OBSERVATIONAL STUDY PROTOCOL

European multicenter retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialization phase– Study Z7219N02

Version 1.2, 17 February 2016

Signature page

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PRINCIPAL INVESTIGATOR DECLARATION:

I read the protocol and I agree to conduct it in accordance with all Protocol Study stipulations, with Ethical principles outlined in the Helsinki Declaration and with the European Pharmacovigilance legislation.

According to European Pharmacovigilance legislation the undersigned PI declares that he/she will inform Zambon or the Contract Research Organization immediately in writing about any changes affecting the access rights (e.g. end of employment with the registered organization, change of department within the registered organization etc.)

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PASS information

Title	European multicenter retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialization phase– Study Z7219N02
Protocol version identifier	1.2
Date of last version of protocol	17 February 2016
EU PAS register number	Study not yet registered
Active substance	Safinamide (N04BD03)
Medicinal product	Xadago® 50 mg and 100 mg film coated tablets
Product reference	Marketing Authorization number: EU/1/14/984/001-010
Procedure number	EMEA/H/C/002396
Marketing authorisation holder(s)	Zambon S.p.A.
Joint PASS	No
Research question and objectives	During the initial marketing authorization procedure, at day 180 the European Medicines Agency (EMA) recommended to the Applicant to provide additional real world data on Safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely patients aged > 75 years and those with concomitant psychiatric conditions such as psychosis, cognitive dysfunction and depression. Following this request, a Drug Utilization Study (DUS) aimed at investigating how Safinamide is prescribed and used in routine clinical practice was designed, including also Parkinson's Disease (PD) patients with relevant concomitant diseases. It will allow to evaluate not only the extent of these

	categories of patients, but also safety data (in terms of occurrence of adverse events) will be provided. Whit this approach the opportunity of collecting and disseminating relevant data concerning the use of Safinamide in a real life setting was seized. In order to improve the knowledge about the product beyond the findings of clinical trials, the study will provide data on drug safety profile and on Safinamide treatment patterns. Primary objective: To describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators. The analysis will be conducted overall and in some subgroups of interest, namely in patients aged >75 years and those with relevant concomitant conditions. Secondary objectives: 1. To describe the characteristics of patients treated with Safinamide according to clinical practice (demographics, disease duration, disease severity, previous treatment for PD, concomitant relevant conditions with particular focus on psychiatric ones and related treatments). 2. To describe Safinamide treatment patterns in real-life setting (treatment duration, dose adjustments and interruptions, dose discontinuation and reason, changes in concomitant PD therapies, treatments for PD administered after Safinamide).
Country(-ies) of study	Belgium, France, Germany, Italy, Spain, Switzerland, United Kingdom.
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1. Table of contents

2. List of abbreviations

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AES	Apathy Evaluation Scale
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CGI	Clinical global impression
CI	confidence interval
DUS	Drug Utilization Study
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EU	European
GAMP	Good Automated Manufacturing Practice
GPP	Good Pharmacoepidemiology Practice
IT	Information technology
L-dopa	Levodopa
MAO-B	Mono-Amine Oxidase type B
MDS	Movement Disorder Society
MedDRA	Medical Dictionary for Regulatory Activities
PD	Parkinson's disease
PT	Preferred Term
REM	Rapid eye movement
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States

3. Responsible parties

Countries participating in the observational data collection are Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom.. In each country a draft list of sites participating in the observational data collection is currently available and will be provided upon request, but the final list of countries and sites will depend on Xadago® authorization and site capability to administer the treatment in clinical practice.

4. Abstract

Title

European multicenter retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialization phase – Study Z7219N02

Protocol version 1.2, 17 February 2016

Main author: Gabriele Camattari – Zambon S.p.A.

Rationale and background

PD occurs when, because of an unknown cause, dopamine-producing cells progressively degenerate. This leads to progressive deterioration of motor function, progressive loss of muscle control and trembling. The impairment varies from individual to individual.

Not only neuromusculoskeletal and movement-related functions are involved by impairments, but also non-motor areas. In fact, it is noticed a considerable reduction in quality of life. Examples of early non-motor impairments are depression, olfactory dysfunction, REM sleep behavior disorder and constipation. In addition, mental impairments, specifically impaired executive function and memory, as well as prolonged reaction time can be present at diagnosis.

The overall goal of PD management is to optimize activities, participation and quality of life of patients. Currently, the focus is on symptom control and compensation. Symptomatic treatments include a variety of drugs and rehabilitation. No treatment slows disease progression down.

L-dopa remains the most effective single therapy, but after years of administration it promotes often incapacitating motor fluctuations and might accelerate disease progression through free radical formation.

Safinamide was developed as a new strategy for the therapy of PD, by combining inhibition of both MAO-B and sodium channels, leading to both dopaminergic and non-dopaminergic activities.

Safinamide is an α-aminoamide indicated as add-on therapy for the treatment of patients with idiopathic PD, in mid-to late-stage fluctuating patients receiving a stable dose of L-dopa alone or in combination with other PD medications.

Efficacy and safety of Safinamide were studied in a large number of clinical trials. In particular, the benefits of Safinamide as add-on therapy to L-dopa and other dopaminergic treatments in mid-stage to late-stage PD patients with motor fluctuations were demonstrated in the Study 016. In this double-blind, placebo-controlled 24-week trial, 669 patients were equally randomized to receive 50 mg/day Safinamide, 100 mg/day Safinamide or placebo as add-on therapy to the stable L-dopa dose. Based on patient diary, Safinamide 50 mg/day and 100 mg/day increased total daily "on" time with no or nontroublesome

dyskinesia. Concerning safety, overall, incidences of treatment emergent adverse events (TEAEs), drug-related TEAEs and discontinuation due to TEAEs with Safinamide were similar to placebo.

Research question and objectives

During the initial marketing authorization procedure, at day 180 the European Medicines Agency (EMA) recommended to the Applicant to provide additional real world data on Safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely patients aged > 75 years and those with concomitant psychiatric conditions such as psychosis, cognitive dysfunction and depression. Following this request, a Drug Utilization Study (DUS) aimed at investigating how Safinamide is prescribed and used in routine clinical practice was designed, including also PD patients with relevant concomitant diseases. It will allow to evaluate not only the extent of these categories of patients, but also safety data (in terms of occurrence of adverse events) will be provided. Whit this approach the opportunity of collecting and disseminating relevant data concerning the use of Safinamide in a real life setting was seized. In order to improve the knowledge about the product beyond the findings of clinical trials, the study will provide data on drug safety profile and on Safinamide treatment patterns.

This observational study will allow obtaining information on Safinamide safety profile and pattern of use in clinical practice during 1 year in the first post-commercialization phase of the product.

The aim of the study is merely descriptive and there are no pre-specified hypotheses.

Primary objective:

To describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators.

The analysis will be conducted overall and in some subgroups of interest, namely in patients aged >75 years and those with relevant concomitant conditions.

Secondary objectives:

1. To describe the characteristics of patients treated with Safinamide according to clinical practice (demographics, disease duration, disease severity, previous treatment for PD, concomitant relevant conditions with particular focus on psychiatric ones and related treatments).
2. To describe Safinamide treatment patterns in real-life setting (treatment duration, dose adjustments and interruptions, dose discontinuation and reason, changes in concomitant PD therapies, treatments for PD administered after Safinamide).

Study design

Multi-country multicentre retrospective-prospective cohort observational study.

The study will last 36 months, including 24-months enrollment period and 12-months follow-up period.

Population

Adult patients treated with Safinamide according to clinical practice will be consecutively enrolled in each participating site during the 24-month recruitment period.

Involved countries will be Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom.

About 140 neurology centers, specialist centers dealing with PD and geriatric centers, identified as those primarily involved in the administration of Safinamide, will be involved in the study and asked to consecutively enroll patients in the study, according to inclusion/ exclusion criteria reported below.

