with exclusions from the randomized defined and justified in the SAP.

Following the randomized principle, patients will be analyzed according to the treatment they have been assigned to at the randomization.

The FAS will be used to produce summaries of baseline patient characteristics and for the analysis of all efficacy endpoints.

Safety Population

The Safety Population will comprise all patients who provide Informed Consent and received at least 1 dose or partial dose of IMP.

Patients will be analyzed according to the treatment they actually received.

The Safety Population will be used to produce summaries of all safety related endpoints and demography.

Per-protocol Population

The Per-protocol Population (PP) will include all FAS patients who were compliant with study drug administration had no major protocol deviations that were considered as potentially impacting the efficacy results. Major protocol deviations might include, but are not be limited to, patients taking a not-permitted concomitant medication, the IMP not being administered during the trial as defined in the protocol, patients receiving a treatment different than the one assigned by randomization; others will be defined in the SAP.

Results of the primary and secondary efficacy endpoints analyses conducted in the PP will be considered as supportive.

Exclusion of patients from the PP analyses will be decided jointly by the CRO and Sponsor's Medical Monitor, Clinical Trial Manager and Statistician prior to unblinding of the randomization code and database release.

The patients or observations to be excluded, and the reasons for their exclusion will be documented and approved by the above mentioned persons prior to database release. The documentation will be filed together with the remaining trial documentation.

The number of patients in each analysis population will be reported. Violations excluding patients from any particular population will be described, reporting the number of protocol violators per each criterion. All protocol violations, minor ones included, will be listed.

### *20.4.3 Efficacy Data*

The FAS population will be used for the primary analyses of each of the efficacy endpoints whilst results from supplemental analyses using the Per Protocol Population will be compared to those based on the FAS population to assess the effects of dropouts, missing data, protocol violations and deviations.

The distributions of all the efficacy endpoints listed in Section 20.2 will be summarized by treatment group and time point. Counts and percentages will be reported with the latest computed based on the numbers of patients with non-missing observations. The percentages will be suppressed when the count is zero in order to draw attention to the non-zero counts. Furthermore, efficacy endpoints will be further summarized by arithmetic means, standard deviations, medians quartiles, minima and maxima.

#### *20.4.3.1 Analysis of Primary Endpoint*

The primary objective of the study is to evaluate the change from baseline to week 16 in the mean "OFF" time, as assessed by the 24-hour patient diary, of safinamide 100 mg/day compared to placebo, given as add-on therapy in PD patients with motor fluctuations on stable doses of L-dopa. The analysis of primary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline mean "OFF" time measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.
The main time point for comparison between treatment groups is week 16, but other available measurements at other visits will be analysed as well.

#### *20.4.3.2 Analysis of Key Secondary Endpoint*

The key secondary objective of the study is to evaluate the change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS), of safinamide 100 mg/day compared to placebo. As for the analysis of the primary endpoint, the analysis of key secondary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline NRS measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.

The main time point for comparison between treatment groups is week 16, but other available measurements at other visits will be analyzed as well.

#### *20.4.3.3 Analyses of Other Secondary Endpoints*

- Change from baseline to week 16 in the mean total daily "ON" time, as assessed by 24-hour patient diary cards: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above (i.e. as for the primary and key secondary endpoint), with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- Change from baseline to week 16 in the mean daily "ON" time with no/non-troublesome dyskinesia, as assessed by 24-hour patient diary cards: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.

- Change from baseline to week 16 in the UPDRS total score during the "ON" phase: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value..
- Change from baseline to week 16 in the UPDRS part II (ADL) score during the "ON" phase: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- Change from baseline to week 16 in the UPDRS part III (motor function) score during the "ON" phase: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- CGI-S score assessed at week 16: the hypothesis of superiority of safinamide compared to placebo will be assessed using the Wilcoxon-Mann-Whitney test stratified by centre, whilst point estimate of treatment differences will be reported as Hodges-Lehmann estimators together with associated two-sided nonparametric 95% confidence intervals.
- Change from baseline to week 16 in the CGI-C: the hypothesis of superiority of safinamide compared to placebo will be assessed using the Wilcoxon-Mann-Whitney test stratified by centre, whilst point estimate of treatment differences will be reported as Hodges-Lehmann estimators together with associated two-sided nonparametric 95% confidence intervals.
- Change from baseline to week 16 in the PDQ-39 score: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.

#### *20.4.4 Handling of missing data*

Missing data on the primary and key secondary efficacy endpoints will be imputed using multiple imputation (MI) as the primary imputation method and last observation carried forward (LOCF) as sensitivity analysis. Missing data on all the other secondary efficacy endpoints will be imputed only using LOCF method. Details regarding the multiple imputation approach (i.e. number of imputations, the randomization seed and the imputation and analysis models that will be used) will be reported in the SAP.

#### *20.4.5 Multiplicity*

The overall type I family-wise error rate for testing the primary and the key secondary efficacy endpoints will be controlled at the two-sided 0.05 significance level using a Fixed Sequence Procedure (6). Following this procedure, progression to next step will only occurs as long as null hypothesis (H0: Active effect = Vehicle effect) from previous step is rejected at 0.05

significance level. The testing procedure is stopped and all the remaining null hypotheses accepted if an acceptance occurs. All individual hypothesis tests will be 2 sided.

1. The first step will test the primary efficacy parameter. The p-value for the null hypothesis must be less than 0.05 to be considered to have met the primary efficacy objective. If the null hypotheses is not rejected (i.e., p-value >0.05), the subsequent statistical test (second step) will not be considered statistically significant.
2. The second step will test the key secondary efficacy parameter "change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale".

For the analyses of supportive secondary efficacy end-points (not key) no adjustment of significance level will be made to account for multiple comparisons.

### *20.4.6 Multicenter study*

As additional analysis, ANCOVA models for the analysis of primary endpoint and key secondary endpoint described in sections 20.4.3.1 and 20.4.3.2 will be fitted again including the site-by-treatment interaction, in order to test if that interaction is statistically significant, using an alpha=0.1. Also, in order to graphically assess the possible heterogeneity of the treatment effect across centres forest plots will be generated to display the results at each center. In case that the number of patients in each site were scarce, sites will be gathered into "region". Upon completion of the study and prior to unblinding, study statisticians in consultation with the clinical team will determine the pooling based on enrolment numbers and geographical proximity.

### *20.4.7 Interim Analyses*

No interim analyses are planned.

### *20.4.8 Safety data*

All safety endpoints will be summarized and analyzed using the Safety Population.

Incidence of Treatment Emergent Adverse Events

The number and the percentage of patients reporting TEAEs, treatment emergent SAEs, severe TEAEs, TEAEs leading to discontinuation and TEAEs leading to death will be presented by treatment group, along with the number of events occurring.

TEAEs will be summarized also by System Organ Class and Preferred Term according to MedDRA; they will be additionally summarized by severity and relationship to treatment. A separate summary table will be provided for SAEs.

Only TEAEs, i.e. events with an onset date on or after the date of IMP start, will be included in the summary tables. Individual data listings will include all AEs recorded; a separate listing will be provided for treatment-emergent SAEs.

Vital Signs

Descriptive statistics for vital signs at each visit will be presented overall and by treatment.

Physical examination data.

Descriptive statistics for physical examination data at each visit will be presented overall and by treatment.

Haematology and clinical chemistry

Haematology and clinical chemistry results at Visit 1 and Visit 3 will be converted to standard international units and summarized by treatment group using descriptive statistics for continuous variables. Summaries for change from Visit 1 at Visit 3 will be also provided. Frequency of patients with values appearing outside the central laboratory normal range will be reported by visit for each treatment group. All values appearing outside the laboratory normal range will be highlighted in listings.

12-lead Electrocardiogram

Descriptive statistics for ECG results will be presented overall and by treatment.

Handling missing data on safety variables

Generally, there will be no imputation of missing values and only observed safety data will be included in the analyses.

If an AE has a partial or fully missing date, and it is unclear whether the AE is treatment-emergent, it will be assumed that it is. In the AEs analysis, when relationship to study drug is missing for a treatment-emergent adverse event it will be imputed to be drug related.

Additional details of handling of missing data for each type of analyses will be provided in the SAP.

# 21.0 INFORMED CONSENT

Written informed consent will be obtained by the Investigator or other authorised person from all patients.

The Investigator is responsible for correctly obtaining the informed consent in accordance with the applicable regulatory requirements, GCP and the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the study, the Investigator should have received the EC written approval of Informed Consent Form (ICF).

Written informed consent must be obtained prior to the initiation of any procedures specific to the study. The record of the informed consent must be available to be audited/inspected by the Sponsor/CRO designees and by CAs, whenever requested.

The informed consent documentation must be personally dated and signed by the study patient. Illiterate patients can be enrolled in the study by “making their mark” on the informed consent, when consistent with applicable local law.

Neither the Investigator, nor the study staff, should coerce or unduly influence a patient to participate or to continue to participate in a study.

Before informed consent may be obtained, the Investigator or other authorised person, should provide the patient ample time and opportunity to inquire about details of the study and to

decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient.

The patient should receive a copy of the signed and dated Informed Consent Form and any other written information provided to him/her, and updates.

## 22.0 ETHICS COMMITEE APPROVAL

This study will be undertaken only after written and dated approval from EC has been received by the Investigator and by the Sponsor/CRO for the CTP, all its appendices, ICF and patients recruitment procedures (i.e. advertisement) if applicable.

In addition to the above mentioned documents, the EC will be provided with the current Investigator's Brochure, SmPC and Investigational Medicinal Product Dossier (IMPD, where applicable), the Investigator's up-to-date Curriculum Vitae and/or other documentation evidencing qualifications, and any other documents that the EC may need to fulfil its responsibilities.

During the study, on regular basis, the Investigator will have to submit written summaries of the trial status (i.e. recruitment rate) to the EC, if requested.

## 23.0 REGULATORY REQUIREMENTS

This study will be conducted in full conformance with the ICH E6 R2 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study is to be conducted in compliance with the CFDA GCP and ICH-GCP E6 Rev2.
Selection of patients will not start prior to the approval of the EC has been obtained and the trial notified to or authorised by CAs.

## 24.0 QUALITY ASSURANCE

This CTP has been audited by the Sponsor's Quality Assurance.

The Audit Plan for the study includes site audits at study centres. These audits will be planned and conducted according to the Sponsor's SOPs.

## 25.0 INSURANCE

The Sponsor is concerned with the safety of the patients in the clinical study and wishes to protect the Investigator (and as applicable per local regulations, the site, the monitor and all the Investigator's staff involved in the trial) in the event of claims or lawsuits alleging injury as a result of administration of the study drug, providing that the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor.

In consideration of undertaking a human study in patients according to this CTP the Sponsor will:

- Indemnify the Investigator and hold him/her without liability for claims for damages arising out of the above described investigation in excess to those covered by his/her own professional liability insurance.

- Defend the Investigator against any claims or lawsuits initiated by, or on behalf of, patients who seek damages for bodily injury alleged to have been sustained as a result of administration of the study drug.
- Pay any settlements of judgement resulting therefrom, providing that for all of the aforementioned cases, the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor.

Indemnification is not valid for claims for damages arising from malpractice and/or negligence on the part of the Investigator or those under the Investigator's supervision.

The protection afforded by this policy does not take the place of the Investigator's professional liability insurance, but covers damages in excess of such insurance protection. Further, this indemnity is conditional upon the Investigator giving the Sponsor information as soon as reasonably practicable and upon the Investigator assisting the Sponsor and its authorised representatives in the investigation and defence of any suit for which coverage is provided.

## 26.0 CLINICAL TRIAL REPORT

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

## 27.0 USE OF INFORMATION AND PUBLICATION

The Investigator agrees to inform Zambon in advance about his/her intention to divulge any data, results concerning the Confidential Information and/or the study patient to this Agreement. As a consequence hereof, the Investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon’s rights to preserve and protect its intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the study is conducted.

Furthermore, without any prejudice to the Investigator’s right to divulge and save for what stated hereinabove, the Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the study hereto.

# 28.0 REFERENCES


1. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's Disease: a review of the evidence. Eur J Epidemiol 2011; 26 Suppl 1: S1-S58.
2. Chaudhuri K, Schapira AH. Non-motor symptoms of Parkinson's Disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009; 8(5): 464-474.
3. De Lau LM, Giesbergen PC, De Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson's Disease in a general population: the Rotterdam Study. Neurology 2004; 63(7): 1240-1244.
4. Fox SH. Non-dopaminergic treatments for motor control in Parkinson's disease. Drugs 2013; 73: 1405-1415.
5. Cattaneo C, Ferla RL, Bonizzoni E, Sardina M. Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's Disease patients: a post-hoc analysis. J Parkinsons Dis 2015; 5(3): 475-481.
6. Cattaneo C, Barone P, Bonizzoni E, Sardina M. Effects of safinamide on pain in fluctuating Parkinson's Disease patients: a post-hoc analysis. J Parkinsons Dis 2017; 7(1): 95-101.
7. Cattaneo C, Müller T, Bonizzoni E, Lazzeri G, Kottakis I. Long-term effects of safinamide of safinamide on mood fluctuations in Parkinson's Disease. J Parkinsons Dis 2017; 7(4): 629-634.
8. Cattaneo C, Kulisevsky J, Tubazio V, Castellani P. Long-term efficacy of safinamide on Parkinson's Disease chronic pain. Adv Ther 2018; 35:515-522.
9. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D et al. Randomized trial of safinamide add-on to levodopa in Parkinson's Disease with motor fluctuations. Mov Disord 2014; 29(2): 229-237.
10. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's Disease and motor fluctuations: a randomized clinical trial. JAMA Neurol 2017; 74(2): 216-224.
11. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's Disease. Mov Disord 2014; 29(10): 1273-1280.
12. Xadago® (safinamide) SmPC.
13. Safinamide Investigator's Brochure, Edition Number 4, dated 13 February 2018.
14. National Collaborating Centre for Chronic Conditions. Parkinson's Disease: national clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians, 2006.
15. Murray D, Stoessl J. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. Pharmacol Ther 2013; 140: 306-318.
16. Goetz CG, Wuu J, McDeermott M, adler C et al. Placebo response in Parkinson's disease: comparison among 11 trials covering medical and surgical interventions. Mov Disord 2008; 23(5): 690-699.

17. ICH Topic E10. Note for guidance on choice of control groups in clinical trials. CPMP/ICH/364/96 January 2001.

18. Position statement on the use of placebo in clinical trials with regard to the revised Declaration of Helsinki. EMEA/17424/01London, 28 June 2001.

19. Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. J Clin Neuropharmacol. 2000; 23:75-81.

20. Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17(5):427-42.

21. Fahn S, Elton R, members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information. 1987; 153-63, 293-304.

22. Guy W. Clinical Global Impression. In ECDEU Assessment Manual for Psychopharmacology. Revised DHEW Pub (ADM). Rockville, MD: National Institute for Mental Health 1976; 218-222.

23. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well-being for individuals with Parkinson's disease. Qual Life Res 1995; 4:241-248.

24. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain 2011; 152(10):2399–2404.

25. Maurer, Hothorn, Lehmacher. Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In Biometrie in der chemisch-pharmazeutischen Industrie. Vollmar J (Editor). Stuttgart: Fischer Verlag. 1995; 6: 3-18.

26. Rascol O, Zesiewicz T, Chaudhuri KR, Asgharnejad M, Surmann E, Dohin E et al. A randomized controlled exploratory pilot study to evaluate the effect of rotigotine transdermal patch on Parkinson's Disease-associated chronic pain. J Clin Pharmacol 2016; 56(7): 852-861.

27. Dmitrienko, A., Pulkstenis, E. Clinical Trial Optimization Using R. Chapman & Hall/CRC Biostatistics Series, 2017; 4-28.

