OBSERVATIONAL STUDY PROTOCOL

AN OBSERVATIONAL, PROSPECTIVE, MULTINATIONAL, MULTICENTRE STUDY COMPARING THE EFFECTIVENESS OF SAFINAMIDE, RASAGILINE AND OTHER "STANDARD OF CARE" AS ADD-ON THERAPY TO LEVODOPA (L-DOPA) IN PARKINSON'S DISEASE (PD) FLUCTUATING PATIENTS

SUCCESS

Protocol Code: Z7219N04

Date: 08-May-2019

Version: Final 1.0

Zambon SpA
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APPROVAL PAGE

Clinical Study Title:	An observational, prospective, multinational, multicentre study comparing the effectiveness of safinamide, rasagiline and other "standard of care" as add-on therapy to levodopa (L-dopa) in Parkinson's Disease (PD) fluctuating patients.
Short Title:	SUCCESS
Protocol Code	Z7219N04
Date:	08-May-2019
Authors:	Erminio Bonizzoni, Carlo Cattaneo
Sponsor Name and Address:	Zambon SpA Via Lillo del Duca 10 20091 Bresso, Milan, Italy

As agreed and approved:

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Accepted for the Sponsor

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Date (dd/Mmm/yyyy)	**Global Chief Medical Officer and Patient's Access Head**	**SIGNATURE**

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE

Declaration of Principal Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and guidelines.

Principal Investigator's Name: _____

Role: _____

Affiliation: _____

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Principal Investigator's Signature: _____

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- Prof. Wolfgang Jost, Parkinson-Klinik, Ortenau (Germany)
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1.0 TABLE OF CONTENTS

2.0 ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATE	Average Treatment Effect
ATT	Average Treatment effect on the Treated
CA	Competent Authority
CFR	Code of Federal Regulations
COMT	Catechol-O-Methyltransferase
eCRF	electronic Case Report Form
CRA	Clinical Research Associate
CRO	Contract Research Organization
DDI	Dopa-Decarboxylase Inhibitor
EC	Ethics Committee
EDC	Electronic Data Capture
EDB	Exposure During Breastfeeding
EDP	Exposure During Pregnancy
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
ICF	Informed Consent Form
IPD	Idiopathic Parkinson’s Disease
IPTW	Inverse Probability of Treatment Weighting
L-dopa	Levodopa
LID	Levodopa-induced dyskinesia
MAO-B	Monoamine Oxidase-B
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
ml	Millilitrers
MI	Multiple Implication
MMAS-8	8-item Morisky Medication Adherence Scale
NRS	Numerical Rating Scale

PD	Parkinson’s Disease
PDQ-39	Parkinson’s Disease Questionnaire-39 items
PT	Preferred Term
Qi	Quality improvement
SADR	Serious Adverse Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SoC	Standard of Care
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SSL	Secure Sockets Layer
TMF	Trial Master File
UPDRS	Unified Parkinson’s Disease Rating Scale
VAS	Visual Analogue Scale
WHO-DD	World Health Organization-Drug Dictionary

3.0 SUMMARY

Title: AN OBSERVATIONAL, PROSPECTIVE, MULTINATIONAL, MULTICENTRE STUDY COMPARING THE EFFECTIVENESS OF SAFINAMIDE, RASAGILINE AND OTHER "STANDARD OF CARE" AS ADD-ON THERAPY TO LEVODOPA (L-DOPA) IN PARKINSON'S DISEASE (PD) FLUCTUATING PATIENTS

Short title: **SUCCESS**

Protocol Code: Z7219N04

Phase: n/a

Medicinal Product(s): Safinamide film-coated tablets; rasagiline tablets; and other "Standard of Care" (SoC) (any anti-Parkinson drug as add-on to L-dopa other than rasagiline).

Dosage: Safinamide 50 mg and 100 mg film-coated tablets; rasagiline 1 mg tablets.

Objectives: Primary objective:

To evaluate how safinamide, rasagiline and other SoC drugs are associated with the quality of life of PD patients by means of the Parkinson's Disease Questionnaire (PDQ)-39 items.

Secondary objectives:

- To evaluate how they are associated with motor symptoms by means of the Unified Parkinson's Disease Rating Scale (UPDRS) part III.
- To evaluate how they are associated with pain severity assessed with the Numerical Rating Scale (NRS).
- To evaluate the use of concomitant pain-killer medications (dosage, addition or withdrawal of pain-killer drugs).
- To evaluate any change in anti-Parkinson treatment medications (introduction of new drugs, withdrawal, augmentation or decrease of anti-Parkinson drugs).
- To evaluate the compliance to PD treatment by means of the 8-item Morisky Medication Adherence Scale (MMAS-8).
- To evaluate the use of healthcare resources (number of and reason for hospitalizations, number of hospitalization days, number of visits to the emergency room, number of visits to PD specialists, number of diagnostic exams, and

number of rehabilitation visits).
- To evaluate the number of lost working days.
- To evaluate the safety of the products.

Design:

This is an observational, prospective, multinational, multicentre study.

The enrolment phase will be approximately 9 months. The total duration of the study (from the first patient in, to last patient out) will be approximately 21 months.

Adult patients treated with safinamide, rasagiline or other SoC medications according to clinical practice and meeting the inclusion/exclusion criteria will be consecutively enrolled in each participating site during the 9-month recruitment period.

The decision to prescribe safinamide, rasagiline or other SoC drug has to be taken by the physician before and regardless of the inclusion of the patient in this study and must be defined by patients' medical need and routine clinical practice.

Overall enrolment of patients will be monitored. A cap per country will be introduced in case a balance between the 3 treatment groups is not achieved.

Demographic and anamnestic data concerning PD (age and main clinical signs and symptoms at diagnosis, pharmacological therapy at the time of enrolment, Hoehn and Yahr stage) will be collected for the three groups of treatment (safinamide, rasagiline, other SoC drugs).

Study participation will be up to a maximum duration of approximately 12 months and will comprise three visits: a baseline visit at the start of the observation period, a second visit, approximately 6-months later, and a final visit at the end of the observation period (approximately at 12 months). No visits or examinations, laboratory tests or procedures are mandated as part of this study. The visits will take place during routine clinical practice.

During the study, patients may continue or change the treatment based on their physician's medical judgement. Patients no longer on the safinamide, rasagiline or other SoC treatment they had at baseline will continue to be followed up to 12 months.

Data collected during each visit are summarised in the Study Flow Chart (Appendix 1: Study Flow ChartSection 26.0).

Sample Size: Approximately, 1235 patients will be enrolled in 3 groups:

- Group 1: 500 patients already receiving safinamide (50 or 100 mg/day) as add-on to L-dopa for no more than 2 months.
- Group 2: 500 patients receiving rasagiline 1 mg/day as add-on to L-dopa for no more than 2 months.
- Group 3: 235 patients receiving other SoC drugs as add-on to L-dopa for no more than 2 months.