A total of 1600 patients are expected to be included in the study, corresponding to approximately 11 patients/ site. Participating sites will be given the possibility of including a higher number of patients in case a competitive enrolment strategy will be adopted. This strategy will be decided by Zambon and communicated throughout MediNeos to all centers in any country in case of poor enrolment rate observed.

Inclusion criteria (at enrolment visit):

- Adult male and female patients (≥18 years).
- Patients who start treatment with Safinamide at enrolment visit or who started it in the previous 4 months, according to clinical practice after its commercialization. This is an observational study, hence physician's decision of starting treatment with Safinamide has been taken before the patient inclusion in the study and is completely independent from the study protocol.
- Patients who have signed informed and privacy form consent according to local legal requirement.

Exclusion criteria (at enrolment visit):

- Patients participating in any clinical trial on Safinamide at study inclusion.

Exit criteria (any time during the study):

- Informed and privacy consent withdrawn
- Loss to follow-up
- Patients included in any clinical trial on Safinamide
- Pregnancy
- Death

Variables

The following variables are expected to be collected with respect to each time point, as per clinical practice. For data not available, the Investigator will report "NA".

	Start of treatment with Safinamide [a]	**4 (±1) months after start of treatment**	**8 (±1) months after start of treatment**	**12 (±1) months after start of treatment**	**Study completion**
Inclusion/ exclusion criteria, informed consent and privacy signature (to be evaluated at enrolment)	X *				
Socio-demographics (gender, age, race)	X				
Medical history: concomitant relevant conditions with particular focus on psychiatric ones and related treatments	X	X	X	X	
Anamnesis of PD or Parkinsonism (year of first diagnosis, year of first symptom onset, motor and non-motor symptoms, Hoehn & Yahr stage, caregiver y/n)[b]	X			X[e]	
Previous treatments for PD or Parkinsonism – last 3 months (active, dose, start, end date) [b]	X				
Treatment with Safinamide (start date, initial daily dose and number of tablets, dose changes and interruptions, dose discontinuation with reason, end date/ ongoing at study completion)		*continuum*			
Concomitant treatments for PD or Parkinsonism and related conditions (active, start date, initial dose, dose changes/ interruptions/ discontinuation, end date/ ongoing at study completion) [b]	X	X	X	X	
Concomitant treatments for any other medical condition			*continuum*		

Treatments for PD or Parkinsonism subsequent to Safinamide (active, dose, start date, end date/ ongoing at study completion) [b]		X	X	X	
Adverse Events (AEs)		*continuum*			
Occurrence of other safety special events y/n		X	X	X	
Pregnancy y/n		*continuum*			
Unified Parkinson's Disease Rating Scale (UPDRS) [c]	X[d]	X[d]	X[d]	X[d]	
Change in fluctuating/no fluctuating and type of fluctuation [c]	X	X	X	X	
Last available cognitive evaluation, if any	X				
Observation completed y/n, if no date and reason of withdrawal					X

Table 1. Collected variables.
[*] in case of retrospective observation, inclusion/ exclusion criteria will be evaluated and informed consent and privacy signature will be obtained at enrolment visit.
[a] If the patient started treatment with Safinamide before the inclusion visit, these data will be retrospectively collected at enrolment visit.
[b] In case of patients with diagnosis other than PD or other Parkinsonisms which are not related to PD, the collection of these data will be adapted.
[c] Only for PD patients.
[d] The questionnaires will be administered during the prospective observation period (i.e., excluding the retrospective period).
[e] Only Hoehn & Yahr stage

Data sources

Given the observational nature of the study all activities concerning patient management, including medical charts updating and maintenance, will be conducted in compliance with the clinical practice of the participating centres.

For all patients enrolled in the study after the signature of the Informed Consent, data will be prospectively recorded on the Study eCRF by the Investigator both by retrieving already available data from the medical charts and by interviewing the patient in order to collect information that, as per single center practice, would not be reported in the patient's medical chart.

The Investigator will be asked to report all the AEs (serious or not, related or not to Safinamide) and pregnancy cases occurred during the observation period of which he/she becomes aware.

For patients starting treatment with Safinamide (Xadago®) before the enrolment visit, data on treatments and on safety outcomes will be collected retrospectively by each patient's medical charts at the moment of the enrolment in the study and later will be integrated/updated with information routinely available in the patient's medical charts and with those specifically collected interviewing the patient at each subsequent study visit.

Data will be collected also administering the Unified Parkinson's Disease Rating Scale (UPDRS) to PD patients at each study visit.

Study size

The primary objective of the study is to describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators.

A total of 1600 patients are expected to be enrolled in the study. This sample size was defined based on feasibility considerations concerning the length of the enrolment period and site capacity. Considerations on the achievable precision of the estimates are presented below.

Since no results from studies investigating Safinamide in real-life setting are available, thus safety data are only available from clinical trials. The Study 016 was a double-blind, placebo-controlled, parallel-group, randomized, multi-center, multi-national, phase III trial, comparing two fixed doses of Safinamide (50 and 100 mg/day, p.o.) versus placebo as add-on therapy to an optimized dose of L-dopa along with other PD drugs (Borgohain et al 2014). On 447 patients treated with Safinamide for 24 weeks, 65.8% experienced any Treatment-Emergent Adverse Event (TEAE). In detail, for example, 14.1% of Safinamide patients experienced musculoskeletal and connective tissue disorders and 4.9% back pain.

Assuming 1600 enrolled patients, 20% as drop-out rate (leading to 1280 evaluable patients) and the expected proportions described above, the 95% confidence interval (CI) of the expected proportion was evaluated and it is shown in Table 2.

	N. of evaluable patients	**Expected proportion**	**Two-sided 95%CI of the expected proportion**
% patients with any TEAE	1280	65.8%	(63.2% ; 68.4%)
% patients with any musculoskeletal and connective tissue disorder	1280	14.1%	(12.2% ; 16.0%)
% patients with back pain	1280	4.9%	(3.7% ; 6.1%)

Table 2. Two-sided 95% confidence interval of the expected proportion of patients with listed events, assuming 1280 evaluable patients.

A sample size of 1280 evaluable patients will allow to observe expected proportions equal to or higher than 3.3% with ≤ 30% relative error (computed as the ratio between the 95%CI half-width and the expected proportion).

Furthermore, it will be of interest to examine safety variables in subgroups of interest, namely those aged >75 years and those with concomitant psychiatric conditions. The proportion of those aged >75 years is expected to be about 25% according to clinicians' opinion and demographic characteristics of PD patients popular in literature.

In the double-blind, placebo-controlled studies in late stage PD patients (Studies 016/018 and 27919 (SETTLE)), in which patients could be treated for up to 2 years, a total of 27 patients >75 years of age

were randomized to safinamide, while 20 patients in this age range received placebo. Out of 27 Safinamide patients, 25 (92.6%) experienced any TEAE. In detail, for example, 4 (14.8%) experienced any respiratory, thoracic and mediastinal disorder.

Table 3 shows the 95%CI of the expected proportion in the subgroup of patients >75 years old assuming 1600 enrolled patients, 25% aged >75 years and 20% as drop-out rate (leading to 320 evaluable patients).

	N. of evaluable patients	**Expected proportion**	**Two-sided 95%CI of the expected proportion**
% patients with any TEAE	320	92.6%	(89.7% ; 95.5%)
% patients with any respiratory, thoracic and mediastinal disorder	320	14.8%	(10.9% ; 18.7%)

Table 3. Two-sided 95% confidence interval of the expected proportion of patients with listed events, assuming 320 evaluable patients aged >75 years.

When the sample size is 320, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 3.9% from the observed proportion for an expected proportion of 14.8%.

If the sample size of 1600 patients is not reachable due to lower-than-expected actual accrual rate or duration of enrolment period in some countries or sites, a worst estimate precision will be obtained.

Considering 14.8% as the expected proportion of patients with any respiratory, thoracic and mediastinal disorder in the subgroup of >75-years-old patients, then the number of evaluable patients leading to a relative error of the estimate lower than 30% is 246, corresponding to 307 enrolled patients. Assuming that patients aged >75 years constitute the 25% of the whole sample, this means 1228 enrolled patients.