# 29.0 APPENDICES

Appendix 1: Study Flow Chart

Appendix 2: United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria

Appendix 3: Hoehn and Yahr Scale

# APPENDIX 1

## STUDY FLOW CHART

| Study Period | Screening period | Baseline | Treatment period | | | End of Treatment (EOT) / Early Termination (ET)[1] | Telephone follow-up | Unscheduled visit |
|---|---|---|---|---|---|---|---|---|
| **Week** | **-2 to 0** | **0** | **2** | **6** | **10** | **16** | **17** | |
| **Day** | **-14 to -2** | **1** | **14 ±3** | **42 ±3** | **70 ±3** | **112 ±3** | **119 ±3** | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | |
| Informed consent | X | | | | | | | |
| Eligibility criteria | X | X | | | | | | |
| Randomization | | X | | | | | | |
| Demographics | X | | | | | | | |
| Medical history/diagnosis | X | | | | | | | |
| Hoehn & Yahr staging | X | | | | | | | |
| Neurological examination[2] | X | | | | | | | |
| Prior and concomitant medications[3] | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | | X |
| 12-lead ECG | X | | | | | X | | X |
| Physical examination | X | | | | | X | | X |
| Diary Issue and Training[4] | X | X | X | X | X | | | |
| Diary Review | | X | X | X | X | X | | |
| UPDRS [5] | | X | X | X | X | X | | |
| CGI-S[5] | | X | X | X | X | X | | |
| CGI-C[5] | | | X | X | X | X | | |
| PDQ-39[5] | | X | X | X | X | X | | |
| NRS[6] | | X | X | X | X | X | | |
| Laboratory exams | X | | | | | X | | |
| Pregnancy test (urine)[7] | X | | | | | X | | |
| Adverse events | | X | X | X | X | X | X | X |
| Dispense randomised medication | | X[8] | X | X | X | | | X |
| Drug accountability | | | X | X | X | X | | X |

ECG: electrocardiogram; UPDRS: Unified Parkinson's Disease Rating Scale; CGI-S: Clinical Global Impression-Severity; CGI-C: Clinical Global Impression-Change; PDQ-39: Parkinson's Disease Questionnaire-39 items; NRS: Numerical Rating Scale.

1. Subjects who prematurely withdraw from the study while receiving study medication should complete the EOT Visit assessments, when possible.
2. Neurological examination at screening visit only.
3. Details of excluded and permitted concomitant treatments are presented in Section 11.0 of the protocol.
4. The diary should be completed by the subject two days before the baseline visit and the visits at weeks 2, 6, 10 and 16 (visits 3,4,5 and 6) for recording of "OFF" and "ON" time
5. To be evaluated at approximately the same time of day as at the baseline visit, if possible at least 1 hour after the subject has taken their morning dose of safinamide and is in the optimal "ON" state.
6. NRS will record PD pain intensity in the evening before going to sleep prior to the baseline visit and the visits at weeks 2, 6, 10 and 16 (visits 3,4,5 and 6), as the worst pain experienced in the past 24 hours (at any time during the day). If the patient suffers for more than one pain, the more severe pain must be recorded.
7. All women of child-bearing potential.
8. The first dose of safinamide or placebo (50 mg once daily) will be administered at the study centre. The dose of safinamide or placebo will be titrated the day after the Visit 3/week 2, ideally at day 15 at home to 100 mg once daily. See Section 7.0 of the protocol.

# APPENDIX 2

## UNITED KINGDOM PARKINSON'S DISEASE BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA

Eligible subjects must have a diagnosis of IPD according to the United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria, as described below:

**Step 1. Diagnosis of Parkinsonian Syndrome**

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) - and at least one of the following:

- Muscular rigidity.
- 4-6 Hz rest tremor.
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

**Step 2. Exclusion Criteria for IPD**

- Repeated strokes with stepwise progression of parkinsonian features.
- Repeated head injury.
- History of definite encephalitis.
- Oculogyric crises.
- Neuroleptic treatment at onset of symptoms.
- More than one affected relative.
- Sustained remission.
- Strictly unilateral features after 3 years.
- Supranuclear gaze palsy.
- Cerebellar signs.
- Early severe autonomic involvement.
- Early severe dementia with disturbances of memory, language, and praxis.
- Babinski sign.
- Presence of cerebral tumour or communicating hydrocephalus on computed tomography scan.
- Negative response to large doses of L-dopa (if malabsorption excluded).

- Methyl-phenyl-tetrahydropyridine exposure.

**Step 3. Supportive Prospective Positive Criteria for IPD (three or more required for diagnosis of definite PD)**

- Unilateral onset.
- Rest tremor present.
- Progressive disorder.
- Persistent asymmetry affecting side of onset most.
- Excellent response (70-100%) to L-dopa.
- Severe L-dopa-induced chorea.
- L-dopa response for 5 years or more.
- Clinical course of 10 years or more.

# APPENDIX 3

## HOEHN AND YAHR SCALE

Eligible subjects must be Hoehn and Yahr Scale Stage 1-4 during the "ON" phase (Table 5).

**TABLE 5 STAGING OF PARKINSON'S DISEASE (ACCORDING TO HOEHN AND YAHR)**

| Stage | Description |
|---|---|
| 0 | No signs of disease |
| 1 | Symptoms on one side only (unilateral) |
| 1.5 | Symptoms unilateral and also involving the neck and spine |
| 2 | Symptoms on both sides (bilateral) but no impairment of balance |
| 2.5 | Mild bilateral symptoms with recovery when the "pull" test is given |
| 3 | Balance impairment. Mild to moderate disease. Physically independent |
| 4 | Severe disability but still able to walk or stand unassisted |
| 5 | Needing a wheelchair or bedridden unless assisted |

From: Hoehn M, Yahr M. (1967) Parkinsonism: onset, progression and mortality. Neurology. 17(5):427-442.

# CLINICAL TRIAL PROTOCOL

## A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SAFINAMIDE, AS ADD-ON THERAPY, IN IDIOPATHIC CHINESE PARKINSON'S DISEASE (PD) PATIENTS WITH MOTOR FLUCTUATIONS TREATED WITH STABLE DOSES OF LEVODOPA

Protocol Code: Z7219L05

Date: 08 October 2019

Amended Protocol Version: Final 2.0

Zambon SpA
Via Lillo del Duca 10
20091 Bresso - Milan - Italy

# APPROVAL PAGE

| | |
|---|---|
| **Clinical Trial Title:** | A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide, as add-on therapy, in idiopathic Chinese Parkinson's Disease (PD) patients with motor fluctuations treated with stable doses of levodopa. |
| **Protocol Code** | Z7219L05 |
| **Date:** | 08 October 2019 |
| **Authors:** | PPD |
| **Sponsor Name and Address:** | Zambon SpA<br>Via Lillo del Duca 10<br>20091 Bresso, Milan, Italy |

**As agreed and approved:**

| _____/_____/_____ | _____ | _____ |
|---|---|---|
| **Date (dd/Mmm/yyyy)** | **Principal Investigator** | **SIGNATURE** |

**Accepted for the Sponsor**

| PPD | PPD | PPD |
|---|---|---|
| **Date (dd/Mmm/yyyy)** | PPD | **SIGNATURE** |

# LIST OF ZAMBON PERSONNEL

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| Role | Name | Contact Data |
|---|---|---|
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| PPD | PPD | Phone: PPD |
| PPD | PPD | Phone: PPD |
| PPD | PPD | Phone: PPD |
| PPD | PPD | Phone: PPD 1 |

# LIST OF CONTRACT RESEARCH ORGANISATION PERSONNEL

PAREXEL

| Role | Name | Contact Data |
|---|---|---|
| Project Manager | PPD | Phone: PPD |
| Biostatistician | PPD | Phone: PPD |
| Biostatistician | PPD | Phone: PPD |
| Medical Monitor | PPD | Phone: PPD |
| Medical Writer | TBC | |
| Contact for serious adverse event/pregnancy reporting | Safety Services Project Leader | PPD |

# OTHER INSTITUTIONS

| Role | Name | Contact Data |
|---|---|---|
| Interactive Web Response System (IWRS) | Perceptive Customer Care | PPD |
| Investigational Medicinal Product (IMP) Packaging and Labelling; Logistics | PPD | PPD<br>Phone: PPD |

# LIST OF COMMITTEES

**Steering committee**

Study protocol and study results will be clinically reviewed and valued by the *Study Outcome Review Board*, composed of expert neurologists with a long-standing experience in Parkinson's disease. The Chairman of this Steering Committee will be PPD PPD, PPD

# SUMMARY OF CHANGES HISTORY

| Protocol Version | Key Changes |
|---|---|
| Protocol Version: Final 1.0 | Original Protocol |
| Amended Protocol Version: Final 2.0 | Non-substantial changes |

# 1.0 TABLE OF CONTENTS

# 2.0 ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of daily living |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| BUN | Blood Urea Nitrogen |
| CA | Competent Authority |
| 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 |
| CTP | Clinical trial protocol |
| CYP | Cytochrome P450 |
| 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 |
| GMP | Good Manufacturing Practice |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| 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 |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mL | Millilitres |
| NRS | Numerical Rating Scale |
| od | Once daily |
| PD | Parkinson's Disease |
| PDQ-39 | Parkinson's Disease Questionnaire-39 items |
| po | Per os (By mouth) |
| PP | Per protocol |
| PT | Preferred term |
| QA | Quality assurance |
| PR | Prolonged release |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SETTLE | SafinamidE Treatment as add-on To LEvodopa in idiopathic Parkinson's disease with motor fluctuations |
| SNRI | Serotonin-norepinephrine reuptake inhibitor |
| SOC | System organ class |
| SOP | Standard operating procedures |
| SmPC | Summary of Product Characteristics |
| SSRI | Selective serotonin reuptake inhibitor |
| TEAE | treatment-emergent adverse event |
| TMF | Trial Master file |
| WHO-DD | World Health Organization-Drug Dictionary |

# 3.0 SUMMARY

**Title:** A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide, as add-on therapy, in idiopathic Chinese Parkinson's Disease (PD) patients with motor fluctuations treated with stable doses of levodopa.

**Protocol Code:** Z7219L05

**Phase:** III

**Test Product:** Safinamide film-coated tablets.

**Control Product / Placebo:** Placebo-film coated tablets.

**Dosage:** Safinamide film-coated tablets for oral administration at an initial dose of 50 mg once daily (od) and increased the day after the Visit 3/week 2 (ideally at day 15) to the final dose of 100 mg od. Treatment will continue daily for a total of 16 weeks.

**Objectives:**

Efficacy:

To evaluate the efficacy of safinamide, compared with placebo, as add-on therapy in idiopathic Chinese PD patients with motor fluctuations treated with stable doses of levodopa (L-dopa).

Safety:

To evaluate the safety and tolerability of safinamide.

**Design:** This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study in idiopathic Chinese PD patients, experiencing motor fluctuations while on stable doses of levodopa (alone or in combination with other anti-Parkinson drugs). Study participation will be up to a maximum duration of 18 weeks and will comprise a screening period (up to 2 weeks) and a treatment period (16 weeks).

Screening Period

After providing written informed consent to participate in the study, patients will enter a screening period up to 2 weeks. During the screening period, patients will undergo all the evaluations necessary to establish their eligibility for the study. Patients considered non-eligible ("screening failures") due to clinically significant abnormalities in laboratory exams, ECG, vital signs or traditional Chinese medicine (TCM) not related to nervous system disease, could be re-screened again only once during the study after a reasonable interval of time, based on the judgement of the Investigator that should be fully documented and explained in the

clinical records and in the CRF. They would need to sign a new consent form. Patients who will be confirmed to be non-eligible in this second screening visit should definitively be excluded from the study.
Patients and their caregivers will be trained on the completion of a 24-hour diary card and the last two days of recording prior to each study visit will be used for data analysis.

*The dose of L-dopa and of the other anti-Parkinson drugs (if any) must be kept constant during the screening period.*

Treatment Period

At baseline (day 1), eligible patients will enter the treatment period and will be randomised to receive either safinamide (initial 50 mg titrated to 100 mg the day after the Visit 3/week 2, ideally at day 15) or matching placebo, orally od in a 1:1 ratio. The investigational medicinal product (IMP) will be taken in the morning at breakfast time, in addition to the morning dose of L-dopa and other (if any) PD medications.
Following completion of all baseline assessments, they will receive the first dose of safinamide or placebo (50 mg) at the study centre. The day after the Visit 3/week 2 (ideally at day 15) the dose will be increased at home to 100 mg od. Each patient will receive treatment for 16 weeks, with visits at week 0/day 1 (baseline) and at weeks 2, 6, 10 and 16 (or early termination). A telephone follow-up will be performed 1 week after the end of treatment for safety reasons.
Patients who prematurely withdraw from the study while receiving study medication should complete the early termination visit assessments, when possible.
At the end of the study, the patients will be instructed to contact immediately the Investigator in case of appearance of any adverse reactions. Any ongoing adverse event or clinically abnormal laboratory parameter will be followed until resolution. In addition, all SAEs occurring within 30 days after a patient's last dose of study drug will be followed to their conclusion.

*The dose of L-dopa and/or of the concomitant anti-Parkinson treatments must be kept constant throughout the study.*

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

Efficacy will be assessed by the changes in "OFF" and "ON" time from the 24-hour patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Clinical Global Impression (CGI), the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the Numerical Rating Scale (NRS).
Safety will be assessed by clinical laboratory tests (haematology and serum chemistry), vital signs, 12-lead electrocardiogram, physical examination, adverse events and concomitant medications.
The visit procedures are summarised in the Study Flow Chart Section 29.0, Appendix 1.

**Sample Size:** Sample size was computed through a Monte Carlo study with 1000 runs and using a fixed sequence procedure to account for multiplicity over the study primary endpoint (change from baseline to week 16 in the mean total daily "OFF" time) and the key secondary endpoint (change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS). The fixed sequence procedure implies that the key secondary endpoint will be verifiable provided that the primary endpoint has achieved statistical significance (namely two-tailed p-value ≤ 0.05).
Based on the Monte Carlo simulation it was estimated that a total sample size of 260 patients (130 in the safinamide and 130 in the placebo groups) ensures 90% power to detect a mean difference in the 'off' time at least 0.9 h between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming standard deviations of 2.35 for safinamide and 2.06 for placebo.
Moreover, the same Monte Carlo study showed that the total sample size of 260 patients would also permit a marginal power equal to 88% to detect 1 point treatment difference in the NRS between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming a pooled standard deviations of 2.0.
Assuming an attrition rate equal to 15% a total of approximately **306 patients** will be **randomized** (153 in the safinamide and 153 in the placebo groups).

**Population:** **Inclusion criteria:**

1. Male or female patients aged ≥18 years old.
2. Chinese ethnicity.
3. Able to understand and willing to provide written informed consent.
4. Able to maintain an accurate and complete 24-hour diary with the help of a caregiver if needed.
5. Diagnosis of idiopathic Parkinson's Disease (IPD) using the United Kingdom Parkinson's Disease Society Brain Bank criteria of more than 3 years duration.

6. Be levodopa responsive and receiving treatment with stable daily doses 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 dopamine agonists, anticholinergics and/or amantadine for at least 4 weeks prior to the screening visit.
7. A Hoehn and Yahr stage between 1-4 inclusive during the "ON" phase.
8. Experiencing motor fluctuations with a minimum of 1.5 hours/day of "OFF" time during the day (excluding morning akinesia), based on historical data.
9. If female, be post-menopausal for at least one year or have undergone hysterectomy or, if of child-bearing potential, must have a negative pregnancy test, must neither be breast-feeding nor become pregnant during the study and must use adequate contraception for 1 month prior to randomisation and for up to 1 month after the last dose of study drug. Adequate contraception is defined as:

a) Hormonal oral, implantable, transdermal, or injectable contraceptives or a non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 1 month prior to randomization
b) a male sexual partner who agrees to use a male condom with spermicide or a sterile sexual partner.

For all women of child-bearing potential, urine pregnancy test result at screening must be negative.

**Exclusion criteria:**

1. Any form of Parkinsonism other than IPD.
2. Diagnosis of chronic migraine (>15 days per month) or cancer pain.
3. L-dopa infusion.
4. Hoehn and Yahr stage 5 during the "ON" phase.
5. If female, pregnancy or breast-feeding.
6. Neurosurgical intervention of PD or stereotactic brain surgery.
7. Severe peak dose or biphasic dyskinesia, unpredictable or widely swinging fluctuations.
8. History of major depression or other clinically significant

psychotic disorder which may compromise the ability to provide the informed consent or to participate to the study.