In this study, the primary endpoint is the change of the PDQ-39 total score over an observation period of 12 months. The validated PDQ-39 assesses health-related quality improvement (Qi); an improvement in Qi corresponds to a decrease of the PDQ-39 total score. In an analysis of covariance study, sample sizes of 453 and 453 patients need to be treated in safinamide and rasagiline groups whose mean changes from baseline are to be compared using a planned comparison (contrast). The value of the contrast of the means between safinamide and rasagiline is set to 2 points. The covariate (baseline PDQ-39) has a hypothesized R-squared of 0.200 (conservative ballpark estimate). The total sample of 906 subjects achieves 80% power to detect a non-zero contrast of the means versus the alternative that the contrast is zero using an F test with a 0,05-significance level. The common standard deviation within a group is assumed to be 12. Considering a drop-out rate equal to 10% the projected sample size is augmented to 1000 patients (namely 500 enrolled patients in safinamide and rasagiline groups). Given the most interesting comparison from the clinical point of view between safinamide and rasagiline, the other SoC cohort will be left for the purpose of internal validation control. Keeping safinamide and rasagiline groups fixed at 453 patients and the estimated standard deviations equal to 12, 212 patients in the other SoC group produce a two-sided 95% confidence interval with a distance from the difference in means to the limits equal to 2 points with a probability close to 80% (tolerance probability). The total sample size (including other SoC group) adjusted for a 10% drop-out rate will be of 1235 patients. All computations were performed using the PASS 16 software.

Population: Inclusion criteria:

1. Patients of both genders ≥ 18 years of age, with a clinical diagnosis of idiopathic PD according to UK

Brain Bank diagnostic criteria (12), for whom safinamide, rasagiline or any other anti-Parkinson drugs are prescribed according to the current Summary of Product Characteristics (SmPC).

2. Willing to participate in the study and able to understand and sign the written informed consent form.
3. Patients on a stable anti-Parkinson therapy, always including L-dopa + dopa-decarboxylase inhibitor (DDI), with or without other anti-Parkinson medications.
4. Patients must be treated with safinamide, rasagiline or other SoC drugs as add-on to L-dopa for no more than 2 months prior to the baseline visit, according to the clinical practice.

The decision of starting treatment with safinamide, rasagiline or other SoC drug has to be taken by the physician before the patient inclusion in this study and must be defined by patients' medical need and routine clinical practice and be completely independent from the participation in this study.

Exclusion criteria:

1. Patients with any form of Parkinsonism other than idiopathic PD.
2. Patients for whom safinamide, rasagiline or any other anti-Parkinson drug are contraindicated according to the current SmPC.
3. Patients known to be pregnant.
4. Patients treated with safinamide or rasagiline who receive other concomitant monoamine oxidase-B (MAO-B) inhibitors.
5. Patients treated with other SoC who receive safinamide or rasagiline.
6. Previous participation in a clinical trial with an investigational drug or device in the 3 months prior to the baseline visit.

Endpoints:

Primary Endpoint:

- The change from baseline to the end of study (12 months) in the PDQ-39 total score.

Secondary Endpoints:

- The change from baseline to 6 months in the PDQ-39 total score.
- The change from baseline to 6 months and to the end of study (12 months) in the PDQ-39 sub-scores (domains and

single items).

- The change from baseline to 6 months and to the end of study (12 months) in the UPDRS III score.
- The change from baseline to 6 months and to the end of study (12 months) in the NRS.
- The change in anti-Parkinson drugs number from baseline to 6 months and to the end of the study (12 months).
- The introduction of new anti-Parkinson drugs, withdrawal, augmentation and decrease at 6 and 12 months, respectively.
- The use of concomitant pain-killer medications at 6 and 12 months, respectively.
- The change in the number of pain-killer medications from baseline to 6 months and to the end of the study (12 months).
- The introduction of new pain-killer medications, withdrawal, augmentation, decrease and the daily dosage of pain-killer medications at 6 and 12 months, respectively.
- The change in the MMAS-8 score from baseline to 6 months and to the end of study (12 months).
- The use of healthcare resources from baseline to 6 months and to the end of study (12 months): number of and reason for hospitalizations, number of hospitalization days, number of visits to the emergency room, number of visits to PD specialists, number of diagnostic exams, number of rehabilitation visits.
- The number of lost working days from baseline to 6 months and to the end of study (12 months).

Safety Endpoints:

- The nature, frequency, severity, relationship to study drugs, actions taken, and outcome of adverse events (AEs) and serious adverse events (SAEs).

Statistical Analysis:

The primary objective of the study is to evaluate the change from baseline to the end of the study (12 months) in the PDQ-39 total score. Because the treatments will not be randomly assigned to patients, potential confounding and selection biases will be addressed by developing a propensity score for each of the treatment in study (considering other SoC as a single group), using multinomial logistic regression with study treatment as dependent variable and a set of selected covariates (confounders) as independent variables. The propensity score calculated from the logistic analysis for each patient represents the probability that a patient would be treated with safinamide rather than with

rasagiline, rather than with other SoC drug. The calculated propensity scores will be then used to compute weights for a weighted outcome analysis. Details of the multinomial logistic model, the list of confounders and the computations needed to obtain weights for estimate the average treatment effect on the population (ATE) or the average treatment effect on the treated ones (ATT) will be specified in a statistical analysis plan (SAP) to be approved prior to performance of any analyses. Outcome analysis will be performed through the “Inverse Probability of Treatment Weighting” approach (IPWT) carried-out by resorting to a weighted analysis of covariance (ANCOVA) with ATE-weights (or ATT-weights) derived from propensity scores, change from baseline as dependent variable and baseline PDQ-39 total score and treatment indicator (safinamide, rasagiline, other SoC) as independent variables (covariates). Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals and corresponding two-sided p-values. Secondary endpoints will be analysed using the same statistical model described for the primary endpoint analysis if not otherwise stated.

In the case of multiple statistical tests, these will be performed exploratorily without adjustment for multiplicity.

The analyses will be performed as observed-case analyses using all eligible subjects included in the study who gave their informed consent. As sensitivity analysis for the primary endpoint, the testing of the change of the PDQ-39 total score, will be repeated using imputed values obtained from a multiple imputation procedure.

An administrative, descriptive interim analysis will be performed after completion of the 6-month visit in all the patients.

Study Duration: Estimated:

First Patient In: ~ Q4/2019

Recruitment Period: approximately 9 months

Last Patient Out: ~ Q2/2021

Clinical Study Report: ~ Q4/2021

Treatment Duration:	Observation period per patient: approximately 12 months
Participating Countries:	5 countries (Belgium, Germany, Italy, Spain, UK)
Number of Sites:	Approximately 135 centres

4.0 INTRODUCTION AND RATIONALE

Parkinson's disease (PD) is a neurodegenerative disease characterized by a progressive loss of nigrostriatal dopaminergic neurons (1). Besides dopamine, other neurotransmitters, including glutamate, are thought to play a role in PD progression (2). The incidence of idiopathic Parkinson's disease (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).

Standard treatments for PD act by enhancing intracerebral dopamine concentrations or stimulating dopamine receptors. These drugs include levodopa, dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, and monoamine oxidase-B (MAO-B) inhibitors (4).