Data analysis

Data will be described on all enrolled patients fulfilling inclusion/ exclusion criteria.

The aim of the study is merely descriptive and there are no pre-specified hypotheses.

Categorical variables will be described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max.

The primary objective of the study is to describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators. The proportion of patients experiencing any AE, overall and by system organ class (SOC) and preferred term (PT), according to MedDRA will be provided. The proportion of those experiencing any serious adverse events (SAEs) and adverse drug reactions (ADRs) related to Safinamide, serious or not, will be provided as well.

The analyses will be provided overall and by subgroups of interest, namely patients aged >75 years and those concomitantly suffering from relevant concomitant conditions.

Specifically, data will be provided in the group of patients suffering from psychosis, bipolar disorder, depression and anxiety.

Furthermore seriousness, severity, relation with Safinamide according to Investigator judgment, action taken and outcome of the event will be summarized.

Milestones

Milestone	**Planned date**
Registration in the EU PAS register	March 2016
Start of data collection	June 2016
End of data collection	May 2019
Final report of study results	October 2019

5. Amendments and updates

None.

6. Milestones

Milestone	Planned date
Registration in the EU PAS register	March 2016
Start of data collection	June 2016
End of data collection	May 2019
Final report of study results	October 2019

7. Rationale and background

Parkinson's Disease (PD) is the second most common neurodegenerative disease following Alzheimer's disease. Approximately 1.2 million people live with PD throughout Europe and the number is expected to increase as the population is ageing. The incidence is approximately 1.5 times higher in males than females. The prevalence increases with age, from about 1.4% over the age of 60 to about 4.3% over the age of 85.[1]

PD occurs when, because of an unknown cause, dopamine-producing cells progressively degenerate.[1] This leads to progressive deterioration of motor function, progressive loss of muscle control and trembling. The impairment varies from individual to individual.

Not only neuromusculoskeletal and movement-related functions are involved by impairments, but also non-motor areas. In fact, it is noticed a considerable reduction in quality of life. Examples of early non-motor impairments are depression, olfactory dysfunction, REM sleep behavior disorder and constipation. In addition, mental impairments, specifically impaired executive function and memory, as well as prolonged reaction time can be present at diagnosis.[1]

The overall goal of PD management is to optimize activities, participation and quality of life of patients. Currently, the focus is on symptom control and compensation. Symptomatic treatments include a variety of drugs and rehabilitation. No treatment slows disease progression down.[1]

Current pharmacological management is largely based on the dopamine precursor L-dopa and dopamine agonists. L-dopa offers the best symptomatic relief of rigidity, bradykinesia and tremor. In addition to L-dopa, dopamine agonists are prescribed to alleviate other disabling complications such as restless legs syndrome, sleep fragmentation and early morning akinesia or dystonia.

L-dopa remains the most effective single therapy, but after years of administration it promotes often incapacitating motor fluctuations and might accelerate disease progression through free radical formation. Mono-Amine Oxidase (MAO)-B inhibitors improve motor function in PD patients when used as adjunctive therapy to L-dopa. Recently it has been suggested that they might also slow disease progression by reducing oxidative damage.

Beyond dopamine, perturbations in neurotransmission in the basal ganglia of PD patients are known to involve glutamate and other transmitters, and these are believed to play important roles in the pathogenesis of primary symptoms, motor fluctuations, and possibly neuronal cell loss. Increasingly, non-dopaminergic agents are being studied to determine their potential to supplement, or delay the use of, established dopaminergic therapies.

Safinamide was developed as a new strategy for the therapy of PD, by combining inhibition of both MAO-B and sodium channels, leading to both dopaminergic and non-dopaminergic activities.

Safinamide is an α-aminoamide indicated as add-on therapy for the treatment of patients with idiopathic PD, in mid-to late-stage fluctuating patients receiving a stable dose of L-dopa alone or in combination with other PD medications[10].

Efficacy and safety of Safinamide were studied in a large number of clinical trials. In particular, the benefits of Safinamide as add-on therapy to L-dopa and other dopaminergic treatments in mid-stage to late-stage PD patients with motor fluctuations were demonstrated in the Study 016[11]. In this double-blind, placebo-controlled 24-week trial, 669 patients were equally randomized to receive 50 mg/day Safinamide, 100 mg/day Safinamide or placebo as add-on therapy to the stable L-dopa dose. Based on patient diary, Safinamide 50 mg/day and 100 mg/day increased total daily "on" time with no or nontroublesome dyskinesia.[11] Motor symptoms (Unified Parkinson's Disease Rating Scale (UPDRS) III), activities of daily living (UPDRS II), Clinical global impression (CGI)-S and quality of life (PDQ-39) also improved when compared with placebo. Concerning safety, overall, incidences of treatment emergent adverse events (TEAEs), drug-related TEAEs and discontinuation due to TEAEs with Safinamide were similar to placebo.[11] This safety profile was similar to that observed in the 18-month extension study (Study 018), in which treatment with Safinamide (50 and 100 mg/day) was generally well tolerated[12].

8. Research question and objectives

During the initial marketing authorization procedure, at day 180 the European Medicines Agency (EMA) recommended to the Applicant to provide additional real world data on Safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely patients aged > 75 years and those with concomitant psychiatric conditions such as psychosis, cognitive dysfunction and depression. Following this request, a Drug Utilization Study (DUS) aimed at investigating how Safinamide is prescribed and used in routine clinical practice was designed. It will allow to evaluate not only the extent of these categories of patients, but also safety data (in terms of occurrence of adverse events) will be provided. Whit this approach the opportunity of collecting and disseminating relevant data concerning the use of Safinamide in a real life setting was seized. In order to improve the knowledge about the product beyond the findings of clinical trials, the study will provide data on drug safety profile and on Safinamide treatment patterns.

This observational study will allow obtaining information on Safinamide safety and pattern of use in clinical practice during 1 year in the first post-commercialization phase of the product.

The aim of the study is merely descriptive and there are no pre-specified hypotheses.

Primary objective:

To describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators.

The analysis will be conducted overall and in some subgroups of interest, namely in patients aged >75 years and those with relevant concomitant conditions.

Secondary objectives:

1. To describe characteristics of patients treated with Safinamide according to clinical practice (demographics, disease duration, disease severity, previous treatment for PD, concomitant relevant conditions with particular focus on psychiatric ones and related treatments).
2. To describe Safinamide treatment patterns in real-life setting (treatment duration, dose adjustments and interruptions, dose discontinuation and reason, changes in concomitant PD therapies, treatments for PD administered after Safinamide).

9. Research methods

9.1. Study design

This is a multi-country multicenter retrospective-prospective cohort observational study.

The study will last 36 months, including 24-month enrollment period and 12-month follow-up period.

The cohort study was defined according to the primary objective of the study, that is the description of the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators.

Primary endpoints:

- Number of patients with adverse events (AEs), overall and by event description, not only considering all AEs but also for serious adverse events (SAEs) and adverse drug reactions (ADRs) related to Safinamide, serious or not, separately.
- Description of some attributes of AEs occurred, namely severity, seriousness, relation with Safinamide according to clinician's judgment, action taken and outcome.
- Primary endpoints will be also stratified by age (>75) and relevant concomitant conditions.

Furthermore, the following secondary endpoints will be evaluated:

- Description of demographic and clinical baseline characteristics, including anamnesis of PD and previous treatments, or order to characterize the treated population.
- Description of Safinamide treatment duration.
- Description of Safinamide dose adjustments and interruptions, described by means of the proportion of patients experiencing at least one Safinamide dose increase, dose decrease and dose interruption, respectively. If episodes of overdose will be reported in the electronic case report form (eCRF) they will be provided in the analyses.
- Description of Safinamide discontinuation (proportion of patients experiencing such event) and reason.
- Description of changes in PD therapies concomitant to Safinamide, intended as proportion of patients adding one or more active, stopping one or more active, changing dose of one or more active.
- Description of treatments for PD administered after Safinamide.