9. Drug and/or alcohol abuse within 12 months prior to the screening visit.
10. History of dementia or severe cognitive dysfunction.
11. Use of any investigational drug or device within 30 days prior to screening or 5 half-lives, whichever is the longest, or during the study.
12. Allergy/sensitivity or contraindications to the investigational medicinal products (IMPs) or their excipients, to anticonvulsants or to anti-Parkinson drugs.
13. Any clinically significant condition (including laboratory values) which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for patients while in the study.
14. Moderate or severe liver failure using the Child-Pugh classification score, or human immunodeficiency virus (HIV).
15. Treatment with monoamine oxidase inhibitors (MAOIs), pethidine, opiates, opioids, fluoxetine, fluvoxamine in the 4 weeks prior to the screening visit. These drugs are not allowed throughout the study and up 2 weeks after the last dose of study drug.
16. 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.

**Endpoints**

Primary Endpoint:

- The change from baseline to week 16 in the mean total daily "OFF" time, as assessed by 24-hour patient diary cards.

Key Secondary Endpoint:

- The change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS).

Other Secondary Endpoints:

- The change from baseline to week 16 in the mean total daily "ON" time, as assessed by 24-hour patient diary cards.
- The change from baseline to week 16 in the mean daily "ON" time with no/non-troublesome dyskinesia, as assessed by 24-hour patient diary cards.

- The change from baseline to week 16 in the UPDRS total score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part II (ADL) score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part III (motor function) score during the "ON" phase.
- The CGI-S score at week 16.
- The change from baseline to week 16 in the CGI-C.
- The change from baseline to week 16 in the PDQ-39 score.

Safety Endpoints:

- The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TSAEs).
- Physical examination findings (clinically significant).
- Vital signs (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities.
- 12-lead electrocardiogram (ECG) parameter measures, including occurrence of abnormalities.
- Clinical chemistry and haematology values, including shifts from baseline and occurrence of abnormalities.

**Statistical Analysis**

All efficacy analyses will be performed on the Full Analysis Set (FAS) population. Analysis of the primary and secondary efficacy variables will be also carried out on the Per Protocol (PP) population to assess the robustness of the findings. Safety outcomes will be analysed on the Safety population.

The primary objective of the study is to evaluate the change from baseline to week 16 in the mean "OFF" time, as assessed by the 24-hour patient diary, of safinamide 100 mg/day compared to placebo, given as add-on therapy in PD patients with motor fluctuations on stable doses of L-dopa. The analysis of primary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline mean "OFF" time measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.
The key secondary objective of the study is to evaluate the change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS), of safinamide 100 mg/day compared to placebo. Exactly as for the analysis of the primary

endpoint, the analysis of key secondary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline NRS measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.

The overall type I family-wise error rate for testing the primary endpoint and key secondary endpoint will be controlled at the two-tailed 0.05 significance level using a fixed sequence procedure. This procedure will be fully described in the protocol.

The same statistical approach (ANCOVA) will be taken for the analysis of change from baseline to week 16 of all the other supportive secondary end-points listed above with the exclusion of CGI-S and CGI-C scores which will be analysed using the Wilcoxon-Mann-Whitney test stratified by centre. For the analyses of supportive secondary efficacy end-points no adjustment of significance level will be made to account for multiple comparisons.

The main time point for comparison between treatment groups is week 16, but other available measurements at other visits will be analysed as well.

Missing data on the primary and key secondary efficacy endpoints will be imputed using multiple imputation (MI) as the primary imputation method and last observation carried forward (LOCF) as sensitivity analysis. Missing data on all the other secondary efficacy endpoints will be imputed only using LOCF approach.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The analysis of adverse events will include summary tables displaying counts and percentages of patients experiencing adverse events by system organ class (SOC) and preferred term (PT). If a patient has more than one AE which codes to the same PT, the patient will be counted only once for that PT. The total number of events documented per SOC and PT will also be displayed. All other safety data will be analysed descriptively.

**Concomitant Treatments**

- 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.

Concomitant medications that are considered necessary for the safety and well-being of the patient are permitted during the study at the discretion of the Investigator, with the exception of the non-permitted drugs described here below.

**Non-permitted concomitant drugs are:**

- L-dopa infusion and MAOIs
- Opioids and opiates
- Fluoxetine or fluvoxamine
- Pethidine
- Any other investigational agent
- Traditional Chinese medicine related to nervous system disease
- Acupuncture for treatment IPD

*The dose of L-dopa and of the other anti-Parkinson drugs (if any) must be kept constant throughout the study.*

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

In addition, patients must not participate in any other clinical study of an investigational product or device whilst participating in this study.

**Estimated Trial Duration:**

First Patient In: 01 August 2019

Recruitment Period: Approximately 12 months.

Last Patient Out: 30 November 2020

| | |
|---|---|
| | Clinical Study Report: 31 March 2021 |
| **Treatment Duration:** | The study comprises a screening period of 1 to 2 weeks, a treatment period of 16 weeks, and a 1-week telephone follow-up. |
| **Participating Countries** | 1 country (China) |
| **Number of Sites** | Approximately 35 centres |

# 4.0 INTRODUCTION AND RATIONALE

## 4.1 Idiopathic Parkinson's Disease

Idiopathic Parkinson's Disease (IPD) is a neurodegenerative condition characterised 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 aetiology of IPD remains unknown but the involvement of genetic and environmental factors, such as exposures to different toxins, is most probable (1).

The main symptoms of IPD are resting tremor, bradykinesia and rigidity. The disease is also associated with non-motor symptoms such as depression, apathy, erectile dysfunction and gastrointestinal disturbances (2). The incidence of IPD increases with age, with incidence rates in the general population increasing from 0.3 per 1,000 person-years in patients aged 55 to 65 years, to 4.4 per 1,000 person-years for those aged ≥85 years (3).

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 patients will require therapies combining L-dopa and adjunct dopamine agonists, COMT inhibitors and/or MAO-B inhibitors.

Beyond dopamine, perturbations in neurotransmission in the basal ganglia of PD patients are known to involve glutamate and other transmitters and play important roles in the pathogenesis of primary symptoms, motor fluctuations, non-motor symptoms and possibly neuronal cell loss. Targeting non-dopaminergic systems may thus be an alternative approach to improve and control PD motor complications (4).

## 4.2 Background on Safinamide

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 a glutamate modulator. These molecular mechanisms increase brain dopamine, extend L-dopa induced "ON" time (dopaminergic actions) and reduce the severity of L-dopa induced dyskinesia and of some non-motor symptoms such as pain and depression (non-dopaminergic action) (5,6,7,8). By combining inhibition of both MAO-B and sodium channels, safinamide may represent a new strategy for the therapy of PD.

Safinamide has been approved by the European Medicines Agency (EMA) 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) and by the Food and Drug Administration (FDA) as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's Disease experiencing "OFF" episodes. At the current date safinamide is on the market in 11 European countries, in Switzerland and in US.

### *4.2.1 Pharmacokinetics*

Safinamide is almost completely absorbed after oral administration and is cleared from systemic circulation primarily by metabolism, with excretion of the formed metabolites mainly by the kidney and partly by the liver. The elimination half-life of safinamide is approximately 20-24 hours.

The potential for clinically relevant drug interaction due to cytochrome P450 (CYP) induction or inhibition is considered remote as demonstrated by in vitro studies and in a dedicated drug-drug interaction study performed with CYP1A2 and CYP3A4 substrates (caffeine and midazolam). Other drug-relevant CYPs, monoamine oxidase-A and L-dopa decarboxylase, as well as the most important drug transporters, are not inhibited by safinamide or its main human metabolites.

Safinamide does not require any restrictions related to dietary tyramine intake, as assessed by three Phase I trials in healthy volunteers specifically investigating the pressor effect of tyramine, given intravenously or orally (po), during safinamide administration up to 350 mg po (supratherapeutic dose).

### *4.2.2 Toxicology*

Safinamide did not exert pathophysiological relevant effects on the function of the cardiovascular, respiratory, renal and gastrointestinal system nor of the central nervous system.

Retinal degeneration was observed in repeated-dose studies in rat but not in monkey studies. However, these changes have not been noted in any human or non-human primate species despite detailed investigations having been performed for extended periods of time.

Treatment with safinamide was associated with effects on female fertility, embryo-foetal development and post-natal development in rats and rabbits. Fertile women have been excluded from clinical studies with safinamide unless practising adequate contraception.

### *4.2.3 Summary of Clinical Development Data*

More than 3,000 subjects have been enrolled in safinamide studies to date. Of these, >2,600 subjects were enrolled in therapeutic studies, including >2,500 with PD.

The clinical efficacy of safinamide 50 mg/day and 100 mg/day as add-on therapy to levodopa in mid- to late-stage PD patients experiencing motor fluctuations was evaluated in two 24-week, multicentre, double-blind, placebo-controlled trials: study 016 and the SETTLE study (9,10).

The long-term efficacy and safety of safinamide 50−100 mg/day in this patient population were evaluated in study 018, a 18-month, double-blind, placebo-controlled extension of the study 016 (11).

The primary efficacy variable in studies 016 and SETTLE was the change (increase) from baseline to endpoint (week 24) in the mean daily "ON" time ("ON" time without dyskinesia plus

"ON" time with non-troublesome dyskinesia). In both trials there was a statistically significant result in the safinamide group compared with placebo, confirmed by a statistically significant reduction in the "OFF" time.

The benefits achieved in the "ON" and "OFF" time in the study 016 were maintained after 2-years treatment, as observed in extension study 018. There was no significant difference between the safinamide and placebo in the overall incidence of adverse events (AEs), serious adverse events (SAEs), laboratory tests, vital signs, ECGs, physical, neurological, dermatological or ophthalmological examinations. Safinamide treatment was not associated with an increase in daytime sleepiness or impulsive compulsive behaviour.

## 4.3 Evaluation of the anticipated risk/benefit ratio

Safinamide has both dopaminergic and non-dopaminergic activities. It is a MAO-B inhibitor (dopaminergic activity), and has also been shown to inhibit the stimulated release of glutamate through the sodium channels blockade (non-dopaminergic activity).

Altogether, these pharmacological properties indicate that safinamide may be beneficial in the treatment of patients with Parkinson's Disease.

The existing clinical data on safinamide, derived from trials performed in >2,500 PD patients, supports an overall, favourable benefit/risk profile. Safinamide administration has been found to be generally well tolerated and may represent a new treatment strategy for PD, by offering better control of motor symptoms and motor complications with an acceptable safety profile.

Further information is available in the Summary of Product Characteristics (SmPC) (12) and in the Investigator's Brochure (13).

## 4.4 Study Rationale

The efficacy of safinamide has been demonstrated in patients with motor fluctuations when administered as add-on therapy alongside standard of care therapy including L-dopa, dopamine agonists, catechol O-methyltransferase inhibitors, anticholinergics and amantadine, thus emphasizing the additional benefits it can offer when patients are no longer optimally controlled on their current treatment regimen. Importantly, a notable improvement in motor fluctuations is achieved without an increase in troublesome dyskinesia and the benefits are long lasting.

This study is designed to collect data on the impact of safinamide on the motor complications of Chinese PD fluctuating patients over a treatment period of up to 16 weeks. Further information on the effect of safinamide on motor symptoms and quality of life in a clinical setting environment will also be gathered.

The study will be conducted in accordance with the Clinical Trial Protocol (CTP), any approved protocol amendments, International Conference on Harmonization Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.

## 4.5 Discussion of Study Design

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study to evaluate the effects of 100 mg safinamide, administered orally once daily (od), in Chinese PD patients, experiencing motor fluctuations while on stable doses of L-dopa (alone or in

combination with other anti-Parkinson drugs). Eligible patients are required to meet the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria (14).

The double-blind design is adopted to minimize systematic bias in ratings resulting from the knowledge of the treatment received. Randomization helps achieve statistical balance across the two treatment groups. The principal efficacy measure, i.e., the increase in mean daily "OFF" time during the 24-hr diary recording period, was chosen based on regulatory guidance and prior use in other trials in similar populations. Other efficacy measures ("ON" time, UPDRS, CGI, PDQ-39 and NRS) were selected based on the domains of symptoms affected in patients with PD. Tolerability was assessed by changes in laboratory evaluations, vital signs, 12-lead ECG, physical and neurological examinations, and adverse events.

The dose of safinamide (100 mg/day titrated from 50 mg/day after 2 weeks) was selected based on the results of the previous pivotal trials (in particular the study SETTLE), and according to the recommendations of the SmPC. The modulation of glutamate is maximized with the dose of 100 mg. Moreover, this is the dose that has shown to improve significantly dyskinesia (in moderate-severe dyskinetic patients) and PD non-motor symptoms such as chronic pain and mood deterioration. In the SETTLE study, the same dose of 100 mg/day has been administered to a cohort of 168 Asian-Pacific patients, reaching significant positive improvement of fluctuations and motor symptoms.

The study involves a placebo group. Placebo will be added to the standard stabilized treatment as a control of the safinamide group, hence patients on placebo will have benefit from other ongoing anti-PD medication. In addition, patients will be observed during the study more frequently than in the normal clinical practice and in case of any safety issue or lack of efficacy can withdraw from the study at any time.

It is commonly accepted to use a placebo as a control group because a placebo effect can be observed in PD patients (15). A meta-analysis of 11 randomized, double-blind, placebo-controlled clinical trials in PD found an overall placebo response of 16% (16).

The use of placebo is also based on the ICH E10 Guidance for Industry "Choice of control groups and related issues in clinical trials" (CPMP/ICH/364/96), accepted by the FDA in May 2001, stating that (chapter 1.3.1) *"…the placebo control design, by allowing blinding and randomization and including a group that receives an inert treatment, controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug…"* (17), 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) (18).

Moreover, due to its unique mechanism of action (MoA), different from the other PD drugs, safinamide has not a direct comparator.

# 5.0 OBJECTIVES

## 5.1 Efficacy

The objective of the study is to evaluate the efficacy of safinamide compared with placebo, given as add-on therapy, in idiopathic Chinese PD patients with motor fluctuations treated with stable doses of levodopa (L-dopa).

### 5.2 Safety

The safety objective of the study is to evaluate the safety and tolerability of safinamide compared with placebo in Chinese PD patients with motor fluctuations.

## 6.0 ETHICS REQUIREMENTS

This study will be conducted in compliance with the last version of the Declaration of Helsinki (refer to the link https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/), with Good Clinical Practice (GCP), with the applicable regulatory requirements of the country where the study will be conducted and with Zambon and Parexel standard operating procedures (SOPs).

## 7.0 DESIGN AND DURATION OF CLINICAL TRIAL

### 7.1 Clinical Trial Design

This is a Phase III, multicentre, randomised, double-blind, placebo-controlled study in idiopathic Chinese PD patients, experiencing motor fluctuations while on stable doses of levodopa (alone or in combination with other anti-Parkinson drugs).

A total of 306 patients will be randomised into this study (153 in the safinamide and 153 in the placebo groups).

The visit procedures are summarised in the Study Flow Chart Section 29.0, Appendix 1.

**Screening Period**

After providing written informed consent to participate in the study, patients will enter a screening period up to 2 weeks. During the screening period, patients will undergo all the evaluations necessary to establish their eligibility for the study. Patients considered non-eligible ("screening failures") due to clinically significant abnormalities in laboratory exams, ECG, vital signs or traditional Chinese medicine not related to nervous system disease, could be re-screened again only once during the study after a reasonable interval of time, based on the judgement of the Investigator that should be fully documented and explained in the clinical records and in the CRF. They would need to sign a new consent form. Patients who will be confirmed to be non-eligible in this second screening visit should be definitively excluded from the study.

Patients and their caregivers will be trained on the completion of a 24-hour diary card and the last two days of recording prior to each study visit will be used for data analysis.