Levodopa (L-dopa) remains the "gold standard" for the therapy, however, with the progression of the disease, there is the emergence of disabling complications such as motor fluctuations and levodopa-induced dyskinesia (LID). Nearly 40% of PD patients develop motor fluctuations after 4 to 6 years of levodopa treatment (the so-called "honeymoon" period), and up to 90% develop LIDs after 10 years (5). Moreover, patients also experience many non-motor symptoms (such as chronic pain, depression, sleep problems and cognitive deterioration), that have a strong impact on their quality of life (6).

The Parkinson´s Disease Questionnaire-39 (PDQ-39) is one of the most frequently used instruments to measure treatment effect on the quality of life in patients with PD. The PDQ-39 includes questions regarding the eight "domains" of mobility, activities of daily living, emotions, stigma, social support, cognition, communication and bodily discomfort. It has been validated in many languages and it is used in routine care for PD (7).

Safinamide is an alpha-aminoamide derivative, structurally unrelated to any other drug for the treatment of PD, with a dual mechanism of action (dopaminergic and non-dopaminergic). In particular, it is a potent, selective and reversible MAO-B inhibitor, and it is a glutamate modulator through the sodium channels blockade (8).
Safinamide has been approved in Europe for the treatment of mid- to late-stage patients with idiopathic PD and fluctuations as add-on therapy to a stable dose of levodopa (alone or in combination with other PD medications).

Rasagiline is an irreversible MAO-B inhibitor, with unknown activity on other neurotransmitters. Rasagiline has been approved in Europe for the treatment of idiopathic PD as monotherapy or as add-on to levodopa in patients with end of dose fluctuations.

The aim of this observational study is to evaluate the effectiveness of safinamide, rasagiline and other "standard of care" (SoC) drugs when prescribed in clinical routine as add-on to L-dopa in terms of quality of life, improvement of chronic pain, change in Anti-Parkinson treatment (modification of doses, addition or withdrawal or other Anti-Parkinson drugs, etc.), use of concomitant pain-killer medications, compliance to the PD treatment, hospitalizations and use of other healthcare resources, and number of lost working days.

5.0 OBJECTIVES

Primary objective:

To evaluate how safinamide, rasagiline and other SoC drugs are associated with the quality of life of PD patients by means of the Parkinson's Disease Questionnaire (PDQ)-39 items.

Secondary objectives:

- To evaluate how safinamide, rasagiline and other SoC drugs are associated with motor symptoms by means of the Unified Parkinson's Disease Rating Scale (UPDRS) part III.
- To evaluate how safinamide, rasagiline and other SoC drugs are associated with pain severity assessed with the Numerical Rating Scale (NRS) version of the visual analogue scale (VAS).
- To evaluate the use of concomitant pain-killer medications (dosage, addition or withdrawal of drugs).
- To evaluate the use of anti-Parkinson drugs (introduction of new drugs, withdrawal, augmentation or decrease of anti-Parkinson medications).
- To evaluate the compliance to the treatment by means of the 8-item Morisky Medication Adherence Scale (MMAS-8).
- To evaluate the use of healthcare resources: number of and reason for hospitalizations, number of hospitalization days, number of visits to the emergency room, number of visits to PD specialists, number of diagnostic exams, and number of rehabilitation visits).
- To evaluate the number of lost working days.
- To evaluate the safety of the products.

6.0 ETHICS REQUIREMENTS

To ensure the quality and integrity of research, 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/). The study will also be conducted in compliance with the Guidelines for Good Clinical Practice (GCP) (9), the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (10) and the Good Pharmacovigilance Practices (GVP) Guidelines (11), with the applicable regulatory requirements of the participating countries, and with the Zambon and CRO Standard Operating Procedures (SOPs).

7.0 DESIGN AND DURATION OF STUDY

7.1 Study Design

This is an observational, prospective, multinational, multicenter study.

The target population is comprised of patients with a diagnosis of PD, who have been treated with safinamide, rasagiline or other SoC medications as add-on to L-dopa for a

maximum of 2 months.

Adult patients treated with safinamide, rasagiline or other SoC medications according to clinical practice and meeting the inclusion/exclusion criteria will be consecutively enrolled in each participating site during the 9-month recruitment period.

The decision to prescribe safinamide, rasagiline or other SoC drugs has to be taken by the physician before and regardless of the inclusion of the patient in this study and must be defined by patients' medical need and routine clinical practice.

Overall enrolment of patients will be monitored. A cap per country will be introduced in case a balance between the three treatment groups is not achieved.

Demographic and anamnestic data concerning PD (age and main clinical signs and symptoms at diagnosis, pharmacological therapy at the time of enrolment, Hoehn and Yahr stage) will be collected at baseline for the three groups of treatment.

Patients will be followed up over a period of approximately 12-months to evaluate the effectiveness of these treatments in terms of quality of life, improvement of chronic pain, change in use of Anti-Parkinson treatment (modification of doses, addition or withdrawal or other Anti-Parkinson drugs, etc.), use of concomitant pain-killer medications, compliance to the PD treatment, hospitalizations and use of other healthcare resources, and number of lost working days , at approximately 6-months and 12-months after inclusion in the study. No visits or examinations, laboratory tests or procedures are mandated as part of this study. The follow-up visits will be scheduled per standard/routine clinical practice.

Patients no longer on the safinamide, rasagiline or other SoC treatment they had at baseline will continue to be followed up to 12 months.

Data will be collected by the site and entered in an electronic case report form (eCRF) on an ongoing basis for adverse events; and at baseline, 6-months and 12-months, after study entry, for other study related information.

At baseline and 6-month study visits, patients will be given a patient paper diary to be filled in manually every month, during 5 consecutive days starting on the 24th of every month. Patients are to return the completed diaries at the 6-month and 12-month visits.

The data to be collected is summarized in the Study Flow Chart (Appendix 1: Study Flow ChartSection 26.0).

7.2 Duration of Study

Study duration will be up to approximately 12 months per patient and will comprise three study visits: a baseline visit at the start of the observation period, a second visit approximately 6-months later, and a final visit at the end of the observation period (approximately 12-months). The visits will take place during routine clinical care.

The enrolment phase will be approximately 9 months. The total duration of the study (from the first patient in to last patient out) will be approximately 21 months.

8.0 STUDY POPULATION

8.1 Number of Patients

Approximately 1235 patients will be enrolled in 3 groups:

- Group 1: 500 patients already receiving safinamide (50 and 100 mg/day) as add-on to L-dopa for no more than 2 months.
- Group 2: 500 patients receiving rasagiline 1 mg/day as add-on to L-dopa for no more than 2 months.
- Group 3: 235 patients receiving other SoC drugs as add-on to L-dopa for no more than 2 months.

The decision to prescribe safinamide, rasagiline or other SoC drugs has to be taken by the physician before and regardless of the inclusion of the patient in this study and must be defined by patients' medical need and routine clinical practice.

During the study, patients may continue or change the treatment based on their physician's medical judgement.

Approximately 135 sites will participate in the study.

The sample size calculation is described in Section 18.3.