All study endpoints will be provided using descriptive statistics. In fact, the aim of the study is merely descriptive and there are no pre-specified hypotheses.

The study design allows the description of treatment patterns at enrolment and during the longitudinal observation. In most of the involved countries the study onset is expected to coincide with the drug commercialization. For this reason a prospective observation was chosen. Moreover, in order to include also patients starting treatment before study onset, if any, a retrospective part of the observation period (expected to be experienced by a small number of patients) was allowed.

9.2. Setting

Involved countries will be Belgium, France, Germany, Italy, Spain, Switzerland and United Kingdom. The start of data collection will be at June 2016. For countries in which the drug will be commercialized after that date, the study will start according to drug availability on the market and duration of the authorization phase.

The following table shows the expected time of Safinamide availability on the market in each of the participating countries.

Country	**Safinamide availability**
Belgium	*Already available*
France	July 2016
Germany	*Already available*
Italy	*Already available*
Spain	*Already available*
Switzerland	*Already available*
United Kingdom	May 2016

About 140 neurology centers, specialist centers dealing with PD and geriatric centers, identified as those primarily involved in the administration of Safinamide, will be involved in the study and asked to consecutively enroll patients in the study, according to inclusion/ exclusion criteria reported below.

A total of 1600 patients are expected to be included in the study, corresponding to approximately 11 patients/ site. Participating sites will be given the possibility of including a higher number of patients in case a competitive enrolment strategy will be adopted. This strategy will be decided by Zambon and communicated throughout MediNeos to all centers in any country in case of poor enrolment rate observed.

Adult patients treated with Safinamide according to clinical practice will be consecutively enrolled in each participating site during the 24-month recruitment period.

Inclusion criteria (at enrolment visit):

- Adult male and female patients (≥18 years).
- Patients who start treatment with Safinamide at enrolment visit or who started it in the previous 4 months, according to clinical practice after its commercialization. This is an observational study, hence physician's decision of starting treatment with Safinamide has been taken before the patient inclusion in the study and is completely independent from the study protocol.
- Patients who have signed informed and privacy form consent according to local legal requirement.

Exclusion criteria (at enrolment visit):

- Patients participating in any clinical trial on Safinamide at study inclusion.

In order to ideally observe the largest population of patients administered with Safinamide according to clinician's decision in the first post-commercialization phase, this study will avoid any selection of patients by means of broad inclusion/ exclusion criteria. As for inclusion criteria, adult patients giving their consent to participate in the study will be eligible if they start treatment at the enrolment visit or in the previous 4 months according to clinical practice. This limit was set in order to allow no more than one time point (start of treatment) for which data are retrospectively collected, leading to the exclusion of a reasonably negligible number of patients given the time elapsed from drug commercialization. PD was not defined as an inclusion criterion in order to have the possibility of observing patients with a different diagnosis than PD if they are administered Safinamide. This should allow for a more complete picture of drug utilization in a real-life setting.

The only exclusion criterion consists in patients receiving Safinamide in clinical trial, according to the observational nature of the study.

Exit criteria (any time during the study):

- Informed consent withdrawn
- Loss to follow-up
- Patients included in any clinical trial on Safinamide
- Pregnancy
- Death

Patients will be included in the study when they start treatment with Safinamide or in the following 4 months. This is an observational study, hence physician's decision of starting treatment with Safinamide has been taken before the patient inclusion in the study and is completely independent from the study protocol. All patients will be followed for 12 months after the start of treatment. If a patient discontinues treatment

with Safinamide during the study, the observation will continue. Data at treatment start, 4 (±1) , 8 (±1) and 12 (±1) months after will be collected during study visits. If the patient will be enrolled at the start of treatment, then all data will be prospectively collected. Otherwise, if the patient will be enrolled after the start of treatment, then the data collection will be partially retrospective.

The study scheme is shown in Figure 1.

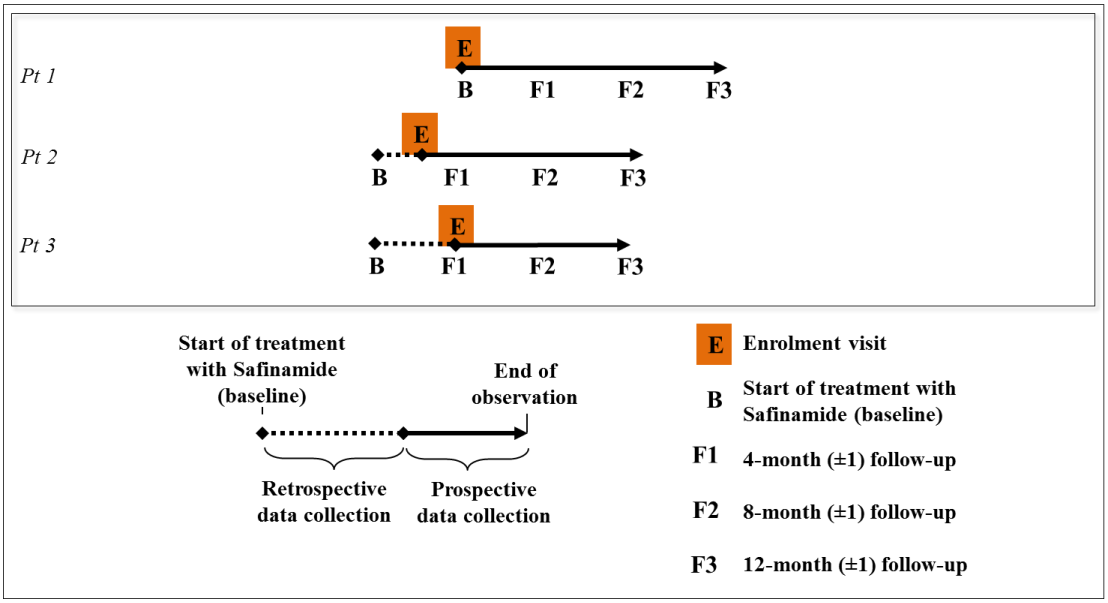

Figure 1. Study scheme.
Pt 1. Patient enrolled at the start of treatment with Safinamide. The enrolment visit is performed at treatment start and then the patient is prospectively followed for 12 months, performing 4-, 8- and 12-month follow-up.
Pt 2. Patient enrolled 2 months after the start of treatment with Safinamide. Data at the start of treatment are retrospectively collected at enrolment visit, as well as data regarding the 2 months passed, while the patient is prospectively followed until 12 months after the start of treatment, performing 4-, 8- and 12-month follow-up visits.
Pt 3. Patient enrolled 4 months after the start of treatment with Safinamide. Data at the start of treatment and at 4 months after are collected at enrolment visit, as well as data regarding the 4 months passed, while the patient is prospectively followed until 12 months after the start of treatment, performing 8- and 12-month follow-up visits.

9.3. Variables

Exposure

The exposure of interest is the treatment with Safinamide, administered to all eligible patients as per clinical practice. All patients receiving at least one dose of Safinamide will be considered as exposed. Treatment with Safinamide will be recorded since its start: in fact patients are enrolled either when they start Safinamide or up to 4 months after Safinamide start. Data on Safinamide treatment will be recoded according to clinical practice and updated in continuum during the course of the study.

Investigated outcomes

- Number of patients with AEs, intended as the proportion of patients experiencing at least one AE from the start of treatment with Safinamide until the end of the observation period, overall, by

System Organ Class (SOC) and by Preferred Term (PT), according to Medical Dictionary for Regulatory Activities (MedDRA).