*The dose of L-dopa and of the other anti-Parkinson drugs (if any) must be kept constant during the screening period.*

**Treatment Period**

At baseline (day 1), eligible patients will enter the treatment period and will be randomised to receive either safinamide (initial 50 mg titrated to 100 mg the day after the Visit 3/week 2, ideally at day 15) or matching placebo, orally od in a 1:1 ratio. The investigational medicinal

product (IMP) will be taken in the morning at breakfast time, in addition to the morning dose of L-dopa and other (if any) PD medications.

Following completion of all baseline assessments, they will receive the first dose of safinamide or placebo (50 mg) at the study centre. The day after the Visit 3/week 2 (ideally at day 15) the dose will be increased at home to 100 mg od. Each patient will receive treatment for 16 weeks, with visits at week 0/day 1 (baseline) and at weeks 2, 6, 10 and 16 (or early termination). A telephone follow-up will be performed 1 week after the end of treatment for safety reasons.

Patients who prematurely withdraw from the study while receiving study medication should complete the early termination visit assessments, when possible.

At the end of the study, the patients will be instructed to contact immediately the Investigator in case of appearance of any adverse reactions. Any ongoing adverse event or clinically abnormal laboratory parameter will be followed until resolution. In addition, all SAEs occurring within 30 days after a patient's last dose of study drug will be followed to their conclusion.

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

**Efficacy** will be assessed by the changes in "OFF" and "ON" time from the 24-hour patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Clinical Global Impression (CGI), the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the Numerical Rating Scale (NRS).

**Safety** will be assessed by clinical laboratory tests (haematology and serum chemistry), vital signs, 12-lead electrocardiogram, physical examination, treatment emergent adverse events and concomitant medications.

## 7.2 Duration of Clinical Trial

Study participation will be up to a maximum duration of 18 weeks and will comprise a screening period (up to 2 weeks), a treatment period (16 weeks) and a 1-week telephone follow-up.

The start of the study is defined as the date of the first visit of the first patient participating in the study.

The end of the study is defined as the date of the last visit of the last patient participating in the study.

# 8.0 CLINICAL TRIAL POPULATION

## 8.1 Number of Patients

Assuming a screening failure rate of 10%, a total of approximately 340 patients will be screened. Assuming an attrition rate equal to 15% a total of approximately 306 patients will be randomized (153 in the safinamide and 153 in the placebo groups).

Approximately 35 study centres will participate in the study. The enrolment will be competitive among sites.

The sample size calculation is described in Section 20.3.

## 8.2 Selection of Patients

### *8.2.1 Inclusion Criteria*

Patients can be included in the study if they meet all inclusion criteria listed below:

1. Male or female patients aged ≥18 years old.
2. Chinese ethnicity.
3. Able to understand and willing to provide written informed consent.
4. Able to maintain an accurate and complete 24-hour diary with the help of a caregiver.
5. Diagnosis of idiopathic Parkinson's Disease (IPD) using the United Kingdom Parkinson's Disease Society Brain Bank criteria of more than 3 years duration.
6. Be levodopa responsive and receiving treatment with stable daily doses 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 dopamine agonists, anticholinergics and/or amantadine for at least 4 weeks prior to the screening visit.
7. A Hoehn and Yahr stage between 1-4 inclusive during the "ON" phase.
8. Experiencing motor fluctuations with a minimum of 1.5 hours/day of "OFF" time during the day (excluding morning akinesia), based on historical data.
9. If female, be post-menopausal for at least one year or have undergone hysterectomy or, if of child-bearing potential, must have a negative pregnancy test, must not be breast-feeding nor become pregnant during the study and must use adequate contraception for 1 month prior to randomisation and for up to 1 month after the last dose of study drug. Adequate contraception is defined as:

    a) Hormonal oral, implantable, transdermal, or injectable contraceptives or a non-hormonal intrauterine device or female condom with spermicide or contraceptive sponge with spermicide or diaphragm with spermicide or cervical cap with spermicide for at least 1 month prior to randomization.

    b) a male sexual partner who agrees to use a male condom with spermicide or a sterile sexual partner.

For all women of child-bearing potential, urine pregnancy test result at screening must be negative.

### *8.2.2 Exclusion Criteria*

Patients are not eligible for the study if they meet one or more of the exclusion criteria listed below:

1. Any form of Parkinsonism other than IPD.
2. Diagnosis of chronic migraine (>15 days per month) or cancer pain.
3. L-dopa infusion.
4. Hoehn and Yahr stage 5 during the "ON" phase.
5. If female, pregnancy or breast-feeding.
6. Neurosurgical intervention of PD or stereotactic brain surgery.
7. Severe peak dose or biphasic dyskinesia, unpredictable or widely swinging fluctuations.
8. History of major depression or other clinically significant psychotic disorder which compromise the ability to provide the informed consent or to participate to the study.
9. Drug and/or alcohol abuse within 12 months prior to the screening visit.
10. History of dementia or severe cognitive dysfunction.
11. Use of any investigational drug or device within 30 days prior to screening or 5 half-lives, whichever is the longest, or during the study.
12. Allergy/sensitivity or contraindications to the investigational medicinal products (IMPs) or their excipients, to anticonvulsants or to anti-Parkinson drugs.
13. Any clinically significant condition (including laboratory values) which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for patients while in the study.
14. Moderate or severe liver failure using the Child-Pugh classification score, or human immunodeficiency virus (HIV) infection.
15. Treatment with monoamine oxidase inhibitors (MAOIs), pethidine, opiates, opioids, fluoxetine, fluvoxamine in the 4 weeks prior to the screening visit. These drugs are not allowed throughout the study and up 2 weeks after the last dose of study drug.
16. 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.

# 9.0 OVERALL CLINICAL TRIAL SCHEDULE

The current trial will include 4 planned clinical visits. A Study Flow Chart detailing all clinical study assessments and procedures is provided in Section 29.0, Appendix 1. The following sections outline the procedures to be performed at the individual visits.

## 9.1 Screening Period

Potential patients will be screened prior to entry into the study. Laboratory assessments may be repeated once for any laboratory parameter that falls outside the relevant exclusion criteria

provided they are completed and reviewed within the screening period. Patients considered non-eligible ("screening failures") due to clinically significant abnormalities in laboratory exams, ECG, vital signs or traditional Chinese medicine not related to nervous system disease, could be re-screened again only once during the study after a reasonable interval of time, based on the judgement of the Investigator that should be fully documented and explained in the clinical records and in the CRF. They would need to sign a new consent form. Patients who will be confirmed to be non-eligible in this second screening visit should be definitively excluded from the study.

#### *9.1.1 Visit 1 - Screening Visit (Day -14/-2)*

The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Obtain written informed consent (Section 21.0).
- Assignment of unique screening number; numbers will be allocated in sequence within each study center.
- Check of inclusion and exclusion criteria (Sections 8.2.1 and 8.2.2).
- Recording of demographic data, including age, sex, ethnicity, smoking and alcohol use (Section 10.1.1).
- Recording of medical history and PD diagnosis using the United Kingdom Parkinson's Disease Society Brain Bank (Section 29.0, Appendix 2), including Hoehn and Yahr (20) stage (Section 29.0, Appendix 3).
- Physical examination including height and body weight (Section 10.1.2).
- Neurological examination (Section 10.1.2).
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position) (Section 10.1.3).
- 12-lead ECG in the supine position (Section 10.1.4).
- Daily diary training (Section 10.1.6).
- Blood sampling for clinical laboratory assessments (haematology and clinical chemistry, including liver function tests) (Section 10.1.5).
- Urine sampling for urine (dipstick) pregnancy test for women of child-bearing potential (Section 10.1.5).
- Recording of prior medications, concomitant medications and therapies (Section 11.0).
- Recording of AEs which occur following written informed consent (Section 17.0).
- Issue daily diary with instructions to be completed two days before the baseline visit (visit 2).
- Issue NRS to be completed the night before the baseline visit (visit 2).

## 9.2 Treatment Period

Following completion of all the screening assessments and procedures and review of the results, eligible patients will enter the treatment period. Details regarding the method of assignment to treatment are presented in Section 12.2.

### *9.2.1 Visit 2 - Baseline Visit (Week 0 / Day 1)*

The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Check of inclusion and exclusion criteria (note: inclusion and exclusion criteria must be fulfilled before patient is randomized).
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of UPDRS, PDQ-39 and CGI-S by the rater (Section 10.1.6).
- Completion of NRS by the patient (the night before the visit) (Section 10.1.6).
- Recording of prior medications, concomitant medications and therapies.
- Recording of AEs (Section 17.0).
- Review and evaluate daily diary (Section 10.1.6).
- Provide additional daily diary training, as required.
- Issue daily diary with instructions to be completed two days before the visit at week 2 (visit 3).
- Randomisation to study treatment.
- Following completion of the relevant assessments and procedures, patients will take their first 50 mg dose of oral safinamide or placebo at the study center.
- Dispense study medication (safinamide or placebo 50 mg od) for the next 14 days. Patients will take 50 mg/day safinamide at home in the morning for 2 weeks, then the dose will be increased at home to 100 mg/day the day after the Visit 3/week2, ideally at day 15. Safinamide can be taken with or without food.

### *9.2.2 Visit 3 (Week 2 / Day 14 ± 3 days), Visit 4 (Week 6 / Day 42 ± 3 days) and Visit 5 (Week 10 / Day 70 ± 3 days)*

At weeks 2, 6 and 10 (visits 3, 4 and 5), the following assessments and procedures will be performed as indicated in the Study Flow Chart (Section 29.0, Appendix 1):

- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of UPDRS, PDQ-39, CGI-S and GCI-C by the rater.
- Completion of NRS by the patient (the night before the visit).
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Review and evaluate daily diary.

- Provide additional daily diary training, as required.
- Issue daily diary at weeks 2, 6 and 10, with instructions to be completed two days before the next visit (weeks 6, 10 and 16).
- Drug accountability.
- Dispense study medication (safinamide or placebo 50 and 100 mg od). Patients will take 100 mg/day safinamide at home in the morning for 14 weeks. In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.

#### *9.2.3 Visit 6 (Week 16 / Day 112 ± 3 days) / End of Treatment (EOT) / Early Termination (ET)*

Following completion of 16 weeks treatment with safinamide or in the event of premature discontinuation, the following EOT/ET assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Physical examination including body weight.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- 12-lead ECG in the supine position.
- Completion of UPDRS, PDQ-39, CGI-S and GCI-C by the rater.
- Completion of NRS by the patient (the night before the visit).
- Blood sampling for clinical laboratory assessments (haematology and clinical chemistry).
- Urine sampling for urine (dipstick) pregnancy test for women of child-bearing potential.
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Review and evaluate daily diary.
- Drug accountability.

## 9.3 Telephone Follow-up

A telephone follow-up call will be performed 1 week after the end of treatment for safety reasons. The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Recording of concomitant medications and therapies.
- Recording of AEs.

### 9.4 Unscheduled Visit

An unscheduled visit should be performed in case of down-titration of safinamide or placebo from 100 to 50 mg for safety reasons. The following assessments and procedures will be performed as detailed in the Study Flow Chart (Section 29.0, Appendix 1):

- Physical examination including body weight.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- 12-lead ECG in the supine position.
- Recording of concomitant medications and therapies.
- Drug accountability and drug dispensing.
- Recording of AEs.

## 10.0 METHODOLOGY

### 10.1 Methods of Assessment

#### *10.1.1 Demography and Medical History*

Age, sex and ethnicity will be recorded at screening (visit 1) as well as other baseline characteristics (smoking and alcohol use), including the patient's Hoehn and Yahr stage (Section 29.0, Appendix 3) and duration of PD.

Medical history will be recorded at screening (visit 1). Any significant and relevant past conditions and any current medical conditions prior to screening will be recorded.

#### *10.1.2 Physical and Neurological Examination*

A physical examination will be performed by a physician at the screening (visit 1),at week 16 (visit 6/EOT/ET) and at unscheduled visits and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system.

Height will be recorded at screening (visit 1) only. Body weight will be measured at screening (visit 1) and week 16 (visit 6/EOT/ET) only.

A neurological examination will be performed by a physician at the screening visit (visit 1) only.

#### *10.1.3 Vital Signs*

Systolic and diastolic blood pressure (measured after at least 5 minutes in the supine position) and pulse rate (measured after at least 5 minutes in the supine position) will be recorded at each study visit Automatic or manual devices may be used, but the same device should be used for any given patient throughout the study. The same arm should be used for all measurements.

The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant', or 'abnormal not clinically

significant'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements may be performed to confirm values if needed.

#### *10.1.4 12-lead Electrocardiogram*

Computerised 12-lead ECG recordings will be obtained locally at each study centre at screening (visit 1), at week 16 (visits 6/EOT/ET) and at unscheduled visits, after the patient has rested for at least 5 minutes in the supine position.

The Investigator should document the occurrence of any clinically significant 12-lead ECG abnormalities within the electronic case report form (eCRF). Repeat measurements will be performed if needed.

#### *10.1.5 Laboratory Evaluation*

Routine laboratory evaluations will be performed at screening (visit 1) and at week 16 (visit 6/EOT/ET). The haematology and clinical chemistry parameters detailed in Table 1 will be analysed at each local clinical laboratory, using standard, validated laboratory methods.

Urine (dipstick) pregnancy tests will be performed at the study centre at screening (visit 1) and week 16 (visit 6/EOT/ET) using commercially-sourced kits. If a positive pregnancy test is recorded at any time, the instructions detailed in Section 17.10 should be followed.

Clinical laboratory tests will be reviewed for results of potential clinical significance. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

**TABLE 1 CLINICAL LABORATORY EVALUATIONS**

| | | |
|---|---|---|
| **Haematology:** | | |
| Haemoglobin | Platelet count | |
| Haematocrit | Red blood cell count | |
| White blood cell count and absolute differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) | | |
| **Clinical Chemistry:** | | |
| Urea or BUN | Alkaline phosphatase (ALP) | Chloride |
| Creatinine | Alanine aminotransferase (ALT) | Sodium |
| Bilirubin (direct and total) | Aspartate aminotransferase (AST) | Calcium |
| Uric acid | Gamma-glutamyltranspeptidase (GGT) | Potassium |
| **Pregnancy Tests:** | | |
| Dipstick - urine pregnancy test at visit 1 (screening) and visit 6 (week 16/EOT/ET) | | |

An estimate of the total blood volume to be taken from each patient during scheduled study visits (visits 1 and 6) is summarized in Table 2.

**TABLE 2 ESTIMATE OF TOTAL PER PATIENT BLOOD SAMPLING VOLUME (VISITS 1 AND 6)**

| Sampling For: | Sample Volume (mL) | No of Samples | Total Volume (mL) |
|---|---|---|---|
| Haematology and clinical chemistry | 5 | 2 | 10 |

The maximum volume of blood to be drawn from each patient for routine safety monitoring across all scheduled visits is estimated to be approximately 10 mL; however, this figure may vary according to local clinical laboratory practices. Additional or repeat safety laboratory samples may also be taken during the study if required by the Investigator.

### *10.1.6 Efficacy Evaluations*

The efficacy will be assessed by the changes in "OFF" and "ON" time from the 24-hour patient diary, the Unified Parkinson's Disease Rating Scale (UPDRS), the Clinical Global Impression (CGI), the Parkinson's Disease Questionnaire-39 items (PDQ-39) and the Numerical Rating Scale (NRS).

The following parameters are to be completed by the rater: UPDRS, PDQ-39, CGI-S and CGI-C.

Site personnel who are to be involved in performing the efficacy assessments must be expert in the use of the various scales and questionnaires. At least two raters (the primary and a back-up) must be available to perform the required key efficacy evaluations at each study centre. To ensure consistency of ratings on each efficacy measure for each patient throughout their participation in the study, the same rater should perform the assessments where possible.

To minimise intra-patient variability, e.g. due to holidays or changes in personnel, etc., it is recommended that the two raters (the primary and a back-up) perform a co-rating of a patient prior to any change in the rater (either permanent or temporary), and arrive at a consensus on the patient's scores. For scales that require assessing the change in the patient's condition since baseline, it is recommended that both raters are present for the baseline interview, and/or that the primary rater's notes on the patient's baseline status and other background information are provided to the back-up rater.