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. Patients of both genders ≥ 18 years of age, with a clinical diagnosis of idiopathic PD according to UK Brain Bank diagnostic criteria (12) for whom safinamide, rasagiline or any other anti-Parkinson drugs are prescribed according to the current Summary of Product Characteristics (SmPC).
2. Willing to participate in the study and able to understand and sign the written informed consent form.
3. Patients on a stable anti-Parkinson therapy, always including L-dopa + dopa-decarboxylase inhibitor (DDI), with or without other anti-Parkinson medications.
4. Patients must be treated with safinamide, rasagiline or other SoC drugs as add-on to L-dopa **for no more than 2 months prior to the baseline visit**, according to the clinical practice.

The decision of starting treatment with safinamide, rasagiline or other SoC drugs has to be taken by the physician before the patient inclusion in this study and must be defined by patients' medical need and routine clinical practice and be completely independent from the participation in this study.

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. Patients with any form of Parkinsonism other than idiopathic PD.
2. Patients for whom safinamide, rasagiline or any other anti-Parkinson drug are contraindicated according to the current SmPC.
3. Patients known to be pregnant.
4. Patients treated with safinamide or rasagiline who receive other concomitant MAO-B inhibitors.
5. Patients treated with other SoC drugs who receive safinamide or rasagiline.
6. Previous participation in a clinical trial with an investigational drug or medical device in the 3 months prior to the baseline visit.

9.0 OVERALL STUDY SCHEDULE

The current study will collect data from 3 clinical visits. Visits will be scheduled per standard clinical practice. A Study Flow Chart detailing all clinical study assessments and procedures is provided in Appendix 1: Study Flow ChartSection 26.0. The following sections outline the procedures to be performed at each visit.

9.1.1 Visit 1 - Baseline Visit (0)

The following assessments and procedures will be performed as detailed in the Study Flow Chart (Appendix 1: Study Flow ChartSection 26.0):

- Obtain written informed consent (Section 19.0).
- Check the inclusion and exclusion criteria (Sections 8.2.1 and 8.2.2).
- Demographic data, including age, sex, ethnicity (Section 10.1).
- Medical history (Section 10.1).
- Physical examination including height and body weight (Section 10.2).
- Neurological examination (Section 10.2) and PD diagnosis using the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria (Section 26.0, Appendix 2), PD duration and severity including the Hoehn and Yahr (13) stage (Section 10.3).
- Assessment of UPDRS part III (Section 10.4.2).
- Completion of PDQ-39 (Section 10.4.1), NRS (Section 10.4.3) and MMAS-8 (Section 10.4.4) by the patient.
- Use of anti-Parkinson medications and use of concomitant pain-killer medications (Section 11.0).
- Use of other concomitant medications (Section 11.0).

  The Investigator will remind patients at the baseline visit to fill in the patient diary every month, during five consecutive days, starting on the 24th to rate their pain (NRS) and to record the use of pain-killer medications. The number of lost working days in the month, will be reported in the 5th page of the diary every month. The completed diaries will be then returned at the next scheduled visits.

Following signature of Inform Consent Form (ICF), patients will be assigned a unique baseline number in sequence within each study center.

9.1.2 Visit 2 (approximately 6-months), Visit 3 (approximately 12-months/end of treatment)

At approximately months 6 and 12 (visits 2 and 3), the following assessments and procedures will be performed as indicated in the Study Flow Chart (Appendix 1: Study Flow ChartSection 26.0):

- Completion of PDQ-39, NRS and MMAS-8 by the patient.
- Assessment of UPDRS part III.
- Use of anti-Parkinson medications and use of concomitant pain-killer medications.
- Use of other concomitant medications.
- Recording of Adverse Events (AEs).
- Use of healthcare resources (number of and reason for hospitalizations, number of hospitalization days, number of visits to the emergency room, number of visits to PD specialists, number of diagnostic exams, and number of rehabilitation visits).
- Number of lost working days.

*The **NRS rating** and the **use of pain-killer medications** are to be completed by the patient at home in a paper diary, every month during five consecutive days, starting on the 24th of the month. The **number of lost working days** will be reported on the 5th page of the diary every month.*

The Investigator will remind patients in Visit 2 (6-months) to fill in the patient diary every month, during five consecutive days, starting on the 24th, and then return the completed diaries at the 12-months' visit.

10.0 METHODOLOGY

At the baseline visit (Visit 1), all baseline assessments should be performed after the patient has signed the ICF.

10.1 Demographics and Medical History

Age, sex and ethnicity will be recorded at baseline (visit 1).

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

10.2 Physical and Neurological Examination

A physical and a neurological examination will be performed by a physician at baseline (visit 1). The physical examination will include height and body weight. The neurological examination will include PD diagnosis, duration and severity, including the patient's Hoehn and Yahr stage. Motor and non-motor symptoms will be assessed.

10.3 Hoehn and Yahr Staging

Hoehn and Yahr Staging (13) will be recorded at baseline (visit 1); it 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 will be used:

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

10.4 Effectiveness Evaluations

The effectiveness will be assessed by the Parkinson's Disease Questionnaire-39 items (PDQ-39), the UPDRS part III (motor score) and the MMAS-8 questionnaire, to be completed at the site at each study visit.

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

The NRS is to be completed by the patient at home *in a paper diary, every month during five consecutive days, starting on the 24th of the month,* and then returned at scheduled visits.

Effectiveness assessments will be undertaken as outlined in the Study Flow Chart (Appendix 1: Study Flow ChartSection 26.0), using the methodologies described below:

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

The PDQ-39 (14) 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 based on exploratory in-depth interviews with patients with PD, and the reliability, validity, and sensitivity to change of the instrument were assessed in a number of large-scale surveys.

10.4.2 Unified Parkinson's Disease Rating Scale (UPDRS) part III

The UPDRS (15) is the most commonly used scale in clinical studies to follow the longitudinal clinical course of PD. It comprises four parts and part III is used to evaluate motor functions.

The UPDRS part III (motor examination) 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.

Parts III contains 27 items, with each item scored on a 5-point scale. Thus, the total score may range from 0 (no disability) to 108 (total disability).

10.4.3 Numerical Rating Scale (NRS)

The NRS (16) is a segmented numeric version of the 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").

At the baseline visit, patients are to rate, using this scale, the worst pain experienced in the past 24 hours. At baseline and 6-months study visits, patients will be given a patient paper diary to be filled in manually every month, during 5 consecutive days, starting on the 24th of the month.

Patients should record at the end of the day, the intensity of their PD-associated worst pain experienced over the past 24 hours.

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

10.4.4 8-item Morisky Medication Adherence Scale

The MMAS-8 (17) is a validated scale designed to estimate the risk of medication non-adherence. The scale contains 8 items: the first seven items are Yes/No responses whereas the last item is a 5-point Likert response. The total score ranges from 0 (no treatment adherence) to 8 (total treatment adherence).

10.4.5 Use of Health Care Resources and lost working days

Use of healthcare resources: number of and reason for hospitalizations, number of hospitalization days, number of visits to the emergency room, number of visits to PD specialists, number of diagnostic exams, and number of rehabilitation visits will be assessed.

The number of lost working days will also be assessed at baseline and then between visits, through a paper diary to be filled in by the patient at home every month, in the 5th page of the diary and returned at the next visit.