- Number of patients with SAEs (adapting the definition of number of patients with AEs accordingly), overall, by SOC and by PT, according to MedDRA.
- Number of patients with ADRs related to Safinamide (adapting the definition of number of patients with AEs accordingly), overall, by SOC and by PT, according to MedDRA.
- Description of AEs occurred in terms of severity, seriousness, relation with Safinamide according to clinician's judgment, action taken and outcome.
- Demographics (gender, age, race)
- Disease duration at the start of treatment with Safinamide, computed as the difference between the year of treatment start and the year of first diagnosis of PD
- Disease severity (Hoehn & Yahr stage)
- Concomitant relevant conditions, with particular focus on psychiatric ones and related treatments
- Previous treatment for PD (last three months)
- Safinamide treatment duration, computed as the difference between:
    - The end of treatment and the date of treatment start for patient discontinuing Safinamide during the study
    - The 12-month follow-up visit/ study withdrawal and the date of treatment start for patient not discontinuing Safinamide during the study
- Safinamide dose adjustments, interruptions, discontinuation and reason for discontinuation.
- Changes in PD therapies concomitant to Safinamide and treatments for PD administered after Safinamide.
- Motor Evaluation (only PD patients), as measured by UPDRS III (see 9.4 Data sources for details)

Details of collected variables are reported in Table 1.

This is an observational study, it does not interfere with, or impose any therapy protocols, diagnostic/ therapeutic procedures or visit schedules. Patients will be treated according to local prescribing information and clinical judgment and assessments performed according to site clinical practice.

Investigators are asked to report the requested data in the eCRF. All data will be reported by the clinician.

The following variables are expected to be collected with respect to each time point, as per clinical practice. For data not available, the Investigator will report "NA".

	Start of treatment with Safinamide [a]	**4 (±1) months after start of treatment**	**8 (±1) months after start of treatment**	**12 (±1) months after start of treatment**	**Study completion**
Inclusion/ exclusion criteria, informed consent and privacy signature (to be evaluated at enrolment)	X *				
Socio-demographics (gender, age, race)	X				
Medical history: concomitant relevant conditions with particular focus on psychiatric ones and related treatments	X	X	X	X	
Anamnesis of PD or Parkinsonism (year of first diagnosis, year of first symptom onset, motor and non-motor symptoms, Hoehn & Yahr stage, caregiver y/n)[b]	X			X[e]	
Previous treatments for PD or Parkinsonism – last three months (active, dose, start, end date) [b]	X				
Treatment with Safinamide (start date, initial daily dose and number of tablets, dose changes and interruptions, dose discontinuation with reason, end date/ ongoing at study completion)		*continuum*			
Concomitant treatments for PD or Parkinsonism and related conditions (active, start date, initial dose, dose changes/ interruptions/	X	X	X	X	

discontinuation, end date/ ongoing at study completion) [b]					
Concomitant treatments for any other medical condition			*continuum*		
Treatments for PD or Parkinsonism subsequent to Safinamide (active, dose, start date, end date/ ongoing at study completion) [b]		X	X	X	
Adverse Events (AEs)			*continuum*		
Occurrence of other safety special events y/n		X	X	X	
Pregnancy y/n			*continuum*		
Unified Parkinson's Disease Rating Scale (UPDRS) [c]	X[d]	X[d]	X[d]	X[d]	
Change in fluctuating/no fluctuating and type of fluctuation [c]	X	X	X	X	
Last available cognitive evaluation, if any	X				
Observation completed y/n, if no date and reason of withdrawal					X

Table 1. Collected variables.
[*] in case of retrospective observation, inclusion/ exclusion criteria will be evaluated and informed consent and privacy signature will be obtained at enrolment visit.
[a] If the patient started treatment with Safinamide before the inclusion visit, these data will be retrospectively collected at enrolment visit.
[b] In case of patients with diagnosis other than PD or other Parkinsonisms which are not related to PD, the collection of these data will be adapted.
[c] Only for PD patients.
[d] The questionnaires will be administered during the prospective observation period (i.e., excluding the retrospective period).
[e] Only Hoehn & Yahr stage

The study is not aimed at evaluating any associations, but investigated outcomes will be described. Thus there are no confounders or effect modifiers which could alter associations. Nevertheless, patient and treatment characteristics will be collected and taken into consideration in the interpretation of results.

9.4. Data sources

The physicians and their staff will be trained before study initiation.

Given the observational nature of the study all activities concerning patient management, including medical charts updating and maintenance, will be conducted in compliance with the clinical practice of the participating centres.

For all patients enrolled in the study after the signature of the Informed Consent, data will be prospectively recorded on the Study eCRF by the Investigator both by retrieving already available data from the medical charts and by interviewing the patient in order to collect information that, as per single center practice, would not be reported in the patient's medical chart.

The Investigator will be asked to report to the Sponsor all the AEs (serious or not, related or not to Safinamide) and pregnancy cases occurred during the observation period of which he/she becomes aware.

For patients starting treatment with Safinamide (Xadago®) before the enrolment visit, data on treatments and on safety outcomes will be collected retrospectively by each patient's medical charts at the moment of the enrolment in the study and later will be integrated/updated with information routinely available in the patient's medical charts and with those specifically collected interviewing the patient at each subsequent study visit.

For applicable sections, the questionnaires detailed below will be administered to patients. In case of patients capable of discernment to answer but not able to read or write, a third person (e.g. site staff or caregiver) can report answers after asking questions to the patient himself and according to his indications.

PD patients/ clinicians will be administered with the **Unified Parkinson's Disease Rating Scale (UPDRS).** UPDRS was originally developed in the 1980s[13] and became the most widely used clinical rating scale for PD[14] in order to follow in a more objective manner the progression of symptoms in patients treated with a specific drug. it consists of 55 items and it is divided in four parts. If all of them are administered, then a sum score for each part is obtained. Only English version is available worldwide and, as the instrument is not designed to be administered directly to the patient, but with the mediation of clinician, the questionnaire will be administered in English language to all the participating sites.

9.5. Study size

The primary objective of the study is to describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators.

A total of 1600 patients are expected to be enrolled in the study. This sample size was defined based on feasibility considerations concerning the length of the enrolment period and site capacity. Considerations on the achievable precision of the estimates are presented below.

Since no results from studies investigating Safinamide in real-life setting are available, thus safety data are only available from clinical trials. The Study 016 was a double-blind, placebo-controlled, parallel-group, randomized, multi-center, multi-national, phase III trial, comparing two fixed doses of Safinamide (50 and 100 mg/day, p.o.) versus placebo as add-on therapy to an optimized dose of L-dopa along with other PD drugs.[11] On 447 patients treated with Safinamide for 24 weeks, 65.8% experienced any TEAE. In detail, for example, 14.1% of Safinamide patients experienced musculoskeletal and connective tissue disorders and 4.9% back pain.

Assuming 1600 enrolled patients, 20% as drop-out rate (leading to 1280 evaluable patients) and the expected proportions described above, the 95% confidence interval (CI) of the expected proportion was evaluated and it is shown in Table 2.

	N. of evaluable patients	**Expected proportion**	**Two-sided 95%CI of the expected proportion**
% patients with any TEAE	1280	65.8%	(63.2% ; 68.4%)
% patients with any musculoskeletal and connective tissue disorder	1280	14.1%	(12.2% ; 16.0%)
% patients with back pain	1280	4.9%	(3.7% ; 6.1%)

Table 2. Two-sided 95% confidence interval of the expected proportion of patients with listed events, assuming 1280 evaluable patients.[24]

A sample size of 1280 evaluable patients will allow to observe expected proportions equal to or higher than 3.3% with ≤ 30% relative error (computed as the ratio between the 95%CI half-width and the expected proportion).

Furthermore, it will be of interest to examine safety variables in subgroups of interest, namely those aged >75 years and those with relevant comorbidities, with a particular focus on psychiatric conditions. The proportion of those aged >75 years is expected to be about 25% according to clinicians' opinion and demographic characteristics of PD patients popular in literature.

In the double-blind, placebo-controlled studies in late stage PD patients (Studies 016/018 and 27919 (SETTLE)) (data not published), in which patients could be treated for up to 2 years, a total of 27 patients >75 years of age were randomized to safinamide, while 20 patients in this age range received placebo. Out of 27 Safinamide patients, 25 (92.6%) experienced any TEAE. In detail, for example, 4 (14.8%) experienced any respiratory, thoracic and mediastinal disorder.

Table 3 shows the 95%CI of the expected proportion in the subgroup of patients >75 years old assuming 1600 enrolled patients, 25% aged >75 years and 20% as drop-out rate (leading to 320 evaluable patients).