**At the baseline visit (visit 2/day 1), all baseline assessments should be completed before the patient receives the first dose of study medication.**

Wherever possible the 24-hours diary and the NRS should be completed by the patient. However, in the case of the patient's incapacity, for example due to dyskinesia, tremor, etc., the patient's caregiver may complete the 24-hours diary and the NRS based on information reported by the patient.

Efficacy assessments will be undertaken as outlined in the Study Flow Chart (Section 29.0, Appendix 1), using the methodologies described here below:

**Daily Diary**

A 24-hour diary will be completed daily by each patient the two days before the baseline (visit 2/day 1) and weeks 2, 6, 10 and 16 visits (visits 3, 4, 5 and 6/EOT/ET).

A home diary was developed and published by Hauser et al (19) to assess functional status in patients with PD with motor fluctuations and dyskinesia. The diary requires patients to indicate their predominant status during 30-minute intervals over a 24-hour period.

*Daily Diary Training*

At the screening visit, patients and their caregivers will be trained on the completion of the daily diary card. The Investigator will review with the patients the definition of "ON", "OFF" and dyskinesia symptoms and agree a consistent interpretation of when "ON" and "OFF" symptoms begin and end, and when dyskinesia occurs. The patients will be given a daily diary to fill out at home two days before the baseline visit (visit 2/day 1).

At the baseline visit, the patient will receive a new daily diary and will be instructed to maintain the diary the day before the visit 3 (week 2). This process will be repeated prior to visits 4, 5 and 6 (weeks 6. 10 and 16). On each occasion, the patient will be instructed to complete the diary two days before the next visit.

*Daily Diary Completion and Assessment*

Patients will complete the daily diary by selecting one of the following five options for each 30-minute time period:

- "OFF".
- "ON" without dyskinesia.
- "ON" with non-troublesome dyskinesia.
- "ON" with troublesome dyskinesia.
- Asleep.

If the patients do not know what category applied during a specific 30-minute period, they should be instructed to enter "not done" rather than leaving the time point value blank. During the study visit, the Investigator will review the daily diary with the patient, and the data recorded for each 30-minute period will be transcribed into the eCRF at study centre.

**Hoehn and Yahr staging**

Hoehn and Yahr Staging (20) is a rating system used to classify the severity of PD. Originally, 5 stages were defined, based upon PD symptoms; recently, 2 intermediate stages have been included. The following stages were used:

- Stage 1: Mild symptoms on only 1 side of the body, which were not disabling, e.g. mild tremor of 1 limb. If there was axial involvement, a rating of stage 1.5 was given.
- Stage 2: Bilateral involvement and posture and gait were affected; however, symptoms caused minimal disability. If balance was also affected (i.e. recovery on pull test), a rating of stage 2.5 was given.
- Stage 3: Moderately severe bilateral disease, significant slowing of body movements, and impairment of equilibrium, although the patient was still physically independent.
- Stage 4: Severe disability, including rigidity and bradykinesia; however, the patient was still able to walk or stand unassisted. At this stage, the patient was no longer able to live alone.
- Stage 5: Unable to walk or stand unaided, and wheelchair-bound or bedridden. At this stage, patients were generally cachectic and required constant nursing care.

**Unified Parkinson's Disease Rating Scale (UPDRS)**

The UPDRS (21) will be completed by the Investigator at baseline (visit 2/day 1) and weeks 2, 6, 10 and 16 (visits 3, 4, 5 and 6/EOT/ET).

The UPDRS is the most commonly used scale in clinical studies to follow the longitudinal course of PD It comprises three parts that are used to evaluate the following key areas of disability, plus a fourth part that evaluates any complication of treatment:

- Part I: Evaluation of mentation or cognition, behavior and mood.
- Part II: Evaluation of the activities of daily life.
- Part III: Evaluation of motor function.
- Part IV: Evaluation of complications of therapy.

The UPDRS should be performed by the Investigator with points assigned to each item in the scale based on the patient's response as well as observation and physical examination.

Together Parts I-III contain 44 items, with each item scored on a 5-point scale. Part IV contains 11 questions with a scale ranging from 0 to 23. Thus, the final total score may range from 0 (no disability) to 199 (total disability).

**Clinical Global Impression (CGI)**

The CGI (22) is the general name for 2 scales, the CGI-Severity scale (CGI-S) and the CGI-Change scale (CGI-C). The CGI-S scale measures global severity of illness at a given point in time. It will be rated on a 7-point Likert-type scale ranging from 1 (normal, not ill at all) to 7 (extremely severe). The CGI-S will be assessed at all visits, starting at baseline. The CGI-C scale will measure the change in the patient's clinical status from baseline using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. The change from the patient's baseline condition will be assessed by the Investigator at all post-baseline visits. In completing the CGI-C, the rater will review all efficacy-related data, and assess its clinical meaningfulness.

**Parkinson's Disease Questionnaire-39 items (PDQ-39)**

The PDQ-39 (23) comprises 39 questions measuring eight dimensions of health: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily pain. Dimension scores are coded on a scale of 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). A summary index score could also be calculated. The contents of the instrument were developed on the basis of exploratory in-depth interviews with patients with Parkinson's disease, and the reliability, validity, and sensitivity to change of the instrument were then assessed in a number of large scale surveys.

**Numerical Rating Scale (NRS)**

The NRS (24) is a segmented numeric version of the visual analogue scale (VAS) in which a patient selects a whole number that best reflects the intensity of his/her pain, ranging from '0' ("no pain") to '10' ("worst possible pain").

Patients should record the intensity of their PD-associated pain, as the worst pain experienced over the past 24 hours (at any time during the day), in the evening before going to sleep.

If the patient suffered from more than one PD-associated pain, the more severe pain will be documented.

#### *10.1.7 Safety Evaluations*

Safety will be assessed throughout the study, i.e. from the provision of informed consent until the last patient visit. In addition, any AE that, in the opinion of the Investigator, requires the patient to withdraw from treatment or from the study, will be followed until the event has subsided or the condition has stabilised. All SAEs that are spontaneously reported within 30 days of a patient's last dose of study drug will also be reported and followed.

Individual safety assessments will be performed using the parameters and time points for collection listed below:

- Physical examination, clinical chemistry and haematology and 12-lead ECG at screening (visit 1) and week 16 (visit 6/EOT/ET).
- Neurological examination at screening (visit 1).
- Vital signs at each study visit AEs at every post-screening visit.

Further details are provided in Section 10.1 and in the Study Flow Chart (Section 29.0, Appendix 1).

Further information regarding AE definitions and reporting is provided in Section 17.0.

## 10.2 Compliance

The prescribed dosage, timing and mode of administration of study medication may not be changed. Study medication accountability and patient compliance will be documented throughout the treatment period using study-specific study medication dispensing and return record forms.

The evaluation of compliance will be done using the following formula:

$$\% \text{ of administered drug} = 100 \times \frac{\text{Total number of administered doses}}{\text{Total number of scheduled doses*}}$$

**1 dose x number of days between visits*

Patients will be asked to return all unused medication. From visits 3 to 6 (weeks 2 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% or more than 120% of study medication during any visit-to-visit evaluation period.

Patients exhibiting non-compliance as assessed by tablet counts should be counselled on the importance of good compliance to the study dosing regimen.

## 10.3 Pharmacodynamics

Not applicable.

## 10.4 Pharmacokinetics

Not applicable.

# 11.0 CONCOMITANT TREATMENTS

Concomitant medication is defined as any medication, other than the study medication, which is taken during the study from the time the patient provides informed consent until the last study visit for the patient, including prescription and over-the-counter medicines. All concomitant medications taken should be recorded on the eCRF.

## 11.1 Excluded Medications

Medications that are excluded prior to the study are listed in the exclusion criteria (Section 8.2.2).

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.

Concomitant medications that are considered necessary for the safety and well-being of the patient are permitted during the study at the discretion of the Investigator, with the following exceptions:

- Opioids and opiates
- L-dopa infusion and MAOIs
- Fluoxetine or fluvoxamine
- Pethidine
- Any other investigational agent
- Traditional Chinese medicine related to nervous system disease
- Acupuncture for treatment IPD

The use of any prohibited concomitant medication is a protocol deviation and should be recorded as such within the eCRF.

In addition, patients must not participate in any other clinical study of an investigational product or device whilst participating in this study.

## 11.2 Permitted Medications

Prior and concomitant medications which are considered necessary for the safety and well-being of the patient are permitted during the study at the discretion of the Investigator provided the medication is not listed within the Exclusion Criteria (Section 8.2.2) or in the Excluded Medications (Section 11.1).

The dose of L-dopa and/or of the concomitant anti-Parkinson treatments must be kept constant throughout the study.

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step.*

*In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg dose should withdraw from the study and complete the early termination visit assessments, when possible.*

# 12.0 INVESTIGATIONAL MEDICINAL PRODUCT

## 12.1 Investigational Medicinal Product Supplies and Packaging

Safinamide will be manufactured according to current Good Manufacturing Practice (GMP) compliance standards and supplied as film-coated tablets containing 50 mg or 100 mg of active substance for oral administration. A description of safinamide is given in Table 3.

**TABLE 3 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT (SAFINAMIDE)**

| Characteristic | Investigational Product |
|---|---|
| Product name | Safinamide |
| Active ingredient | Safinamide methanesulfonate |
| Physical appearance | Orange to copper, round, biconcave film-coated tablets |
| Dosage | Once daily |
| Unit dose strength | 50 mg, 100 mg safinamide (free base) |
| Route of administration | Oral |
| Treatment duration | 16 weeks |
| Manufacturer[1] | Zambon S.p.A. Vicenza |
| Company performing primary packaging | Zambon S.p.A. Vicenza |
| Company performing secondary packaging/labelling[2] | Parexel |

[1] Manufactured according to current Good Manufacturing Practice.
[2] Labelling will conform to applicable regulatory requirements.

Each tablet consists of safinamide methanesulfonate combined with the following inactive ingredients: 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.

Safinamide film-coated tablets, 50 and 100 mg, will be supplied in PVC/PVDC60/Al blisters.

A sufficient quantity of safinamide film-coated tablets (50 mg and 100 mg) will be supplied by the Sponsor, together with certificates of analysis, material safety data sheets, expiry dates and a statement that the study medication has been manufactured in accordance with GMP.

Placebo film-coated tablets are composed of the inactive ingredients used in the safinamide tablets (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. A description of placebo is given in Table 4.

Placebo film-coated tablets, 50 and 100 mg, will be supplied in PVC/PVDC60/Al blisters.

A sufficient quantity of placebo film-coated tablets (50 mg and 100 mg) will be supplied by the Sponsor, together with certificates of analysis, material safety data sheets, expiry dates and a statement that the study medication has been manufactured in accordance with GMP.

**TABLE 4 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT (PLACEBO)**

| Characteristic | Investigational Product |
|---|---|
| Product name | Placebo |
| Physical appearance | Orange to copper, round, biconcave film-coated tablets |
| Dosage | Once daily |
| Unit dose strength | 50 mg, 100 mg |
| Route of administration | Oral |
| Treatment duration | 16 weeks |
| Manufacturer[1] | Zambon S.p.A. Vicenza |
| Company performing primary packaging | Zambon S.p.A. Vicenza |
| Company performing secondary packaging/labelling[2] | Parexel |

[1] Manufactured according to current Good Manufacturing Practice.
[2] Labelling will conform to applicable regulatory requirements.

Study medication will be labelled in accordance with GMP and country-specific regulations as required by the regulatory bodies in the country where the study is conducted. Labels will be printed in the local language.

As part of the drug packaging and distribution process, emergency unblinding envelopes will be produced and distributed to the Sponsor's pharmacovigilance unit. These sealed individual patient unblinding envelopes will bear the medication kit number on the outside and also include the relevant unblinded study treatment on the inside of the security envelope.

## 12.2 Investigational Medicinal Product Dispensing and Administration

The first dose of safinamide or placebo (50 mg) will be administered at the study centre following completion of all baseline assessments and based on randomization list. Patients will take subsequently 50 mg od safinamide (or placebo) at home (i.e. either unsupervised or with the assistance of a caregiver) in the morning (at breakfast time, in addition to the morning dose of L-dopa and other, if any, PD medications) for 2 weeks and increase then the dose to 100 mg/day the day after the Visit 3/week 2, ideally at day 15 (at home).

Treatment with oral safinamide (or placebo) 100 mg od will continue up to week 16 and will be self-administered (i.e. either unsupervised at home or with the assistance of a caregiver) at approximately the same time each day. On study visits after visit 2, patients should take their dose of safinamide/placebo in the morning prior to attending the study centre.

Patients will be asked to return all unused medication to the study centre for compliance calculation (Section 10.2).

*Throughout the study, patients will continue to take their standard, prescribed anti-Parkinsonian treatment; doses must be kept constant.*

*In the case of intolerable dopaminergic adverse events (AEs), e.g. dyskinesia, it is suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of safinamide or placebo from 100 to 50 mg od as a second step. In this second case, patients should undergo an unscheduled visit for safety reasons and maintain the 50 mg dose for the rest of the study. Patients who do not tolerate the 50 mg*

*dose should withdraw from the study and complete the early termination visit assessments, when possible.*

The patients will be provided at each visit with sufficient IMP for the treatment until the following visit, including additional spare tablets.

Study medication will be stored on-site in accordance with the label requirements 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. The Sponsor and their authorised 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.

Once medication has been dispensed to study patients, it should be stored in accordance with the instructions on the label.

## 12.3 Randomisation

Patients who meet all criteria for enrolment will be randomised to double-blind treatment in a 1:1 ratio either to safinamide or placebo at visit 2 (day 1) and will be allocated a medication kit number according to the randomised treatment group. The randomisation will be done with blocks sized of unequal length to guarantee a good balance between safinamide and placebo at any stage of the enrolment minimizing the procedure selection bias.

**Patient identification:**

Each patient who has signed an informed consent form and is screened will be allocated to a 3-digit 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.

The number will be assigned by the eCRF/IWRS upon entry in the system.

**Kit number**

At randomisation, the eCRF/IWRS will allocate a unique medication kit number.

## 12.4 Investigational Medicinal Product Accountability

IMP inventory and accountability records will be kept by the Investigator or Pharmacy. The following rules are to be followed:

a) the Investigator will keep IMP in a pharmacy, or a locked and secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the IMP.

b) the inventory will be maintained by the Investigator or pharmacist or other nominated individual. The inventory will be done by means of a specific "Subject/Study Investigational Product Accountability Record & Investigational Product Reconciliation Log" provided by the CRO/IWRS and will include details of IMP received and a clear record of when they were dispensed and to which patient. The log shall indicate the quantity and description of all IMPs on hand at any time during the course of the clinical trial.

c) at the conclusion or termination of the clinical trial, the Investigator agrees to conduct a final IMP inventory and to record the results of the inventory on an appropriate form

provided by the CRO/IWRS (Investigational Product Return Form). The monitor will check that IMP accountability was correctly performed. According to instructions, the Investigator will return all original IMP containers, whether empty or containing test preparations, to local depot delegated by the CRO for final reconciliation and destruction. Sites can also handle destruction.

d) the IMP can be dispensed to patients only by Investigator/pharmacist who agrees not to supply IMP to any person except those named as Investigators/Co-Investigators as detailed in the Site Signature/Delegation Log, and to patients in this trial.

### 12.5 Treatment of Overdose

Reports of overdose with safinamide have been rare. 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.

## 13.0 CLINICAL TRIAL AMENDMENTS

Changes to the Clinical Trial Protocol (CTP) can be made by preparing written amendments to be agreed and signed by the Investigator and Sponsor. A substantial amendment may not be implemented without a favourable opinion of the Ethics Committee (EC) and Competent Authority (CA), unless the changes consist of urgent safety measures to protect trial patients.

Amendments which are non-substantial amendments as defined by present regulations can be sent to EC/CA for notification and may be implemented at the site before EC/CA notification according to local rules.