10.4.6 Safety Evaluations

Safety will be assessed throughout the study, i.e. from the provision of informed consent until the end of follow-up for the patient. AEs should be followed to resolution or stabilization.

Patients no longer on the safinamide, rasagiline or the other SoC treatment they had at baseline, will continue to be followed up to 12 months.

All AEs that are voluntarily reported within 30 days from the end of the study will also be reported and followed.

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

- Physical examination and neurological examination at baseline (visit 1).
- AEs at visits 2 (approximately 6-months) and 3 (approximately 12-months).

Further details are provided in the Study Flow Chart (Appendix 1: Study Flow ChartSection 26.0).

Further information regarding AE definitions and reporting is provided in Section 15.0.

11.0 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any medication, other than the study medications, 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. In this study, use of anti-Parkinson medications and use of concomitant pain-killer medications will be assessed at baseline, 6-months and at the end of the study (12-months). In addition, the patient is to report the use of pain-killer medications in a paper diary to be filled in manually every month, during 5 consecutive days, starting on the 24th of the month. Diaries will be collected at the study visits (6-months and 12-months).

All concomitant medications taken should be recorded on the eCRF.

12.0 STUDY AMENDMENTS

Any change to this Protocol will be documented in a Protocol Amendment, issued by the Sponsor.

Amendments will be submitted for consideration to the approving independent Ethics Committees (ECs) and/or Regulatory Authority, as applicable.

13.0 DEVIATIONS FROM THE STUDY 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/competent authority [CA]) according to local regulations. A decision will be taken together with the Sponsor whether the patient affected by the deviation from the study protocol is to continue in the study. 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 study protocol 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.

14.0 STUDY WITHDRAWALS/ DROP-OUTS

Participants may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a subject discontinues prior to

completing the study follow-up period, any known reason for the discontinuation should be documented in the eCRF. The participating investigators will make documented efforts (repeated phone calls, emails, contact to relatives, etc.) to keep track of the patient, obtain information about the patient's health status and a reason for study withdrawal.

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

If a patient discontinues from the study prematurely due to an AE or SAE, they will be followed as per standard of care until the event has resolved or has stabilised as described in Section 15.2.2.

Patients no longer on the safinamide, rasagiline or other SoC treatment they had at baseline will continue to be followed up to 12 months.

15.0 MANAGEMENT AND REPORTING OF SAFETY INFORMATION

15.1 DEFINITIONS

15.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage.

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

Examples of AEs include, but are not limited to: abnormal test findings, clinically significant signs and symptoms, changes in physical examination findings, hypersensitivity, progression/worsening of an underlying disease.

Additionally, AEs may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug misuse, drug abuse, off-label use, drug interactions, extravasation, exposure during pregnancy (EDP), exposure during breastfeeding (EDB), medication errors, occupational exposure, falsified medicinal product use.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

15.1.2 At-risk events/special situations

At-risk events/special situations are not AEs per se, but that may increase the risk for the individual to experience an AE.

At-risk events/special situations include: EDP, Exposure During Breastfeeding (EDB), Medication errors, Overdose, Abuse, Misuse, Extravasation, Off-label Use, Occupational exposure, Lack of efficacy, Drug Interactions, Falsified Medicinal Product Use and Unexpected Therapeutic Effect.

Definitions of special situations according to the GVP module VI, section VI.A.1.2 are available in Section 26.0, Appendix 3.

15.1.3 Adverse Drug Reaction (ADR)

An Adverse Drug Reaction (ADR) is any untoward and unintended response to a medicinal product, 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).

Adverse reactions may arise from the use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

15.1.4 Unexpected Adverse Drug Reaction (Unexpected ADR)

An unexpected ADR is "*an adverse reaction, the nature, or severity of which is not consistent with the SmPC*".

The Reference Safety Information for evaluation of AE expectedness in this study will be the SmPC (last approved Oct 2018).

15.1.5 Serious Adverse Events/Serious Adverse Drug Reaction

A Serious Adverse Event (SAE) or Serious Adverse Reaction (SADR) 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 judgement, 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.

Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered serious.

Additionally, any suspected transmission via a medicinal product of an infectious agent is considered an SAE.

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

15.2 RECORDING AND REPORTING OF SAFETY INFORMATION

15.2.1 Recording and reporting of safety information related to Safinamide

This section describes the recording and reporting of AEs/ADRs related to the Zambon Study Drug Safinamide. This section applies to Group 1.

The table below summarizes the requirements for recording safety events on the eCRF and for reporting to the Sponsor Safety. These requirements are delineated for three types of events: (1) SAE/SADR; (2) non-serious AE/ADR; and (3) scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, off-label use, abuse, extravasation, lack of efficacy, occupational exposure drug interaction, falsified medicinal product use and unexpected therapeutic effect. These events are defined in the section definitions.

Safety event	**Recorded on the eCRF**	**Reported on the 'Reporting form' sent to Zambon Safety**	**Reporting timeline to Zambon safety (from awareness)**
SAE/SADR	All	All	24 hours
SAE/SADR (life threating/fatal)	All	All	Immediately
AE/ADR	All	All	5 calendar days
Special scenarios including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, abuse, off-label use,	All (regardless of whether associated with an AE/ADR)	All (regardless of whether associated with an AE/ADR)	5 calendar days

extravasation, lack of efficacy, drug interaction, unexpected therapeutic effect, falsified medicinal product use and occupational exposure			

Safety events listed in the table above must be reported to Zambon by the Investigator regardless of whether the event is determined by the Investigator to be related to a drug under study.

All SAEs shall be reported by the Investigator or designee to Zambon within 24 hours of awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Zambon must be made immediately, irrespective of the extent of available event information. All non-serious adverse events and special scenarios (regardless of whether associated with an AE/ADR) shall be reported by the Investigator to Zambon within 5 calendar days of awareness of the event. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports.

The information must be sent by e-mail or by FAX by filling in appropriate forms to the following country-specific contact details.

Country	Zambon Safety Contact details
Belgium	e-mail: zambon.pv@zambongroup.com
Germany	e-mail: zambon.pv.germany@zambongroup.com Fax: +49 892000203-66
Italy	e-mail: drugsafety@zambongroup.com Phone: +39 02 66524 444 Fax: +39 02 66524 038
Spain	e-mail: farmacovigilancia@zambongroup.com Fax: +34 93 5742166
United Kingdom	e-mail: profile.drugsafety@zambongroup.com Fax: +44 (0) 1243 859 001

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of safinamide and after informed consent signing and lasts through the end of the observation period of the study, which must include at least 30 calendar days following the last administration of the drug under study; a report must be submitted to Zambon Safety for any of the types of safety events listed in the table above occurring during this period.

If the Investigator becomes aware of an SAE that is considered related to the Study Drug and occurs at any other time after completion of the study (i.e., after that subject's active reporting period), the SAE is also reportable.

Medical conditions that exist before the beginning of the study are not considered as an AE, unless the condition worsens after starting the treatment with safinamide.

Causality

The Investigator is required to assess and record the causal relationship between safinamide and the AE(s). The following binary decision for causality is used: related (if there is a reasonable possibility that the Study Drug caused the Event) or not related (if there is NOT reasonable possibility that the Study Drug caused the Event).