	N. of evaluable	**Expected proportion**	**Two-sided 95%CI of the expected proportion**

	patients		
% patients with any TEAE	320	92.6%	(89.7% ; 95.5%)
% patients with any respiratory, thoracic and mediastinal disorder	320	14.8%	(10.9% ; 18.7%)

Table 3. Two-sided 95% confidence interval of the expected proportion of patients with listed events, assuming 320 evaluable patients aged >75 years.

When the sample size is 320, a two-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 3.9% from the observed proportion for an expected proportion of 14.8%.[24]

If the sample size of 1600 patients is not reachable due to lower-than-expected actual accrual rate or duration of enrolment period in some countries or sites, a worst estimate precision will be obtained. Considering 14.8% as the expected proportion of patients with any respiratory, thoracic and mediastinal disorder in the subgroup of >75-years-old patients, then the number of evaluable patients leading to a relative error of the estimate lower than 30% is 246, corresponding to 307 enrolled patients. Assuming that patients aged >75 years constitute the 25% of the whole sample, this means 1228 enrolled patients.

9.6. Data management

An eCRF will be filled in out by the Investigator and/or his/her designee.

All patients who sign the informed and privacy form consent will be databased.

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical terms (e.g. AEs and relevant medical conditions) will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical (ATC) classification.

Once the database is declared complete and accurate, it will be locked and used for statistical analysis. Statistical analysis will be performed using the SAS software.

Only authorized and well-documented updates to the study data will be possible after database lock.

Each participating site will maintain appropriate medical and research records for this study, in compliance with GPP and regulatory and institutional requirements for the protection of confidentiality of patients.

Patient initials or names will not be recorded in the database: patients will be associated to a unique identifier.

The eCRF used for the study is validated according to GAMP5. The IT infrastructure supporting the eCRF solution is monitored and controlled both in terms of Security (i.e. Intrusion Detection, Antiviruses …) and

Operational Performance. Backups and operative controls are properly managed in order to guarantee the business continuity.

Due to the observational nature of the study no independent review of the data will be performed.

Data access rules, as well as data transfer to Zambon, will be detailed in the Data Management Plan.

9.7. Data analysis

Data will be described on all enrolled patients fulfilling inclusion/ exclusion criteria.

Patients with missing values will not be excluded from the analysis, but their data will not be replaced; frequency of missing data will be given for all analyzed variables.

The aim of the study is merely descriptive and there are no pre-specified hypotheses.

Categorical variables will be described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max.

The primary objective of the study is to describe the occurrence of adverse events in patients treated with Safinamide in real-life conditions during 1 year in the first post-commercialization phase as reported by the Investigators. The number of patients with AEs (portion of patients experiencing at least one AE from the start of treatment with Safinamide until the end of the observation period), overall and by SOC and PT according to MedDRA will be provided. The number of patients with SAEs, and ADRs related to Safinamide, serious or not, will be provided as well.

The number of patients with a partially retrospective observation period is expected to be small. However, in order to evaluate the potential impact of recall bias on the primary endpoint, the proportion of patients experiencing any AE excluding those who started treatment with Safinamide before study inclusion will be provided as sensitivity analysis.

The analyses will be provided overall and for subgroups of interest: patients aged >75 years and those with relevant comorbidities other than those concomitantly suffering from psychiatric conditions.

Specifically, data will be provided in the group of patients suffering from psychosis, bipolar disorder and severe depression.

Furthermore seriousness, severity, relation with Safinamide according to Investigator judgment, action taken and outcome of the event will be summarized.

As for the secondary objectives, the following analyses will be provided.

1. <u>To describe the characteristics of patients treated with Safinamide according to clinical practice</u>

   Enrolled patients will be described with respect to demographics, namely gender, age and race, and clinical variables, namely diagnosis, disease duration and severity. Previous treatment for PD (last year) will be summarized. Concomitant relevant conditions, with a particular focus on psychiatric

ones and related treatments will be described.

For patients having a diagnosis other than and not related to PD, the details of diagnosis and relevant previous (last year) treatments will be provided.

2. To describe Safinamide treatment patterns in real-life setting

Safinamide treatment duration will be described, including the number of patients still receiving Safinamide at the end of observation.

The initial administered daily dose and the initial number of daily tablets will be described. The proportion of patients with dose increase and dose decrease will be provided, as well as those of patients temporary interrupting treatment. The number of episodes of overdose will be reported, if any. The proportion of patients discontinuing Safinamide will be described and the reasons will be summarized.

Treatments for PD still ongoing at the start of treatment with Safinamide and changes in concomitant therapies occurred during the treatment period will be described. Finally, treatments for PD administered after Safinamide will be provided as well. For non-PD patients, if any, relevant concomitant and subsequent treatments administered will be considered.

It is known that polypharmacy could have a relevant role due to the presence of this condition in the majority of PD patients. Data about concomitant treatments for PD or Parkinsonism and related conditions will be collected in the study and the possibility of providing stratified analyses for the previous objectives will be evaluated based on the number of observed patients with different co-treatments.

Moreover, as additional objectives evaluated on PD patients, the analyses of UPDRS score will be summarized at each time point .

Data collected on all patients will be considered as pooled for statistical analyses. Stratifications by country are not foreseen because there are no reasons for which differences among countries are expected and they are not of interest for this study anyway. Study objectives will be evaluated overall on the sample of first patients treated with Safinamide in clinical practice.

Study results will be clinically reviewed and valued by the Study Outcome Review Board, composed of expert neurologists with a long-standing experience in PD, namely:

- Prof. Giovanni Abbruzzese
- Prof. Wolfgang Jost
- Prof. Jaime Kulisevsky

9.8. Quality control

The Quality control will be managed in accordance with MediNeos procedures as agreed with Zambon.

9.8.1. Study Monitoring

On site and remote study monitoring will be performed by MediNeos Observational Research who has been designated by Zambon as Study CRO.

It is understood that the monitor(s) will contact and/or visit the Investigator/centre regularly throughout the study, and that they will be permitted to inspect the various study records: eCRFs, filled questionnaires, Investigator study file and all available source data (source data, as first observation recorded elsewhere to the eCRFs), provided that patient confidentiality is respected.

The purposes of these visits/phone contacts are:

- to assess the progress of the study;
- to evaluate the compliance with the study protocol;
- to discuss any emerging issue;
- to check the eCRFs for accuracy and completeness.

In addition, during on-site visits, for a set of variables prior defined by the Sponsor, the monitor will validate the contents of the eCRFs against the source documents (where they are available as for clinical practice).

Prior to each on site monitoring visit, the Investigator or staff will record all data generated since the last visit on the eCRFs. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

During each remote monitoring contact, the Investigator or staff will be expected to be available for the phone call to answer questions and to provide any missing information.

9.8.2. Guidelines for Epidemiological Studies

The guidelines for Good Pharmacoepidemiology Practices (GPP) in non-interventional studies as well as recommendations for non-interventional study and principles of epidemiology studies will be respected. This study is not in the scope of Good Clinical Practice (GCP) studies, but for several applicable aspects it will be managed according to it.

9.8.3. Confidentiality of Study Documents and Subject Records

All study documents are provided by the Sponsor to the Investigator and his/her appointed staff in confidence. None of this material may be disclosed to any party not directly involved in the study without written permission from Zambon.

The Investigator must assure that the patient's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the patient's study numbers, names and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Zambon.

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the patient number will be recorded on the eCRF. Study findings stored on a computer will be stored in accordance with local data protection laws.

The Investigators will maintain a list to enable patients' records to be identified. However, if the results of the study are published, the patient's identity will remain confidential.

Personal data - including sensitive data - collected during the execution of the activities will be processed in accordance with the local laws on data protection.

9.8.4.Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of this cohort study and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) patient clinical source documents.

The Investigator's Study File will contain the observational protocol study/amendments, IEC/IRB and governmental approval with correspondence, sample informed and privacy form consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

Patient clinical source documents would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, pathology and special assessment reports, signed informed consent forms, consultant letters and patient screening and enrolment logs. The Investigator must keep these two categories of documents on file according to local regulations after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Zambon must be notified in advance.