## 14.0 DEVIATIONS FROM THE CLINICAL TRIAL PROTOCOL

Any major or critical deviation which may have an impact on study results and safety of the patients should be immediately reported to Sponsor/CRO and notified to Regulatory Authorities (EC/CA) according to local regulations. A decision will be taken together with the Sponsor whether or not the patient affected by the deviation from the CTP is to continue in the study. The deviation from the CTP can be referred to relevant data points recorded on eCRF. A deviation log will be maintained to track actual deviations and decisions taken, including all deviations occurred.

In case of an emergency deviation from the CTP applicable only when an emergency situation has to be faced for a patient, this deviation will be only applied to that individual.

In such an emergency the Investigator must contact the CRO by telephone as soon as possible.

### 14.1 Code Breaking

The code for any individual patient will not be broken by the Investigator during course of the trial except in the circumstance of an SAE of life-threatening significance.

In case of emergency, unblinding of the treatment code will be done through IWRS. The treatment group will be disclosed and confirmation will follow (by fax and/or notification email). The IWRS will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the site users. Site users will be provided with usernames and passwords to access the IWRS.

Unblinding of the study treatment must be done in case of an emergency situation, where the Investigator considers it essential to know what treatment the patient was taking. Access to the unblinding option will be granted only to the Investigators and sub-Investigators at the sites. If the treatment code has been opened, this must be recorded in the eCRF.

**The IWRS will immediately notify the Sponsor/CRO pharmacovigilance and the Clinical Trial Monitor whenever a treatment code is unblinded.**

Users from CRO and Sponsor Pharmacovigilance will have their own passwords to unblind patients in case of suspected unexpected serious adverse reactions (SUSARs) to be reported to the CA and ECs as applicable.

## 15.0 CLINICAL TRIAL WITHDRAWALS/ DROP-OUTS

Patients may be withdrawn from the study at their own request or at the discretion of the Investigator for one of the following reasons:

- Patient withdraws consent to participate.
- Pregnant female patients must be withdrawn from the study without delay. Follow-up should be performed in accordance with Section 17.10.
- Patient has an AE that, in the opinion of the Investigator, requires the patient's discontinuation. Follow-up should be in accordance with Section 17.9.
- Any clinically significant abnormal findings in physical examination, ECG, vital signs, haematology, chemical chemistry which, in the opinion of the Investigator may compromise the safety of the patient in the study or interfere with evaluation of the IMP or reduce the patient's ability to participate in the study.
- Intercurrent illness requiring pharmacological treatment with a non-permitted drug or a drug which interacts in any way with the test treatment or with study evaluations.
- Patient is non-compliant with the protocol.
- Continuation in the study would be detrimental to the patient's safety in the opinion of the Investigator.
- The Investigator or the Sponsor, for any reason, stops the study.
- Sponsor, CA, or EC terminate the trial at an individual site.

Patients who prematurely withdraw from the study while receiving study medication should complete the EOT Visit assessments, when possible. Patients must return the medications and details regarding AEs and concomitant medications will be collected.

Patients who are withdrawn from the study will not be replaced. In the event that a patient 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 patient from the study or premature discontinuation of the treatment must be fully documented in the eCRF as well in source documents. Follow-up for withdrawn patients follows the procedures described in Section 17.8 and Section 17.9.

# 16.0 STOPPING AND DISCONTINUATION CRITERIA FOR THE TRIAL

The study may be prematurely terminated for one of the following reasons:

- The Sponsor feels that the number and/or severity of AEs justify discontinuation of the study.
- The Sponsor considers the applied doses of the IMP to no longer be relevant.
- Data not previously known become available and raise concern about the safety of the IMP so that continuation would pose potential risks to the patients.
- Difficulties in enrolment that would compromise reasonable timing for study conclusion or would delay study beyond reasonable timing and results.

Premature termination of the study must be reported to the EC and CA according to applicable laws generally within 15 days. A detailed written explanation of the reason should be given and alternative procedures for patients under treatment specified. However, study results have to be reported according to the requirements outlined in this protocol as far as applicable.

If after the termination of the trial, the risk/benefit analyses have changed, the new evaluation should be provided for the best interest of the patients who have participated in the study.

The Sponsor reserves the right to discontinue the study at a particular site or at multiple sites for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all documentation and investigational product pertaining to the study must be returned to the sponsor or its representative.

# 17.0 REPORTING SAFETY INFORMATION

## 17.1 Definition of Adverse Event (AE)

An Adverse Event (AE) is "*any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*".

Adverse events include:

- Worsening (change in nature, severity or frequency) of conditions present at the onset of the study.
- Patient deterioration due to the primary illness.

- Intercurrent illnesses.
- Drug interactions.
- Events related or possibly related to concomitant medications.
- Abnormal laboratory values, as well as significant shifts from baseline within the range of normal, which the Investigator considers to be clinically significant.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

The following medical conditions will not be documented as AEs and will be documented as medical history (or other as applicable):

- Symptoms or laboratory or instrumental abnormalities of a pre-existing (i.e. before patient entered the study) condition which have not worsened since enrolment;
- Surgical interventions or hospitalizations planned before patient entered the study.

## 17.2 Definition of Adverse Event of special interest

No AEs of special interest are defined for this trial.

## 17.3 Definition of Adverse Drug Reaction (ADR)

An Adverse Drug Reaction (ADR) is *"any untoward and unintended response to an IMP related to any dose administered and which implies an AE with at least a reasonable possibility of a causal relationship with the use of the product (i.e. a causal relationship cannot be ruled out, meaning that there is evidence or arguments to suggest a causal relationship). The definition covers also medication error and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP* ".

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

### *17.3.1 Definition of Unexpected Adverse Drug Reaction*

An unexpected ADR is "*an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure [IB] for an unapproved investigational product or Summary of Product Characteristics [SmPC], for approved product)*".

The Reference Safety Information for evaluation of AE expectedness in this trial will be the IB (13).

## 17.4 Definition of Serious Adverse Events or Serious Adverse Drug Reaction

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is: "*any untoward medical occurrence or effect that at any dose"*:

- Results in death.

- Is life-threatening (i.e. the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity (where disability is defined as a permanent or substantial disruption of ability to carry out normal life functions, either reported or defined as per clinical judgement).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation but, according to appropriate medical judgment, it may jeopardise the patient and may require medical or surgical intervention to prevent any of the outcomes listed in the definition above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

A non-serious adverse event (non-SAE) is any AE that does not meet the criteria listed above for an SAE.

#### *17.4.1 Definition of Suspected Unexpected Serious Adverse Reactions*

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs/SARs that, although foreseeable, are potentially related to the IMP and not identified in the reference safety information and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

### 17.5 Definition of Severity of Adverse Events

The term “severe” is used to describe the intensity (severity) of a specific event:

- Mild: causing no limitation of usual activities; the patient may experience slight discomfort.
- Moderate: causing some limitation of usual activities; the patient may experience annoying discomfort.
- Severe: causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

### 17.6 Definition of Adverse Event Causality

Causality shall be determined according to the definition of ADR as given in Section 17.3.

All AEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP qualify as ADRs. The causality assessment given by the Investigator should not be downgraded by the Sponsor.

The following binary decision for causality will be used:

- Reasonable possibility that the IMP caused the event.

- No reasonable possibility that the IMP caused the event.

Features supportive of an association include:

- Temporal plausibility.
- Pharmacological properties of the drug or of the substance class.
- Course of the AE after dechallenge and, if applicable, after rechallenge.
- Specific tests indicating involvement of the drug in the occurrence/worsening of the AE.
- Alternative explanations.

## 17.7 Adverse Event Recording

Each AE occurring to a patient, either spontaneously revealed by the patient or observed by the Investigator, whether believed by the Investigator to be related or unrelated to the IMP, must be recorded on the AE information page of the eCRF. Also for SAEs, information must be recorded in the eCRF (Section 19.1).

The Investigator performs an evaluation with respect to seriousness and causality of the AEs and records it on the appropriate section of the eCRF.

## 17.8 Adverse Event Reporting

The Investigator must report to the CRO all AEs which occur during the study following written informed consent, regardless of their relationship to IMP. All AEs are to be recorded by the Investigator on the AE information page of the eCRF. For SAEs information must be recorded also on the “Adverse Event Form for immediate reporting”.

In addition, an SAE will have to be reported according to the following detailed procedure.

### *17.8.1 Reporting Serious Adverse Events*

Investigators must report SAEs **within 24 hours of first awareness of the event**.

The SAE must be reported through the eCRF to the CRO’s Pharmacovigilance group as per contact details provided in the "List of Zambon/CRO personnel" at the beginning of this CTP.
If there is any issue with the electronic reporting process, such as internet failure or database issues, this must not delay SAE reporting. The back-up procedure is to send the back-up paper Serious Adverse Event Form to the CRO’s Pharmacovigilance group by email or fax using the contact details specified in the SAE guidelines and SAE report form.

Note: Any reports submitted on paper must be retrospectively added to the eCRF as soon as possible.
The national and local standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.
SAEs are reportable from the time a patient signs the informed consent to the follow-up phone call or visit occurring 2 weeks (± 3 days) after the last dose of IMP.
If the Investigator becomes aware of any SAE occurring to a subject within the follow-up window established in this CTP, he/she will report the SAE as above. The SAE will be also reported in the eCRF.

If the Investigator becomes aware of any SAE outside the follow-up window established in this CTP, it is the Investigator's responsibility to report the SAE to the CRO. The Investigator might use the eCRF, as described above. However, the SAE is not an event occurred within the trial period.

#### *17.8.2 Reporting Adverse Events of Special Interest*

Not applicable.

## 17.9 Follow-up for Adverse Events

All AEs resulting in the patient's discontinuation and SAEs will be followed up until they are resolved or closed.

Resolution of an AE is defined as the return to pre-treatment status or stabilisation of the condition with the expectation that it will remain chronic.

The Investigator must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) and answer any question that Sponsor or designee may have regarding the AE.

Regarding SAEs, the timelines and procedure for follow-up reports are the same as those for the initial reports for SAEs.

This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

If follow-up information on SAEs is available, a follow-up e_CRF form will be completed by the Investigator and sent to the CRO as above-described, under Section 17.8.1.

## 17.10 Pregnancy

Patients must be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the Investigator, who must then withdraw the patient from the study without delay. The Investigator should also be notified in case the partner of a male study subject becomes pregnant at any time during the course of the study (in this event a specific ICF for the subject's partner will be obtained).

In the event that a patient is subsequently found to be pregnant after inclusion in the study, then pregnancy will be actively followed up to the term and the status of mother and child will be reported by the Investigator to the CRO through the appropriate pregnancy report provided by the CRO.

The Investigator will send pregnancy reports to the CRO according to the timeframes stated for SAEs (Section 17.8.1), with follow-up information to be actively sought for the outcome of pregnancy.

If pregnancy results in abnormal outcome that the investigator and/or the Sponsor considers to be due to the IMP, this will be treated as an expedited ADR report.

# 18.0 RESPONSIBILITIES

The clinical conduct of this study will be overseen by the CRO. The CRO Medical Monitor will be responsible for daily medical monitoring, including safety monitoring. The specific responsibilities of the CRO are detailed in the relevant study agreement.

## 18.1 Responsibilities of the Sponsor (or delegated CRO)

Responsibilities of the Sponsor include the following:

- Select qualified Investigators.
- Provide each Investigator with the last approved SmPC for the authorised product.
- Submit clinical trial application/notification to the concerned Competent Authorities (CA) involved in the clinical trial.
- Prepare and submit to the EC/CA all the pertinent documentation needed for approvals.
- Implement and maintain quality assurance (QA) and quality control (QC) system with written SOPs to ensure the studies are conducted and data are generated, documented (recorded), and reported in compliance with the CTP, GCPs, and the applicable regulatory requirements.
- Promptly act in case of non-compliance by an Investigator or by members of the Sponsor or CRO.
- Ensure that the IMP is manufactured in accordance with any applicable GMP, is coded and labelled in a manner that protects blinding, if applicable, and labelling complies with applicable regulatory requirements.
- Supply the Investigators/Institutions with the IMP(s).
- Appoint appropriate trained Clinical Trial Monitor(s).
- Ensure the ongoing safety evaluation of the IMP.
- Promptly submit all Suspected Unexpected Serious Adverse Reactions (SUSARs) or other safety issues requiring expedited reporting to ECs and CAs in accordance with local or international regulations and take appropriate measures necessary to safeguard study patients.
- Promptly notify all concerned Investigators, the ECs and the CAs of findings that could adversely affect the health of patients, impact on the conduct of the study, or alter the EC/CA authorisation to continue the study.
- When the study is completed or prematurely terminated, prepare or ensure preparation of a comprehensive Clinical Trial Report (CTR) for regulatory purposes.
- Prepare and submit to ECs and CAs safety updates and Development Safety Update Reports, as applicable.
- Secure agreement from all involved parties to ensure direct access to all study related centres, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

- Provide adequate treatment/compensation for patients in the event of trial-related injury in accordance with the applicable regulatory requirements.
- Provide indemnity for the Investigator in accordance with Section 25.0 of this CTP.
- Terminate the Investigator's/Institution's participation in case of non-compliance.
- Promptly inform the Investigators/Institutions, the CAs and the ECs of premature termination or suspension of a study and the reason(s) for the termination or suspension.
- Designate appropriately qualified medical personnel who will be readily available to advise on study-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

## 18.2 Responsibilities of the Clinical Trial Monitor

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. CRO's monitors will work in accordance with CRO's SOPs, with the exception of the use of the "Adverse Event Form for immediate reporting" provided by the Sponsor.

The Clinical Trial Monitor is the principal communication link between the Sponsor/CRO and the Investigator. Responsibilities of the Clinical Trial Monitor include to:

- Train the Investigator(s) on all applicable SOPs, guidelines and regulations concerning the clinical evaluation of an IMP, including the safety reporting, and ensure a deep understanding of the CTP, the reporting requirements and responsibilities.
- Act according to predetermined SOPs, visit the Investigator periodically to verify adherence to the CTP and assure that all data are correctly and completely recorded. In order to perform his/her role effectively.
- Ensure that the trial site has adequate space, facilities, equipment, lab and staff.
- Ensure that all staff assisting the Investigator in the trial have been adequately informed about the details of the trial, verifying that the Investigator follows the approved CTP and all amendment(s), if any, and that they are performing the specified activities and procedures and have not delegated these functions to unauthorised individuals.
- Verify that informed consent has been obtained and recorded from all the patients prior to their participation to the trial.
- Aid the Investigator and at the same time the Sponsor/CRO, in the maintenance of complete, legible, well-organised and easily retrievable data.
- Inform the Investigator of any eCRF entry error, omission or illegibility. The Clinical Trial Monitor should also ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the Investigator;
- Check that the storage, dispensing, administering, returning of IMPs are safe, handled in accordance with local regulations as well as study requirements and Sponsor/CRO SOPs. All those activities have to be adequately documented.
- Assist the Investigator in any notification procedure of SAE within 24h and verify the seriousness of the AEs.

- Submit promptly to the Sponsor/CRO a written monitoring report after each site visit and written documentation of all relevant telephone calls, letters and other contacts with the Investigator.
- Verify that the Investigator is maintaining the essential documents (Investigator's file) up to end of study and for the required period.