Severity

The Investigator is responsible to record and assess the severity of any AE, by using the following three-point scale:

- 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.

15.2.2 Follow-up Reports/Additional information

For each AE, the Investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE.

For insufficiently documented reports, Zambon may request the Investigator to obtain any missing or incomplete information and query inconsistencies relevant to the assessment of the case. Follow-up attempts will be performed by the Sponsor until the necessary follow-up information is obtained from the Investigator. If after two attempts no contact with the site is established, the Sponsor will escalate to the IQVIA study management team.

In addition, an Investigator may be requested by Zambon to obtain specific follow-up information. This information is more detailed than that recorded on the eCRF. This include, for example, follow-up information for AEs which relate to retinal disorders for which a specific targeted questionnaire will be provided. The eligibility of retinal AEs to be followed-up through the targeted questionnaire will be assessed by Zambon on a case by case basis, according to a standardized list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs).

The timelines and procedure for follow-up reports are the same as those for the initial reports.

15.2.3 Recording and reporting of safety information for non-Zambon medicinal products

This section describes the recording and reporting of AEs/ADRs related to non-Zambon medicinal products. This section applies to Group 2 and Group 3.

All Drug Safety Information related to non-Zambon medicinal products arising during the study must be documented by the Investigator in the specific section of the eCRF.

(S)ADRs related to any medicinal product other than safinamide shall be notified by the Investigator to the CA in the Member State where the reactions occurred or to the Marketing Authorisation Holder of the suspected medicinal product in compliance with the applicable legislation.

15.2.4 Pregnancy

An EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed to safinamide;
- A male has been exposed, to safinamide prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

To ensure patient safety, pregnant patients will be withdrawn from the study and safinamide treatment will be promptly interrupted.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with safinamide, this information must be submitted to Zambon, irrespective of whether an AE has occurred. It must be submitted using the Reporting Form and the Pregnancy Report Form.

A pregnancy is followed until completion or until pregnancy termination. This information is provided as a follow-up to the initial EDP report.

No data concerning the pregnancy will be collected in the eCRF set up for the study.

16.0 RESPONSIBILITIES

The conduct of this observational study will be overseen by the Sponsor. The Sponsor has delegated the CRO and the specific responsibilities of the CRO are detailed in the relevant study agreement.

16.1 Responsibilities of the Investigator/ Health Care Provider

The Investigator/Health Care Provider will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator/Health Care Provider's responsibility to obtain written informed consent from patients prior to inclusion in the study, to fill in the eCRF and to record all data pertinent

to the investigation. She/he will ensure that the information reported in the eCRF is precise and accurate.

Investigator/Health Care Provider, and under the Health Care Provider's responsibility, should fully inform the Patient of all pertinent aspects of the study including the written information. All patients should be as fully informed as possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the study, the written ICF should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.

A copy of the signed and dated written ICF will be provided to the patient.

17.0 RECORDS

17.1 Case Report Forms (CRFs)

All data obtained during this study are captured electronically in a project-specific programmed Electronic Data Capture (EDC) application, also referred to as eCRF. EDC system will be fully validated and United States Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) part 11 compliant. Only authorised staff will have access to the EDC system via a secure website (Secure Sockets Layer [SSL] encryption), using unique user name and password. Data will be entered into eCRFs in accordance with instructions from the Sponsor and/or designee.
The Investigator must ensure that the data required by the study protocol are carefully reported in English in the eCRF in a timely manner and are assigned to the correct patient. The physician confirms this by electronically signing the documentation, equivalent to a traditional handwritten signature.

He/she must also check that the data reported in the eCRF correspond to those in the official files (source data).
Data captured on standardized paper questionnaires and obtained in interviews will be entered into eCRFs by the physician or authorised centre staff. The physician or authorised centre staff will enter the diary data into EDC forms, when patient diary is returned at the visits. The diary will remain at the site as source data.

Before the start of the observational study 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).
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. 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. 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.

17.2 Records Maintained by the Investigator

A copy of all observational study 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.

17.3 Study Master File

The Study or 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 study, 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 study completion.

17.4 Study Monitoring

The study will be monitored by means of one on site visit and one remote visit per site and telephone calls according to specific and pre-defined SOPs and study 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.

17.5 Confidentiality of Subject’s Information

The Investigator has the responsibility to maintain the pseudonymity of patients’ data 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 GPP guidelines, 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 will act in compliance with the term and conditions agreed with the Sponsor.

With reference to EU Regulation no.679/2016 of European Parliament and of the Council of 27 April 2016, the General Data Protection Regulation (GDPR), and other local law provisions the **data protection roles** within the study are the following:

- the Sponsor and the investigational center are autonomous data controllers, and will process the personal and study data of the participants exclusively for study related purposes and for pharmacovigilance purposes.
- The CRO will process the participant's data on behalf of the Sponsor and will be appointed as a data processor by the Sponsor. The CRO may avail itself of subcontractors, who will be appointed as sub processors as well, pursuant to art. 28 of GDPR.
- The principal investigators will process the data as a data processor, on behalf of the study center.

As concerns **the data protection information/notice**, participants must be informed properly about all the data protection elements provided by art. 13 and 14 of GDPR. Investigator or his/her representative will give to the participant a proper data protection information notice compliant with GDPR and will consequently ask to the participant a data protection consent, together with the study informed consent. According to the provisions of the GDPR, the level of disclosure in the informed consent must also be explained to the participant. The participant must be informed that his/her medical records may be examined by Auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

As regards the **organizational and security measures** adopted, all the data processing operations regarding the study data are performed in compliance with GDPR. The Investigator or his/her representative will assign to the participants a unique identifier. Investigator will be the only one who can match the participant's identity with the data referred to the study. Any participant records or datasets that are transferred to the Sponsor will contain the identifier code only; participant names or any other information which would make the participant identifiable will not be transferred to the Sponsor.

18.0 BIOMETRICS

18.1 Data Handling

A data management plan will be developed before the start of data collection specifying all relevant aspects of data processing for the study (including data validation and cleaning). The plan will be maintained and stored at the CRO.

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

- eCRF via EDC system – data capture
- Statistical Analysis System (SAS®) – statistical analysis
- Pharmacovigilance safety database

Subject data will be captured in an eCRF and reviewed by the Clinical Research Associate (CRA) in order to check study protocol adherence and to detect any data inconsistency or discrepancy (data validation step).

The Investigator/physician will enter the diary data into EDC forms, when patient diary is returned at the visits. The diary will remain at the site as source data.

Medical history and underlying diseases and AEs will be coded using the MedDRA latest version current at study start which will be updated at each release of a new version during the study.

Anti-Parkinson medications and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD-Enhanced). Actual versions of coding dictionaries used will be stated in the CSR.

The final data file will be transferred to the Sponsor in the agreed format as soon as possible after the study is completed.

18.2 Endpoints

18.2.1 Primary Endpoint

The primary endpoint of this study is the change from baseline to the end of study (12 months) in the PDQ-39 total score.