9.8.5.Audits and Inspections

This protocol has been audited by sponsor QA.

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's study-related files and correspondence, and the informed consent documentation of this study at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GPP.

The Investigators and Institution must permit study-related monitoring, audits, IRBs/IECs review or regulatory inspection, providing direct access to source data/documents.

9.8.6. Completion of study

The IRB/IEC/competent authority in each country will be notified about the end of the study (date of termination of observational study, last patient out date, number of patients observed) or early termination of the observation accordingly.

9.9. Limitations of the research methods

This observational study will allow obtaining information on Safinamide safety and pattern of use in clinical practice during 1 year in the first post-commercialization phase of the product.

Included patients constitute a convenience sample of all those administered with Safinamide during the study period because no random procedure will be applied in site and patient selection. Consecutive enrolment is requested by protocol, which should minimize selection bias.

Concerning the collection of adverse events, there is a theoretical risk of underestimation of AEs occurred, due to the time elapsed from one study visit to another, mainly for the retrospective observation period. The risk is however considered to be small, in fact the expected number of patients with a partially retrospective observation period is small (however a sensitivity analysis is foreseen as detailed in Data analysis section) and the Investigators will be trained regarding the importance of such a collection. At the same time, a risk of overestimation was also identified due to the fact that clinicians were observed during their clinical practice and this might have changed their behavior, simply because they participated in the study (Hawthorne effect).

Finally, target sample size is considered to be achievable during the enrolment period on the basis of preliminary feasibility considerations. The number of patients included in the subgroups of interest, namely those aged >75 years and those having relevant concomitant conditions (such as psychiatric concomitant conditions), was not set a priori in order not to alter enrolment strategies and in order to include a wide population representative of real-life setting. It will depend on clinical practice and it will be informative of

clinician judgement.

9.10. Other aspects

None.

10. Protection of human subjects

10.1. Ethical and regulatory considerations

This study was designed and shall be implemented and reported in accordance with the Guide on Methodological Standards in Pharmacoepidemiology (Revision 3, July 2014) of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, with the ethical principles laid down in the Declaration of Helsinki and with the laws and regulations of each country in which the research is carried out. The study will be conducted in full conformance with the principles of the "Declaration of Helsinki", the GPP or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection of the individual.

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in each participating country.

Patients selection will not start before the approval of the EC/IRB and notification of the study to (or authorization by) the Health Authorities. This study does not include treatments or diagnostic examinations other than those prescribed in the ordinary clinical practice, therefore no insurance agreements are applicable.

10.2. Informed consent

It is the responsibility of the physicians to obtain written informed and privacy consent from each patient or from the patient's legal representative prior to the collection of any data from the patient's records. The form must be signed before data collection starting.

If the patient and his/her legal representative are unable to read, the informed and privacy consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the patient.

Consents must be documented by the patient's dated signature. The signature confirms that the consents are based on information that have been understood. Moreover, the Investigator must sign and date the informed consent form too.

Each patient's signed informed and privacy consent must be kept on file by the Investigator. One copy must be given to the patient.

11. Management and reporting of safety data

11.1. Definitions

Abuse of a medicinal product.

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

Adverse Event (AE).

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.

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

Adverse Drug Reaction (ADR). A response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from 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.

Drug safety information

- Any adverse event/adverse reaction associated with the Product(s) or with suspected or confirmed falsified Product(s)
- Any report of use of the Product(s) or suspected or confirmed falsified Product(s) in the following special situations, also without any associated adverse event/adverse reaction:
  - pregnancy
  - breastfeeding
  - lack of therapeutic efficacy
  - drug interactions
  - suspected transmission of infectious agents
  - overdose, abuse, off-label use, misuse, medication error, occupational exposure

Medication error

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer.

Misuse of a medicinal product

Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.

Occupational exposure to a medicinal product

For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.

Overdose

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. Clinical judgement should always be applied.

Serious Adverse Event (SAE)/Serious ADR (SADR).

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 hospitalization or prolongation of existing hospitalization
- 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 might not be immediately life threatening or results in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious AE/ADR.

A **non-serious AE/ADR** is any adverse event that does not meet the criteria listed above for a serious AE/ADR.

11.2. Recording of safety data

All Drug Safety Information arising during the study must be documented by the Investigator in the specific section of the eCRF.

All fatal outcomes should be considered as adverse events which should be collected and entered in the eCRF.

For any AE, reported in eCRF, the Investigator is responsible to assess the intensity of the 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.

The reporting Investigator should exercise his/her medical judgment to determine the causal relationship between Safinamide (Xadago®) and the AE(s).

The categories to be used to assess causal relationship are defined as follows:

Category	**Definition**
Not related	The time course between administration of the drug and occurrence or worsening of the adverse event rules out a causal relationship ***and/or*** another cause is confirmed and no indication of involvement of the drug in the occurrence/worsening of the adverse event exists.
Unlikely	The time course between administration of the drug and occurrence or worsening of the adverse event makes a causal relationship unlikely ***and/or*** the known effects of the drug or of the substance class provide no indication of involvement in occurrence/worsening of the adverse event and another cause adequately explaining the adverse event is known ***and/or*** regarding the occurrence/worsening of the adverse event a plausible causal chain may be deduced from the known effects of the drug or the substance class, but another cause is much more probable ***and/or*** another cause is confirmed and involvement of the drug in the occurrence/worsening of the adverse event is unlikely.

Category	Definition
Possible	Regarding the occurrence/worsening of the adverse event, a plausible causal chain may be deduced from the pharmacological properties of the drug or the substance class, but another cause just as likely to be involved is also known ***or*** although the pharmacological properties of the drug or the substance class provide no indication of involvement in the occurrence/worsening of the adverse event, no other cause gives adequate explanation
Probable	The pharmacological properties of the drug or of the substance class ***and/or*** the course of the adverse event after dechallenge and, if applicable, after rechallenge ***and/or*** specific tests (e.g. positive allergy test, antibodies against study drug/metabolites) suggest involvement of the drug in the occurrence/worsening of the adverse event, although another cause cannot be ruled out.
Definite	The pharmacological properties of the drug or of the substance class ***and*** the course of the adverse event after dechallenge and, if applicable, after rechallenge ***and*** specific tests (e.g. positive allergy test, antibodies against drug/metabolites) indicate involvement of the drug in the occurrence/worsening of the adverse event and no indication of other causes exists.
Unclassifiable	The available information is not sufficient for causality assessment.

Only if the reporter has made an explicit statement that a causal relationship between the medicinal product and AE has been excluded (i.e. not related) and Zambon agrees with this, the event should not be reported to Regulatory Authorities. (Section 11.3).

Only ADRs related to Safinamide (Xadago®) will be collected on the eCRF (data regarding side effects from other medicinal products will not be collected/managed as they are outside of the scope of this study protocol).

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 (Xadago®).