## 18.3 Responsibilities of the Investigator

Responsibilities of the Investigator include to:

- Ensure that he/she has sufficient time to conduct and complete the trial; nominate adequate staff and has appropriate facilities.
- Submit an up-to-date curriculum vitae and GCP trainings and awareness of GCPs to the Sponsor/CRO and to EC/CA.
- Agree and sign the CTP with the Sponsor confirming that he/she will work according to the CTP and GCPs and procedures as stated in the paragraph 18.2; assist monitoring and permit auditing.
- Follow the submission of notification/application to EC jointly with the Sponsor/CRO, where appropriate.
- Provide information to all staff members involved with the trial.
- Be thoroughly familiar with the appropriate use of the IMP(s) as described in the SmPC, protocol and any other information sources provided.
- Fully inform trial patients about the clinical trial and obtain their informed consent.
- Certify that all IMP(s) have been correctly delivered, stored, and safely handled, and that reconciliation of IMPs will be done at the end, after any discrepancies are justified.
- Follow the trial randomisation procedure and ensure that the code is broken only in accordance with the CTP.
- Collect, record, and report data properly.
- Notify the Sponsor/CRO within 24h in the case of SAE and take appropriate measures to safeguard patients.
- Promptly report to EC and Sponsor changes increasing the risk to patients and/or affecting significantly the conduct of the trial and new information that may affect adversely the safety of the patients or the conduct of the trial.
- Agree with and sign the Clinical Study Report of the trial, if requested.
- Ensure that the confidentiality of study patients personal data is respected by all persons involved as per laws in force.
- Keep the information supplied by the Sponsor as strictly confidential.
- Make all data available for direct access to the Sponsor/CRO personnel (e.g.: Clinical Trial Monitor, Auditor), EC or CAs for validation/audit/review/inspection purposes.
- Ensure that in the patient medical records it is clearly evident that the patient is participating in the clinical trial.
- Inform the family doctor, with patient's consent, about patient's participation in the trial.

- Provide a list of appropriately qualified persons (Site Signature/Delegation Log) to whom the Investigator has delegated some duties relevant to the conduct of the trial, together with their signatures and initials.
- Provide patients enrolled in the study with a card bearing information that he/she is participating in a clinical study, and where contact addresses/telephone numbers are reported.
- Submit, during the trial, on regular basis, written summaries of the trial status to the EC, when requested.

# 19.0 RECORDS

## 19.1 Case Report Forms (CRFs)

Electronic case report forms will be used in this study. The Investigator must ensure that the clinical data required by the study protocol are carefully reported in English in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the official files (source documentation).

Before the start of clinical activities an agreement will be completed and signed by the Investigator and the Sponsor/CRO, to summarise the source of data captured in the eCRF, specifying those data that will be recorded directly into the eCRF (i.e. for which there will be no prior written or electronic record of data).

ECG measurement results must be printed and signed by the Investigator and kept as source data on site after entering into the eCRF. The investigator will receive the results from the local laboratory by means of a laboratory report: this report should be signed by the investigator, stored as source and a copy should be present in the patient's file.
All other data has to be documented in the patient file as source data first and then entered into the eCRF.

Data must be entered into eCRFs in English by the designated site personnel as soon as possible after a patient visit, and monitors will have access to data recorded. These data will be reviewed versus source documents by trial monitors for completeness and acceptability during monitoring visits. Any correction to the eCRFs' entries must be carried out by the Investigator or a designated member of staff. Corrections are recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRFs should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data. The Investigator or his/her designees named in the clinical staff list will review the eCRF for accuracy and completeness. The Investigator must electronically sign and date the eCRF pages as indicated.

## 19.2 Records Maintained by the Investigator

A copy of all trial records (any documents sent or received from the Sponsor/CRO, correspondence with EC and any other institution or authority and relevant approvals, patients' source data and patients' identification documentation) must be maintained by the

Investigator for at least 5 years, or for a longer period, where so required by other applicable requirements or by an agreement between the Sponsor and the Investigator.

### 19.3 Trial Master File

The Trial Master File (TMF) will be maintained electronically by the CRO according to the respective CRO SOPs with direct access for all study participants.

At the end of the trial, the TMF will be transferred to the Sponsor, where it will be archived according to specific Sponsor SOPs. A copy of the Investigator files will be left on site after trial end.

### 19.4 Trial Monitoring

The trial will be monitored by means of regular visits and telephone calls according to specific and pre-defined SOPs and trial specific monitoring guidelines. Details of the visits will be recorded in appropriate Monitoring Report forms to be submitted regularly to Sponsor. Any relevant protocol deviation must be promptly communicated to designated Sponsor's personnel.

Monitoring will be performed by personnel of the CRO.

### 19.5 Confidentiality of Subject's Information

The Investigator has the responsibility to maintain the pseudonymity of patients in compliance with the applicable data protection law. In all study documents, patients are associated to a code which does not reveal the patient's identity. Only at the site, the Investigator will hold the patient's identity on a Subject Identification Form under his/her responsibility.

The site and the Sponsor shall process personal data of patients involved in the clinical study as Data Controllers and in compliance with the applicable data protection laws, each of them in its area of competence and in accordance with the responsibilities provided by GCP, only in relation to the study performance and for pharmacovigilance purposes. The Investigator will maintain this for the longest period allowed by his/her own institution and, in any case, until further communication from the Sponsor.

Any contracted organisation either as Data Processor including the CRO, the local laboratory and IWRS provider, will act in compliance with the term and conditions agreed with the Sponsor.

## 20.0 BIOMETRICS

### 20.1 Data Handling

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at PAREXEL.

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply

- eCRF and Electronic Data Capture (EDC) system – data capture
- Statistical Analysis System (SAS®) – statistical review and analysis
- Pharmacovigilance safety database

Subject data will be captured in an eCRF system and reviewed by the Clinical Research Associate in order to check CTP adherence and to detect any data inconsistency or discrepancy (data validation step).
Medical/surgical history and underlying diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version current at trial start and which will be updated at each release of a new version during the trial.
Previous and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Actual versions of coding dictionaries used will be stated in the CTR.
The final data file will be transferred to the Sponsor in the agreed format as soon as possible after the trial is completed.

## 20.2 Endpoints

### *20.2.1 Primary Endpoint*

The primary efficacy endpoint of this study is the change from baseline to week 16 in the mean total daily "OFF" time, as assessed by 24-hour patient diary cards, of safinamide 100 mg/day compared to placebo, given as add-on therapy in PD patients with motor fluctuations on stable doses of L-dopa.

### *20.2.2 Secondary Endpoints*

The key secondary efficacy endpoint of this study is:

- The change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS).

Other secondary efficacy endpoints of this study are:

- The change from baseline to week 16 in the mean total daily "ON" time, as assessed by 24-hour patient diary cards.
- The change from baseline to week 16 in the mean daily "ON" time with no/non-troublesome dyskinesia, as assessed by 24-hour patient diary cards.
- The change from baseline to week 16 in the UPDRS total score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part II (ADL) score during the "ON" phase.
- The change from baseline to week 16 in the UPDRS part III (motor function) score during the "ON" phase.
- The CGI-S score at week 16.
- The change from baseline to week 16 in the CGI-C.

- The change from baseline to week 16 in the PDQ-39 score.

#### *20.2.3 Safety Endpoints*

The safety endpoints for this study are:

- The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TSAEs).
- Physical examination findings (clinically significant).
- Vital sign (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities.
- 12-lead electrocardiogram (ECG) parameter measures, including occurrence of abnormalities
- Clinical chemistry and haematology values, including shifts from baseline and occurrence of abnormalities.

## 20.3 Sample Size

Sample size was computed through a Monte Carlo study with 1000 runs and using a Fixed Sequence Procedure (25) to account for multiplicity over the study primary endpoint (change from baseline to week 16 in the mean total daily "OFF" time) and the key secondary endpoint (change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale - NRS). The Fixed Sequence Procedure implies that the key secondary endpoint will be testable provided that the primary endpoint has achieved statistical significance with a two-tailed p-value ≤ 0.05.

Based on the Monte Carlo simulation it was estimated that a total sample size of 260 patients (130 in the safinamide and 130 in the placebo groups) ensures 90% power to detect a mean difference in the 'off' time at least 0.9 h between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming standard deviations of 2.35 for safinamide and 2.06 for placebo. Effect size and standard deviation estimates used in sample size computations are gathered from the Settle Statistical Report (Table 15.2.13).

Moreover, the same Monte Carlo study showed that the total sample size of 260 patients would also permit a marginal power equal to 88% to detect 1 point treatment difference in the NRS between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05 using a two-sample t-test and assuming a pooled standard deviations of 2.0. Standard deviation was estimated on the basis of previous post-hoc analyses of pain (25) whilst a 1 point treatment difference is considered to be a clinically meaningful treatment effect (26).

Assuming an attrition rate equal to 15% a total of approximately 306 patients will be randomized (153 in the safinamide and 153 in the placebo groups). The sample size calculations were performed using the Mediana package (27).

## 20.4 Statistical Analyses

#### *20.4.1 General Statistical Considerations*

All data captured on eCRFs will be available as listings.

The statistical analysis will be performed by the CRO. If not otherwise stated all statistical analyses and data tabulations will be produced using SAS® for Windows release 9.4 (64-bit) or later (SAS Institute Inc., Cary, NC, USA).

Unless stated otherwise, all available data from withdrawn subjects will be included in the analysis up to the time of withdrawal.
The primary study objective will be assessed by testing the superiority of Safinamide compared to placebo and will be achieved if the analysis on primary end-point will be found statistically significant. The key secondary objective will be always assessed through a superiority analysis of Safinamide compared to placebo and, similarly, will be reached if the analysis on key secondary end-point will be found statistically significant. Conversely, the analyses on the remaining secondary efficacy endpoints will be treated as non-key secondary objectives since they will be performed only to support primary endpoints findings.

All tests will be two-sided and performed at the significance nominal level of $\alpha = 0.05$. Details are reported in Section 20.4.5.

### *20.4.2 Trial Populations*

There will be 4 analysis populations defined for the trial analyses:

Randomized Population

The Randomized Population will include all subjects who provided informed consent and received a patient number (randomisation number) whether or not they receive IMP.

Full Analysis Set

The Full Analysis Set (FAS) will comprise all patients who provided informed consent, were randomized and received at least 1 dose or partial dose of the IMP.

Primary analyses will be performed on the FAS population with exclusions from the randomized defined and justified in the SAP.

Following the randomized principle, patients will be analyzed according to the treatment they have been assigned to at the randomization.

The FAS will be used to produce summaries of baseline patient characteristics and for the analysis of all efficacy endpoints.

Safety Population

The Safety Population will comprise all patients who provide Informed Consent and received at least 1 dose or partial dose of IMP.

Patients will be analyzed according to the treatment they actually received.

The Safety Population will be used to produce summaries of all safety related endpoints and demography.

Per-protocol Population

The Per-protocol Population (PP) will include all FAS patients who were compliant with study drug administration had no major protocol deviations that were considered as potentially impacting the efficacy results. Major protocol deviations might include, but are not be limited to, patients taking a not-permitted concomitant medication, the IMP not being

administered during the trial as defined in the protocol, patients receiving a treatment different than the one assigned by randomization; others will be defined in the SAP.

Results of the primary and secondary efficacy endpoints analyses conducted in the PP will be considered as supportive.

Exclusion of patients from the PP analyses will be decided jointly by the CRO and Sponsor's Medical Monitor, Clinical Trial Manager and Statistician prior to unblinding of the randomization code and database release.

The patients or observations to be excluded, and the reasons for their exclusion will be documented and approved by the above mentioned persons prior to database release. The documentation will be filed together with the remaining trial documentation.

The number of patients in each analysis population will be reported. Violations excluding patients from any particular population will be described, reporting the number of protocol violators per each criterion. All protocol violations, minor ones included, will be listed.

### *20.4.3 Efficacy Data*

The FAS population will be used for the primary analyses of each of the efficacy endpoints whilst results from supplemental analyses using the Per Protocol Population will be compared to those based on the FAS population to assess the effects of dropouts, missing data, protocol violations and deviations.

The distributions of all the efficacy endpoints listed in Section 20.2 will be summarized by treatment group and time point. Counts and percentages will be reported with the latest computed based on the numbers of patients with non-missing observations. The percentages will be suppressed when the count is zero in order to draw attention to the non-zero counts. Furthermore, efficacy endpoints will be further summarized by arithmetic means, standard deviations, medians quartiles, minima and maxima.

#### *20.4.3.1 Analysis of Primary Endpoint*

The primary objective of the study is to evaluate the change from baseline to week 16 in the mean "OFF" time, as assessed by the 24-hour patient diary, of safinamide 100 mg/day compared to placebo, given as add-on therapy in PD patients with motor fluctuations on stable doses of L-dopa. The analysis of primary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline mean "OFF" time measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.
The main time point for comparison between treatment groups is week 16, but other available measurements at other visits will be analysed as well.

#### *20.4.3.2 Analysis of Key Secondary Endpoint*

The key secondary objective of the study is to evaluate the change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale (NRS), of safinamide 100 mg/day compared to placebo. As for the analysis of the primary endpoint, the analysis of key secondary efficacy parameter will be done using an analysis of co-variance (ANCOVA) with treatment and centre as independent factor, baseline NRS measurement as covariate and change from baseline as dependent variable. Results will be reported as Least-Square Means

for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values.

The main time point for comparison between treatment groups is week 16, but other available measurements at other visits will be analyzed as well.

#### *20.4.3.3 Analyses of Other Secondary Endpoints*

- Change from baseline to week 16 in the mean total daily "ON" time, as assessed by 24-hour patient diary cards: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above (i.e. as for the primary and key secondary endpoint), with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- Change from baseline to week 16 in the mean daily "ON" time with no/non-troublesome dyskinesia, as assessed by 24-hour patient diary cards: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- Change from baseline to week 16 in the UPDRS total score during the "ON" phase: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value..
- Change from baseline to week 16 in the UPDRS part II (ADL) score during the "ON" phase: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- Change from baseline to week 16 in the UPDRS part III (motor function) score during the "ON" phase: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.
- CGI-S score assessed at week 16: the hypothesis of superiority of safinamide compared to placebo will be assessed using the Wilcoxon-Mann-Whitney test stratified by centre, whilst point estimate of treatment differences will be reported as Hodges-Lehmann estimators together with associated two-sided nonparametric 95% confidence intervals.
- Change from baseline to week 16 in the CGI-C: the hypothesis of superiority of safinamide compared to placebo will be assessed using the Wilcoxon-Mann-Whitney test stratified by centre, whilst point estimate of treatment differences will be reported as Hodges-Lehmann estimators together with associated two-sided nonparametric 95% confidence intervals.
- Change from baseline to week 16 in the PDQ-39 score: the hypothesis of superiority of safinamide compared to placebo will be assessed using an ANCOVA model

parameterized as above, with point estimate of treatment differences reported as Least-Square Mean with associated two-tailed 95% confidence intervals and two-sided p-value.

#### *20.4.4 Handling of missing data*

Missing data on the primary and key secondary efficacy endpoints will be imputed using multiple imputation (MI) as the primary imputation method and last observation carried forward (LOCF) as sensitivity analysis. Missing data on all the other secondary efficacy endpoints will be imputed only using LOCF method. Details regarding the multiple imputation approach (i.e. number of imputations, the randomization seed and the imputation and analysis models that will be used) will be reported in the SAP.

#### *20.4.5 Multiplicity*

The overall type I family-wise error rate for testing the primary and the key secondary efficacy endpoints will be controlled at the two-sided 0.05 significance level using a Fixed Sequence Procedure (6). Following this procedure, progression to next step will only occurs as long as null hypothesis (H0: Active effect = Vehicle effect) from previous step is rejected at 0.05 significance level. The testing procedure is stopped and all the remaining null hypotheses accepted if an acceptance occurs. All individual hypothesis tests will be 2 sided.

1. The first step will test the primary efficacy parameter. The p-value for the null hypothesis must be less than 0.05 to be considered to have met the primary efficacy objective. If the null hypotheses is not rejected (i.e., p-value >0.05), the subsequent statistical test (second step) will not be considered statistically significant.
2. The second step will test the key secondary efficacy parameter “change from baseline to week 16 in pain severity, as assessed by an 11-point Numerical Rating Scale”.

For the analyses of supportive secondary efficacy end-points (not key) no adjustment of significance level will be made to account for multiple comparisons.

#### *20.4.6 Multicenter study*

As additional analysis, ANCOVA models for the analysis of primary endpoint and key secondary endpoint described in sections 20.4.3.1 and 20.4.3.2 will be fitted again including the site-by-treatment interaction, in order to test if that interaction is statistically significant, using an alpha=0.1. Also, in order to graphically assess the possible heterogeneity of the treatment effect across centres forest plots will be generated to display the results at each center. In case that the number of patients in each site were scarce, sites will be gathered into “region”. Upon completion of the study and prior to unblinding, study statisticians in consultation with the clinical team will determine the pooling based on enrolment numbers and geographical proximity.