18.2.2 Secondary Endpoints

The secondary endpoints of this study are:

- The change from baseline to 6 months in the PDQ-39 total score.
- The change from baseline to 6 months and to the end of study (12 months) in the PDQ-39 sub-scores (domains and single items).
- The change from baseline to 6 months and to the end of study (12 months) in the UPDRS III score.
- The change from baseline to 6 months and to the end of study (12 months) in the NRS.
- The change in number of anti-Parkinson drugs from baseline to 6 months and to the end of the study (12 months).
- The introduction of new anti-Parkinson drugs, withdrawal, augmentation and decrease at 6 and 12 months, respectively.
- The use of concomitant pain-killer medications at 6 and 12 months, respectively.
- The change in the number of pain-killer medications from baseline to 6 months and to the end of the study (12 months).
- The introduction of new pain-killer medications, withdrawal, augmentation, decrease and daily dosage of pain-killer medications at 6 and 12 months, respectively.
- The change in the MMAS-8 score from baseline to 6 months and to the end of study (12 months).
- The use of healthcare resources from baseline to 6 months and to the end of study (12 months): number of and reason for hospitalizations, number of hospitalization

days, number of visits to the emergency room, number of visits to PD specialists, number of diagnostic exams, number of rehabilitation visits.
- The number of lost working days from baseline to 6 months and to the end of study (12 months).

The safety endpoints for this study are:

- The nature, frequency, severity, relationship (to Study Drug), actions taken, and outcome of AEs and SAEs.

18.3 Sample Size

In this study, the primary endpoint is the change of the PDQ-39 total score over an observation period of 12 months. The validated PDQ-39 assesses health-related Qi; an improvement in Qi corresponds to a decrease of the PDQ-39 total score. In an analysis of covariance study, sample sizes of 453 and 453 patients are needed in safinamide and rasagiline groups whose mean changes from baseline are to be compared using a planned comparison (contrast). The value of the contrast of the means between safinamide and rasagiline is set to 2 points. The covariate (baseline PDQ-39) has a hypothesized R-squared of 0.200 (conservative ballpark estimate). The total sample of 906 subjects achieves 80% power to detect a non-zero contrast of the means versus the alternative that the contrast is zero using an F test with a 0.05-significance level. The common standard deviation within a group is assumed to be 12. Considering a drop-out rate equal to 10% the projected sample size is augmented to 1000 patients (namely 500 enrolled patients for safinamide and rasagiline groups). Given the most interesting comparison from the clinical point of view between safinamide and rasagiline, the other SoC cohort will be left for the purpose of internal validation control. Keeping safinamide and rasagiline groups fixed at 453 patients and the estimated standard deviations equal to 12, 212 patients in the other SoC group produce a two-sided 95% confidence interval with a distance from the difference in means to the limits equal to 2 points with a probability close to 80% (tolerance probability). The total sample (including other SoC group) adjusted for 10% drop-out rate will be of 1235 patients. All computations were performed using the PASS 16 software.

Treatment Group	Sample Size	Mean Changes from Baseline	Contrast Coefficient	Value of the Contrast
Safinamide	453	2 + k	+1	+1 x (2 + k)
Rasagiline	453	k	-1	-1 x (k)
Other SoC drugs	212	k	0	0 x (k)
ALL	1118 (1235 including 10% drop-out)			

Where k indicates the mean change from baseline of the PDQ-39 total score in rasagiline and other SoC (standard of care) drugs (it is assumed that rasagiline and other SoC drugs have the same effect on the PDQ-39). It is worth pointing out that knowledge of the true value of k is irrelevant for the purposes of calculating the sample size. It is further hypothesized that the improvement (decrease of the PDQ-39 total score from baseline) obtained with Safinamide in comparison with rasagiline and /or other SoC drugs may be put at 2 points.

18.4 Statistical Analyses

18.4.1 Data Management and General Statistical Considerations

Personal data of patients are gathered, stored and processed exclusively in a pseudonymous form according to national data protection laws.

Further details will be described in a project-specific Data Management Plan.

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).

18.4.2 Study Populations

As this is an observational clinical study, the classical definitions of study populations generally used in controlled clinical trials (Intention to Treat, Per Protocol, Safety, Modified Intention to Treat etc.) no longer make much sense. In this context, a suitable approach consists in analysing endpoints performing observed-case analyses for eligible patients who provided the informed consent (enrolled set). Other exploratory analyses sets will consist of patients still receiving the initial treatment at the 6 months and 12 months visits, respectively. Further details will be described in the SAP.

18.4.3 Endpoints

The distributions of all the endpoints listed in Section 18.2 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, endpoints will be further summarized by arithmetic means, standard deviations, medians, quartiles, minima and maxima. The analyses will be performed in the enrolled set and in the exploratory analyses sets. As sensitivity analysis for the primary endpoint, the testing of the change of the PDQ-39 total score may be performed using imputed values obtained from a multiple imputation procedure based on the number of missing data (see below Section 18.4.4).

18.4.3.1 Analysis of Primary Endpoint

The primary objective of the study is to evaluate the change from baseline to the end of the study (12 months) in the PDQ-39 total score. Because the treatments will not be randomly assigned to patients, potential confounding and selection biases will be addressed by developing a propensity score for each of the treatment in study (considering other SoC as a single group), using multinomial logistic regression with study treatment as dependent variable and a set of selected covariates (confounders) as independent variables. The propensity score calculated from the logistic analysis for each patient represents the probability that a patient would be treated with safinamide rather than with rasagiline, rather than with other SoC. The calculated propensity scores will be then used to compute weights for a weighted outcome analysis. Details of the multinomial logistic model, the list of confounders and the computations needed to obtain weights for estimate the average

treatment effect on the population (ATE) or the average treatment effect on the treated (ATT) will be specified in the SAP to be approved prior to performance of any analyses. Outcome analysis will be performed through the Inverse Probability of Treatment Weighting approach (IPTW) carried-out by resorting to a weighted analysis of covariance (ANCOVA) with ATE-weights (or ATT-weights) derived from propensity scores, change from baseline as dependent variable and baseline PDQ-39 total score and treatment indicator (safinamide, rasagiline, other SoC drugs) as independent variables (covariates). Results will be reported as Least-Square Means for treatment differences with associated two-tailed 95% confidence intervals (CIs) and corresponding two-sided p-values.

18.4.3.2 Analyses of Secondary Endpoints

- Change from baseline to 6 months in the PDQ-39 score: The same statistical approach (ANCOVA) described above for the primary endpoint with the same independent variables will be taken for the statistical analysis of data.

- Change from baseline to 6 months and to the end of the study in the PDQ-39 sub-scores (domains and single items) The same statistical approach (ANCOVA) described above for the primary endpoint with the same independent variables will be taken for the statistical analysis of data.

- Change from baseline to 6 months and to the end of the study in the UPDRS part III (motor function) score during the "ON" phase: The same statistical approach (ANCOVA) described above for the primary endpoint with the same independent variables will be taken for the statistical analysis of data.

- Change from baseline to 6 months and to the end of the study in the NRS (pain): The same statistical approach (ANCOVA) described above for the primary endpoint with the same independent variables will be taken for the statistical analysis of data.