11.3. Reporting of Drug Safety Information

11.3.1. Serious Adverse Event (SAE), ADR related to Safinamide (Xadago®)

All SAEs and ADRs to Safinamide (Xadago®) experienced by patients enrolled in the study shall be reported by the Investigators, irrespective of seriousness, to the Sponsor within the timelines here reported starting from first awareness of the event:

Event	**Reporting Timeline**
SAE	5 calendar days
SADR to Safinamide	5 calendar days
ADR to Safinamide	5 calendar days

The information must be sent by e-mail or by FAX (where unable to send by e-mail) by filling in appropriate forms to the following country-specific contact details:

Country	**Pharmacovigilance contact details**
Belgium	Claude Krygier Phone +32 2777 0202 Fax +32 2771 8570 Mobile +32 473720607 e-mail: claude.krygier@zambongroup.com Common Drug Safety contact details: e-mail: zambon.pv@zambongroup.com
France	Farida Grid Phone +33 01 58044120 Fax : +33 1 58044100

	Mobile +33 06 22156594 e-mail: farida.grid@zambongroup.com Common Drug Safety contact details: e-mail: vigiphar.zf@zambongroup.com
Germany	Andrea Klüting Phone: +49 89 2000203-60 Fax: +49 892000203-66 e-mail: andrea.klueting@i-dras.com Common Drug Safety contact details: Phone: +49 89 200020354 Fax: +49 892000203-66 e-mail: zambon.pv.germany@zambongroup.com
Italy	Tiziana Santagada Phone +39 02 66524 621 Fax +39 02 66524 038 Mobile +39 335 7803988 e-mail: tiziana.santagada@zambongroup.com Common Drug Safety contact details: Phone +39 02 66524 444 Fax +39 02 66524 038 e-mail: drugsafety@zambongroup.com
Spain	Antonio Esteras Serra Phone +34 93 5446408 Fax +34 93 5742166 Mobile +34 607738709

	e-mail: antonio.esteras@zambongroup.com Common Drug Safety contact details: e-mail: farmacovigilancia@zambongroup.com
United Kingdom	Monika Bend Phone: +44 (0)1243 859 018 e-mail: monika.bend@zambongroup.com Common Drug Safety contact details: Phone: +44 (0) 1243 859 005 e-mail: Profile.Drugsafety@zambongroup.com
Switzerland	Carlo Regazzoni Phone: +41 91 9604117 Fax: +41 91 9664351 Mobile: +41 79 5121175 e-mail: carlo.regazzoni@zambongroup.com Common Drug Safety contact details: e-mail: drugsafetych@zambongroup.com

11.3.2. Special situations

Any reports of Safinamide (Xadago®) including overdose, abuse, off-label use, misuse, medication error, occupational exposure and use during breastfeeding, as well as cases of suspected drug interaction and lack of efficacy associated to an ADR (irrespective of seriousness) should be reported by the Investigator to the Sponsor within 5 calendar days.

Any situation of overdose, abuse, off-label use, misuse, medication error, occupational exposure, lack of efficacy, suspected drug interaction or use of Safinamide (Xadago®) during breastfeeding with no association to an AE/ADR should only be reported in eCRF.

11.3.3. Follow-Up Reports / Additional Information

Insufficiently documented reports will be followed-up with the Investigator as necessary to obtain supplementary information for scientific evaluation. The Sponsor can request MediNeos assistance for seeking the Investigator about follow-up information.

For adverse events which relate to retinal disorders, a specific targeted questionnaire will be provided to the Investigator for collecting follow-up information. 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 MedDRA PTs.

11.3.4. ADRs related to any medicinal products, other than Xadago®

ADRs related to any medicinal product other than Xadago® (Safinamide) shall be notified by the Investigator to the competent authority 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.

11.4. Pregnancies

Patients must be instructed that pregnancy occurring during the study should be promptly reported to the Investigator.

In the event that a patient is found to be pregnant after inclusion in the study, regardless of whether an AE occurred, the Investigator will notify Zambon within 5 calendar days through the Pregnancy Report Form provided by Zambon, with follow-up information to be actively sought for the outcome of pregnancy.

The same reporting modalities apply to pregnancies occurring during the study but confirmed after its completion and in case the partner of a male study patient becomes pregnant at any time during the whole course of the study.

No data concerning the pregnancy will be collected in the eCRF set up for the study.
The information must be sent by e-mail or by FAX (where unable to send by e-mail) by filling in appropriate forms according to Zambon procedures to the following country-specific contact details:

Country	Pharmacovigilance contact details
Belgium	Claude Krygier Phone +32 2777 0202 Fax +32 2771 8570 Mobile +32 473720607 e-mail: claude.krygier@zambongroup.com Common Drug Safety contact details: e-mail: zambon.pv@zambongroup.com
France	Farida Grid Phone +33 01 58044120 Fax : +33 1 58044100 Mobile +33 06 22156594 e-mail: farida.grid@zambongroup.com Common Drug Safety contact details: e-mail: vigiphar.zf@zambongroup.com
Germany	Andrea Klüting Phone: +49 89 2000203-60 Fax: +49 892000203-66 e-mail: andrea.klueting@i-dras.com Common Drug Safety contact details: Phone: +49 89 200020354 Fax: +49 892000203-66 e-mail: zambon.pv.germany@zambongroup.com

Italy	Tiziana Santagada Phone +39 02 66524 621 Fax +39 02 66524 038 Mobile +39 335 7803988 e-mail: tiziana.santagada@zambongroup.com Common Drug Safety contact details: Phone +39 02 66524 444 Fax +39 02 66524 038 e-mail: drugsafety@zambongroup.com
Spain	Antonio Esteras Serra Phone +34 93 5446408 Fax +34 93 5742166 Mobile +34 607738709 e-mail: antonio.esteras@zambongroup.com Common Drug Safety contact details: e-mail: farmacovigilancia@zambongroup.com
United Kingdom	Monika Bend Phone: +44 (0)1243 859 018 e-mail: monika.bend@zambongroup.com Common Drug Safety contact details: Phone: +44 (0) 1243 859 005 e-mail: Profile.Drugsafety@zambongroup.com
Switzerland	Carlo Regazzoni

	Phone: +41 91 9604117 Fax: +41 91 9664351 Mobile: +41 79 5121175 e-mail: carlo.regazzoni@zambongroup.com Common Drug Safety contact details: e-mail: drugsafetych@zambongroup.com

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

12. Plans for disseminating and communicating study results

In agreement to applicable laws and regulations the final study report and/or progress reports, including interim reports of study results, if applicable and when required, will be submitted to the Competent Authorities (see GVP Module VIII. Section B.4.3).

The final study report, including the statistical and clinical evaluations, will be prepared and sent to Co-ordinating Investigator's, for agreement and signature.

At the end of the study, a summary of the final study report will be provided to all ECs/IRBs, to the Competent Authority of the EU Member State concerned and to Investigators.

Zambon is entitled to publish and/or present any results of this study at scientific meetings; Zambon furthermore reserves the right to use such data for industrial purposes.

Investigators will inform Zambon before using the results of the study for publication or presentation, and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites shall not be published separately without the previous consent of Zambon.

12.1. Operative management of Medical Writing Aspects

The results of this study may be published or presented at scientific meetings. If this is the case, the Investigator agrees to submit all manuscripts or abstracts to Zambon prior to submission. This allows the Sponsor, respectfully of the rights relating to the ownership of the data collected, to provide comments based on information from other studies that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, Zambon will generally support publication of multi-centre studies only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated.

The Investigator has to provide the Sponsor all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials, is the sole responsibility of the Sponsor.

Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Study Site Agreement, which has to be written consequently.

Zambon also adheres to any additional standards concerning authorship required by a specific journal or congress to which the publication is submitted. The responsible individuals at Zambon apply, at a minimum, the following criteria to determine who is named as an author on a publication:

- Substantial contributions to the concept and design, acquisition of data, or analysis and interpretation of data
- Drafting of the publication or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorship criteria and obligations apply equally to Zambon employees and non-employees. Each listed author must have participated in the work enough to take public responsibility for appropriate portions of the content.

Individuals contributing to the publication but not meeting authorship criteria may be appropriately acknowledged in the publication.

12.2. Ghostwriting and Guest/Ghost Authorship

Ghostwriting, guest authorship, and ghost authorship are strictly prohibited. The contribution of a writer, which, when performed under the direction of the author(s), is considered a form of specialized, technical assistance, is acknowledged in the earliest draft in which the writer is involved.

12.3. Determining Order of Authorship

Author order is determined by mutual agreement at the earliest possible time, with due consideration to overall contributions to the study, to the publication, or to scientific knowledge of the subject matter.

13. References

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Annex 1. List of stand-alone documents

Documents listed are maintened separately form the study protocol and provided on request.

Number	Document reference number	Date	Title
1	Annex 1	25 Sept 2015	Annex 1 _Draft list of participating sites

Annex 2. ENCePP checklist for study protocols

The ENCePP checklist is attached to this document.

Annex 3. Additional information

None.