#### *20.4.7 Interim Analyses*

No interim analyses are planned.

#### *20.4.8 Safety data*

All safety endpoints will be summarized and analyzed using the Safety Population.

<u>Incidence of Treatment Emergent Adverse Events</u>

The number and the percentage of patients reporting TEAEs, treatment emergent SAEs, severe TEAEs, TEAEs leading to discontinuation and TEAEs leading to death will be presented by treatment group, along with the number of events occurring.

TEAEs will be summarized also by System Organ Class and Preferred Term according to MedDRA; they will be additionally summarized by severity and relationship to treatment. A separate summary table will be provided for SAEs.

Only TEAEs, i.e. events with an onset date on or after the date of IMP start, will be included in the summary tables. Individual data listings will include all AEs recorded; a separate listing will be provided for treatment-emergent SAEs.

Vital Signs

Descriptive statistics for vital signs at each visit will be presented overall and by treatment.

Physical examination data.

Descriptive statistics for physical examination data at each visit will be presented overall and by treatment.

Haematology and clinical chemistry

Haematology and clinical chemistry results at Visit 1 and Visit 6 will be converted to standard international units and summarized by treatment group using descriptive statistics for continuous variables. Summaries for change from Visit 1 at Visit 6 will be also provided. Frequency of patients with values appearing outside the local laboratory normal range will be reported by visit for each treatment group. All values appearing outside the laboratory normal range will be highlighted in listings.

12-lead Electrocardiogram

Descriptive statistics for ECG results will be presented overall and by treatment.

Handling missing data on safety variables

Generally, there will be no imputation of missing values and only observed safety data will be included in the analyses.

If an AE has a partial or fully missing date, and it is unclear whether the AE is treatment-emergent, it will be assumed that it is. In the AEs analysis, when relationship to study drug is missing for a treatment-emergent adverse event it will be imputed to be drug related.

Additional details of handling of missing data for each type of analyses will be provided in the SAP.

# 21.0 INFORMED CONSENT

Written informed consent will be obtained by the Investigator or other authorised person from all patients.

The Investigator is responsible for correctly obtaining the informed consent in accordance with the applicable regulatory requirements, GCP and the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the study, the Investigator should have received the EC written approval of Informed Consent Form (ICF).

Written informed consent must be obtained prior to the initiation of any procedures specific to the study. The record of the informed consent must be available to be audited/inspected by the Sponsor/CRO designees and by CAs, whenever requested.

The informed consent documentation must be personally dated and signed by the study patient. Illiterate patients can be enrolled in the study by "making their mark" on the informed consent, when consistent with applicable local law.

Neither the Investigator, nor the study staff, should coerce or unduly influence a patient to participate or to continue to participate in a study.

Before informed consent may be obtained, the Investigator or other authorised person, should provide the patient ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the patient.

The patient should receive a copy of the signed and dated Informed Consent Form and any other written information provided to him/her, and updates.

# 22.0 ETHICS COMMITEE APPROVAL

This study will be undertaken only after written and dated approval from EC has been received by the Investigator and by the Sponsor/CRO for the CTP, all its appendices, ICF and patients recruitment procedures (i.e. advertisement) if applicable.

In addition to the above mentioned documents, the EC will be provided with the current Investigator's Brochure, SmPC and Investigational Medicinal Product Dossier (IMPD, where applicable), the Investigator's up-to-date Curriculum Vitae and/or other documentation evidencing qualifications, and any other documents that the EC may need to fulfil its responsibilities.

During the study, on regular basis, the Investigator will have to submit written summaries of the trial status (i.e. recruitment rate) to the EC, if requested.

# 23.0 REGULATORY REQUIREMENTS

This study will be conducted in full conformance with the ICH E6 R2 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study is to be conducted in compliance with the CFDA GCP and ICH-GCP E6 Rev2.

Selection of patients will not start prior to the approval of the EC has been obtained and the trial notified to or authorised by CAs.

# 24.0 QUALITY ASSURANCE

This CTP has been audited by the Sponsor's Quality Assurance.

The Audit Plan for the study includes site audits at study centres. These audits will be planned and conducted according to the Sponsor's SOPs.

# 25.0 INSURANCE

The Sponsor is concerned with the safety of the patients in the clinical study and wishes to protect the Investigator (and as applicable per local regulations, the site, the monitor and all the Investigator's staff involved in the trial) in the event of claims or lawsuits alleging injury as a result of administration of the study drug, providing that the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor.

In consideration of undertaking a human study in patients according to this CTP the Sponsor will:

- Indemnify the Investigator and hold him/her without liability for claims for damages arising out of the above described investigation in excess to those covered by his/her own professional liability insurance.
- Defend the Investigator against any claims or lawsuits initiated by, or on behalf of, patients who seek damages for bodily injury alleged to have been sustained as a result of administration of the study drug.
- Pay any settlements of judgement resulting therefrom, providing that for all of the aforementioned cases, the study drug was administered under the Investigator's supervision and in strict accordance with accepted medical practice, the CTP, and the precautions, indications, and other instructions, provided by the Sponsor.

Indemnification is not valid for claims for damages arising from malpractice and/or negligence on the part of the Investigator or those under the Investigator's supervision.

The protection afforded by this policy does not take the place of the Investigator's professional liability insurance, but covers damages in excess of such insurance protection. Further, this indemnity is conditional upon the Investigator giving the Sponsor information as soon as reasonably practicable and upon the Investigator assisting the Sponsor and its authorised representatives in the investigation and defence of any suit for which coverage is provided.

# 26.0 CLINICAL TRIAL REPORT

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

# 27.0 USE OF INFORMATION AND PUBLICATION

The Investigator agrees to inform Zambon in advance about his/her intention to divulge any data, results concerning the Confidential Information and/or the study patient to this Agreement. As a consequence hereof, the Investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 in case of abstracts) prior written notice, the text and or the content of the concerned publication, divulgation as to allow Zambon to assess properly that such proposed publication respects and/or is not in conflict with Zambon's rights to preserve and protect its intellectual property rights and any confidentiality imposed to Zambon by the prevailing rules of the country where the study is conducted.

Furthermore, without any prejudice to the Investigator's right to divulge and save for what stated hereinabove, the Investigator intends to seek Zambon opinion and advice on and prior to the intended publication and/or disclosure, in consideration also of the contractual relationship in force between Zambon and Investigator and the nature of the study hereto.

# 28.0 REFERENCES


1. Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's Disease: a review of the evidence. Eur J Epidemiol 2011; 26 Suppl 1: S1-S58.
2. Chaudhuri K, Schapira AH. Non-motor symptoms of Parkinson's Disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009; 8(5): 464-474.
3. De Lau LM, Giesbergen PC, De Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson's Disease in a general population: the Rotterdam Study. Neurology 2004; 63(7): 1240-1244.
4. Fox SH. Non-dopaminergic treatments for motor control in Parkinson's disease. Drugs 2013; 73: 1405-1415.
5. Cattaneo C, Ferla RL, Bonizzoni E, Sardina M. Long-term effects of safinamide on dyskinesia in mid- to late-stage Parkinson's Disease patients: a post-hoc analysis. J Parkinsons Dis 2015; 5(3): 475-481.
6. Cattaneo C, Barone P, Bonizzoni E, Sardina M. Effects of safinamide on pain in fluctuating Parkinson's Disease patients: a post-hoc analysis. J Parkinsons Dis 2017; 7(1): 95-101.
7. Cattaneo C, Müller T, Bonizzoni E, Lazzeri G, Kottakis I. Long-term effects of safinamide of safinamide on mood fluctuations in Parkinson's Disease. J Parkinsons Dis 2017; 7(4): 629-634.
8. Cattaneo C, Kulisevsky J, Tubazio V, Castellani P. Long-term efficacy of safinamide on Parkinson's Disease chronic pain. Adv Ther 2018; 35:515-522.
9. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D et al. Randomized trial of safinamide add-on to levodopa in Parkinson's Disease with motor fluctuations. Mov Disord 2014; 29(2): 229-237.
10. Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's Disease and motor fluctuations: a randomized clinical trial. JAMA Neurol 2017; 74(2): 216-224.
11. Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's Disease. Mov Disord 2014; 29(10): 1273-1280.
12. Xadago® (safinamide) SmPC.
13. Safinamide Investigator's Brochure, Edition Number 4, dated 13 February 2018.
14. National Collaborating Centre for Chronic Conditions. Parkinson's Disease: national clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians, 2006.
15. Murray D, Stoessl J. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. Pharmacol Ther 2013; 140: 306-318.
16. Goetz CG, Wuu J, McDeermott M, adler C et al. Placebo response in Parkinson's disease: comparison among 11 trials covering medical and surgical interventions. Mov Disord 2008; 23(5): 690-699.

17. ICH Topic E10. Note for guidance on choice of control groups in clinical trials. CPMP/ICH/364/96 January 2001.

18. Position statement on the use of placebo in clinical trials with regard to the revised Declaration of Helsinki. EMEA/17424/01London, 28 June 2001.

19. Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. J Clin Neuropharmacol. 2000; 23:75-81.

20. Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17(5):427-42.

21. Fahn S, Elton R, members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information. 1987; 153-63, 293-304.

22. Guy W. Clinical Global Impression. In ECDEU Assessment Manual for Psychopharmacology. Revised DHEW Pub (ADM). Rockville, MD: National Institute for Mental Health 1976; 218-222.

23. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well-being for individuals with Parkinson's disease. Qual Life Res 1995; 4:241-248.

24. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain 2011; 152(10):2399–2404.

25. Maurer, Hothorn, Lehmacher. Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In Biometrie in der chemisch-pharmazeutischen Industrie. Vollmar J (Editor). Stuttgart: Fischer Verlag. 1995; 6: 3-18.

26. Rascol O, Zesiewicz T, Chaudhuri KR, Asgharnejad M, Surmann E, Dohin E et al. A randomized controlled exploratory pilot study to evaluate the effect of rotigotine transdermal patch on Parkinson's Disease-associated chronic pain. J Clin Pharmacol 2016; 56(7): 852-861.

27. Dmitrienko, A., Pulkstenis, E. Clinical Trial Optimization Using R. Chapman & Hall/CRC Biostatistics Series, 2017; 4-28.

# 29.0 APPENDICES

Appendix 1: Study Flow Chart

Appendix 2: United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria

Appendix 3: Hoehn and Yahr Scale

# APPENDIX 1

## STUDY FLOW CHART

| Study Period | Screening period | Baseline | Treatment period | | | End of Treatment (EOT) / Early Termination (ET)[1] | Telephone follow-up | Unscheduled visit |
|---|---|---|---|---|---|---|---|---|
| **Week** | **-2 to 0** | **0** | **2** | **6** | **10** | **16** | **17** | |
| **Day** | **-14 to -2** | **1** | **14 ±3** | **42 ±3** | **70 ±3** | **112 ±3** | **119 ±3** | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | |
| Informed consent | X | | | | | | | |
| Eligibility criteria | X | X | | | | | | |
| Randomization | | X | | | | | | |
| Demographics | X | | | | | | | |
| Medical history/diagnosis | X | | | | | | | |
| Hoehn & Yahr staging | X | | | | | | | |
| Neurological examination[2] | X | | | | | | | |
| Prior and concomitant medications[3] | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | | X |
| 12-lead ECG | X | | | | | X | | X |
| Physical examination | X | | | | | X | | X |
| Diary Issue and Training[4] | X | X | X | X | X | | | |
| Diary Review | | X | X | X | X | X | | |
| UPDRS [5] | | X | X | X | X | X | | |
| CGI-S[5] | | X | X | X | X | X | | |
| CGI-C[5] | | | X | X | X | X | | |
| PDQ-39[5] | | X | X | X | X | X | | |
| NRS[6] | | X | X | X | X | X | | |
| Laboratory exams | X | | | | | X | | |
| Pregnancy test (urine)[7] | X | | | | | X | | |
| Adverse events[8] | X | X | X | X | X | X | X | X |
| Dispense randomised medication | | X[9] | X | X | X | | | X |
| Drug accountability | | | X | X | X | X | | X |

ECG: electrocardiogram; UPDRS: Unified Parkinson's Disease Rating Scale; CGI-S: Clinical Global Impression-Severity; CGI-C: Clinical Global Impression-Change; PDQ-39: Parkinson's Disease Questionnaire-39 items; NRS: Numerical Rating Scale.

1. Subjects who prematurely withdraw from the study while receiving study medication should complete the EOT Visit assessments, when possible.
2. Neurological examination at screening visit only.
3. Details of excluded and permitted concomitant treatments are presented in Section 11.0 of the protocol.
4. The diary should be completed by the subject two days before the baseline visit and the visits at weeks 2, 6, 10 and 16 (visits 3,4,5 and 6) for recording of "OFF" and "ON" time
5. To be evaluated at approximately the same time of day as at the baseline visit, if possible at least 1 hour after the subject has taken their morning dose of safinamide and is in the optimal "ON" state.
6. NRS will record PD pain intensity in the evening before going to sleep prior to the baseline visit and the visits at weeks 2, 6, 10 and 16 (visits 3,4,5 and 6), as the worst pain experienced in the past 24 hours (at any time during the day). If the patient suffers for more than one pain, the more severe pain must be recorded.
7. All women of child-bearing potential.
8. The Investigator must report all AEs which occur during the study following written informed consent.
9. The first dose of safinamide or placebo (50 mg once daily) will be administered at the study centre. The dose of safinamide or placebo will be titrated the day after the Visit 3/week 2, ideally at day 15 at home to 100 mg once daily. See Section 7.0 of the protocol.

# APPENDIX 2

## UNITED KINGDOM PARKINSON'S DISEASE BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA

Eligible subjects must have a diagnosis of IPD according to the United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria, as described below:

**Step 1. Diagnosis of Parkinsonian Syndrome**

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) - and at least one of the following:

- Muscular rigidity.
- 4-6 Hz rest tremor.
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

**Step 2. Exclusion Criteria for IPD**

- Repeated strokes with stepwise progression of parkinsonian features.
- Repeated head injury.
- History of definite encephalitis.
- Oculogyric crises.
- Neuroleptic treatment at onset of symptoms.
- More than one affected relative.
- Sustained remission.
- Strictly unilateral features after 3 years.
- Supranuclear gaze palsy.
- Cerebellar signs.
- Early severe autonomic involvement.
- Early severe dementia with disturbances of memory, language, and praxis.
- Babinski sign.
- Presence of cerebral tumour or communicating hydrocephalus on computed tomography scan.
- Negative response to large doses of L-dopa (if malabsorption excluded).

- Methyl-phenyl-tetrahydropyridine exposure.

**Step 3. Supportive Prospective Positive Criteria for IPD (three or more required for diagnosis of definite PD)**

- Unilateral onset.
- Rest tremor present.
- Progressive disorder.
- Persistent asymmetry affecting side of onset most.
- Excellent response (70-100%) to L-dopa.
- Severe L-dopa-induced chorea.
- L-dopa response for 5 years or more.
- Clinical course of 10 years or more.

# APPENDIX 3

## HOEHN AND YAHR SCALE

Eligible subjects must be Hoehn and Yahr Scale Stage 1-4 during the "ON" phase (Table 5).

**TABLE 5 STAGING OF PARKINSON'S DISEASE (ACCORDING TO HOEHN AND YAHR)**

| Stage | Description |
|---|---|
| 0 | No signs of disease |
| 1 | Symptoms on one side only (unilateral) |
| 1.5 | Symptoms unilateral and also involving the neck and spine |
| 2 | Symptoms on both sides (bilateral) but no impairment of balance |
| 2.5 | Mild bilateral symptoms with recovery when the "pull" test is given |
| 3 | Balance impairment. Mild to moderate disease. Physically independent |
| 4 | Severe disability but still able to walk or stand unassisted |
| 5 | Needing a wheelchair or bedridden unless assisted |

From: Hoehn M, Yahr M. (1967) Parkinsonism: onset, progression and mortality. Neurology. 17(5):427-442.