- Change from baseline to 6 months and to the end of study in the MMAS-8. The same statistical approach (ANCOVA) described above for the primary endpoint with the same independent variables will be taken for the statistical analysis of data.

- The change in the number of anti-Parkinson drugs and the change in the number of pain-killer medications at 6 months and at the end of the study analyses will be performed by means of a ATE or ATT weighted negative binomial regression models parameterized with logarithmic link function and negative binomial distribution and with treatment indicator (safinamide, rasagiline, other SoC drugs and number of Anti-Parkinson drugs or pain-killer medications at baseline) as independent variables (covariates).

- The use of pain-killer medications at 6 months and at the end of the study analysis will be performed by means of an ATE or ATT weighted generalized linear model parameterized with logit link function, binomial distribution and with treatment indicator (safinamide, rasagiline, other SoC drugs) as independent variable (covariates). Results will be reported as Odds Ratios with associated two-sided 95% CIs.

- Healthcare resources utilization will be summarized descriptively in the three groups by each single item. ATE or ATT weighted analysis (based on the most appropriate link function and distribution for each item) may be applied. Details will be given in the SAP.

- Lost working days rate will be summarized descriptively in the three groups and with a generalized linear model with logarithmic link function and a negative binomial distribution. ATE or ATT weights might be applied.

18.4.4 Handling of missing data

Missing data on the primary endpoint and covariates will be imputed using multiple imputation (MI). The Monte Carlo Markov Chain technique implemented in SAS Proc MI will be used to obtain “n” imputed datasets. Rubin’s rules implemented in SAS Proc MIANALYZE will be used to combine effect estimates and estimate CIs to allow for uncertainty due to missing data. Details regarding the MI approach (i.e. the random seed and the imputation and analysis models that will be used) will be reported in the SAP.

18.4.5 Multiplicity

For the analyses of secondary contrasts (safinamide vs. other SoC drugs and rasagiline vs. other SoC drugs) and for the analyses of secondary efficacy endpoints no adjustment of significance level will be made to account for multiple comparisons.

18.4.6 Administrative Interim Analyses

An Administrative Interim Analysis will be performed after completion of the 6-months of treatment in all patients enrolled. The objective of such analysis is to provide descriptive statistics of baseline characteristics and primary, secondary and safety endpoints. Details of the interim analysis and the level of data cleanliness will be reported in the SAP.

18.4.7 Sensitivity Analyses

Sensitivity analyses will be performed in order to verify the robustness of primary endpoint findings. In particular, we want to verify if and to what extent the lack of randomisation between treatments may have biased the study results and their interpretation. To achieve this, we will perform two separate analyses. The first one will implement the primary endpoint analysis in a propensity scores matched subset. The second one is an alternative to propensity score analysis and is named “Instrumental-variables” regression (18). Details of both methods will be specified in the SAP to be approved prior to performance of any analyses.

18.4.8 Safety data

Incidence of Adverse Events (IAEs) since the study start:

The incidence rate of AEs, SAEs, severe AEs, AEs leading to discontinuation and AEs leading to death will be presented by treatment group, along with the number of events occurring.

AEs 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.

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.

19.0 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, GPP 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 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 ICF and any other written information provided to him/her, and updates.

20.0 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 study protocol, all its appendices and ICF.

In addition to the above-mentioned documents, the EC will be provided with 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 study status to the EC, if requested.

21.0 REGULATORY REQUIREMENTS

This study will be conducted in full conformance with the principles of the Declaration of Helsinki. The study is to be conducted in accordance with the guidelines for GCP and GPP.

Study will not start prior to the approval of the EC and until the study has been notified to or authorised by CA.

22.0 QUALITY ASSURANCE

This study protocol 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.

23.0 CLINICALSTUDY REPORT

The data and information collected during this study will be reported in a Clinical Study Report prepared by the Sponsor according to the guidelines for Good Epidemiology Practice.

24.0 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.

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26.0 APPENDICES

Appendix 1: Study Flow Chart

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

Appendix 3: Definition of "Special Situations"

APPENDIX 1
STUDY FLOW CHART

STUDY PERIOD	Baseline	Treatment phase	End of treatment
VISIT NUMBER	V1	V2	V3
Study months	**0**	**6-months**	**12-months**
Informed consent	X		
Inclusion/Exclusion Criteria	X		
Demographic characteristics	X		
Medical history	X		
Physical examination	X		
Neurological examination and PD diagnosis, duration and severity. Assessment of motor and non-motor symptoms	X		
H&Y stage	X		
UPDRS III	X	X	X
PDQ-39	X	X	X
NRS – Patient's diary handed at study visits*	X*	X*	X*
MMAS-8	X	X	X
Use of pain-killers – Patient's diary handed at study visits*	X*	X*	X*
Use of anti-Parkinson medications	X	X	X
Use of other concomitant medications	X	X	X
Use of healthcare resources		X	X
Lost working days – Patient's diary handed at study visits*		X*	X*
Adverse Events		X	X

PDQ-39: Parkinson's Disease Questionnaire-39 items; UPDRS III: Unified Parkinson's Disease Rating Scale part III; NRS: Numerical Rating Scale; MMAS-8: 8-items Morisky Medical Adherence Scale.

*To be assessed at the baseline visit, then, a patient paper diary will be handed at the baseline and 6-month visits. The diary is to be completed by the patient at home every month, during five consecutive days, starting on the 24th of the month. Number of lost working days will be recorded in the diary every month, in the 5th page of the diary.

The Investigator will remind patients at the baseline visit and 6-month visit to fill in the paper diaries and to return the completed diaries at the next visit.

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 tumor 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

DEFINITIONS OF "SPECIAL SITUATIONS"

Definitions according to the GVP module VI, section VI.A.1.2:

Overdose: This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. When applying this definition, clinical judgement should always be applied.

Off-label use: This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

Misuse: This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

Abuse: This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Occupational exposure: This refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Medication error (not from GVP module VI): This is an unintentional error in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer.

Falsified medicinal product: This relates to any medicinal product with a false representation of:

- its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;
- its source, including its manufacturer, its country of manufacturing, its country of origin or its Marketing Authorization Holder; or
- its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

Drug Interaction (not from GVP module VI): This refers to pharmacodynamic and pharmacokinetic interactions between a medicinal product and other medicinal products (including biological products) as well as to interactions between a medicinal product and food, other substances (i.e. alcohol) or devices.

Lack of Efficacy (not from GVP module VI): This refers to the failure of expected pharmacological action or therapeutic benefit.

Exposure during pregnancy (not from GVP module VI):

EDP occurs if:

- A female becomes or is found to be pregnant either while receiving or having been exposed to a medicinal product or if the female becomes or is found to be pregnant after discontinuing and/or being exposed to the medicinal product (maternal exposure).
- A male has been exposed due to treatment to a medicinal product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

Exposure during breastfeeding (not from GVP module VI): This refers to the infant exposure to a medicinal product via breast milk.

Extravasation (not from GVP module VI): This refers to the leakage of intravenous drugs into the surrounding perivascular tissue, subcutaneous or interstitial spaces.

Unexpected therapeutic effect (not from GVP module VI): This refers to a beneficial therapeutic effect of a product other than the intended use.