16. APPENDICES

APPENDIX 16.1: STUDY INFORMATION

APPENDIX 16.1.1: PROTOCOL AND PROTOCOL AMENDMENTS

Title Page

Amendment 01 (13-July-2020)

Clinical Trial Title: A 12-WEEKS, MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EXPLORATORY, PILOT STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SAFINAMIDE 200 MG ONCE DAILY, AS ADD-ON THERAPY, IN PATIENTS WITH POSSIBLE OR PROBABLE PARKINSONIAN VARIANT OF MULTIPLE SYSTEM ATROPHY

Short Title: Safinamide for Multiple System Atrophy

Protocol Number: Z7219K01

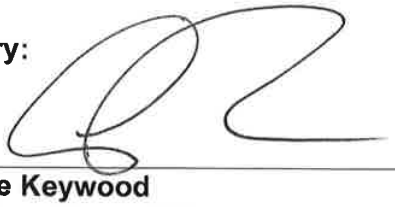
Regulatory Agency Identifier Number(s): EudraCT Number: 2018-004145-16

Sponsor Name: Zambon SpA
Legal Registered Address: Via Lillo del Duca 10 - 20091 Bresso, Milan, Italy

Approval Date: 13-July-2020

Sponsor Approvals:

Signatory:



13.7.20.

Charlotte Keywood
Global Head Open R&D

Date

Investigator Signatory:

I have read this Amendment and I agree to comply with the changes contained in the present Amendment.

Date

Name:

Title:

Affiliation:

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

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in this protocol amendment is to fix some inconsistencies of the original protocol raised from Italian Health Authority and/or Italian Coordinating Site and addressed in a first instance with a Protocol Administrative Letter with the willingness to consolidate everything in the first available protocol amendment. Furthermore some sentences have been rephrased in order to be more clear and details about measures taken during the COVID-19 outbreak have been added.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall design 8 Study assessments and procedures 8.2Efficacy assessments 9.4.2 Efficacy analyses	Original text: The change from baseline to week 12 in the goniometric measurement for "lateral" displacement Amended text: The change from baseline to week 12 in the goniometric measurement for "lateral" and "anterior" displacement	When taking goniometric measurements it's common practice to obtain data about both "lateral" and "anterior" displacement
1.1 Synopsis 4.1 Overall Design	Original text: Study population is patients diagnosed, less than two years ago, with possible or probable parkinsonian variant of Multiple System Atrophy who are on a stable treatment of levodopa Amended text: Study population is patients diagnosed, less than two years ago, with possible or probable parkinsonian variant of Multiple System Atrophy who are on a stable treatment of levodopa and/or dopamine agonist, anticholinergic and/or amantadine	Clarification in order to increase consistency with what is mentioned under the Exclusion Criteria #15
1.1 Synopsis 4.1 Overall Design	Original text: Trial participation will be up to a maximum duration of 14 weeks and will comprise a screening period (up to 2 weeks), a 2-week run in period during which subjects will receive 1 tablet (either 100 mg safinamide or matching placebo), followed by a 10-week period, during which study participants will take 2 tablets of study medication (200 mg safinamide or placebo) once daily, taken in the morning in addition to their morning levodopa dose Amended text: Trial participation will be up to a maximum duration of 14 weeks and will comprise a screening period (up to 2 weeks), a 2-week run in period during which subjects will receive 1 tablet (either 100 mg safinamide or matching placebo), followed by a 10-week period, during which study	Clarification in order to increase consistency with what is mentioned under the Exclusion Criteria #15

Section # and Name	Description of Change	Brief Rationale
	participants will take 2 tablets of study medication (200 mg safinamide or placebo) once daily, taken in the morning in addition to their morning levodopa dose (and/or the above mentioned allowed MSA treatments)	
1.3 Schedule of activities	Original text: *Not applicable* Amended text: - * added close to V3, V4, V5 and V6 - *= COVID-19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, sites have been allowed to perform these visits using phone call and/or video – consultation. Everything has been documented in the source data as per guidance distributed to the affected sites.	Reference to the measures taken during COVID-19 outbreak
Throughout	Original text: UDRS (first five body areas) Amended text: UDRS	The common practice is to complete the full questionnaire
1.3 Schedule of activities	Original text: To be evaluated at approximately the same time of day as at the baseline visit, and this should be at least 1 hour after the patient has taken their morning dose of safinamide and is in the optimal "ON" state, where possible. Amended text: To be evaluated at approximately the same time of day as at the baseline visit, and this should be at least 1 hour after the patient has taken their daily dose of safinamide and is in the optimal "ON" state, where possible.	This change avoid mistakes in the study drug administration which should be taken OD
2.3 Benefit/Risk assessment	Original text: The existing clinical data on safinamide derived from studies supports an overall, favorable benefit/risk profile. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of safinamide may be found in the Investigator's Brochure Amended text: Safinamide has been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of PD patients as add-on therapy to levodopa (alone or in combination with other antiparkinsonian drugs). At the current date, safinamide is on	As per Italian Health Authority request, the section has been modified adding a more detailed risk/assessment evaluation on the basis of the available safinamide data

Section # and Name	Description of Change	Brief Rationale
	the market in 13 European countries and the USA, Canada, Australia, Brazil and Colombia. There are extensive post marketing surveillance data in PD patients for the 50mg and 100 mg doses. With regards to the current trial in which a dose of 200 mg will be taken for 12 weeks, safety data are also derived from trials performed in over 3000 subjects, including 2019 with Parkinson's disease of whom 500 were treated for more than 2 years. For the 200 mg dose, safety data are available for 134 PD patients who had repeated doses of safinamide ≥150mg daily. Of these, long term safety and tolerability data of up to 2 years for safinamide doses ≥ 150 mg/day are available in 89 patients who took part in Study NW-1015/015/III/2003 and in the 69 who continued treatment in the double-blind, placebo-controlled, extension Study NW-1015/017/III/2003. Doses of ≥ 150 mg/day were generally well-tolerated and no safety concerns were observed. The tolerability was similar to the 50mg and 100 mg/day doses, although the proportion of patients experiencing severe TEAEs (approx. 10%) was somewhat higher in the 150 – 200 mg group. The proportion of patients discontinuing due to TEAEs and the number of SAEs was similar for all treatment groups. The most frequent treatment-emergent adverse events (TEAEs) reported in Studies 015 and 017 were in the CNS and GI systems and are consistent with those reported in the SmPC. All TEAEs resolved without sequelae. From the available clinical data, the safety and tolerability of the 200 mg dose in MSA patients is expected to be acceptable. Should patients not tolerate this dose, they may de-escalate to a lower dose or if they still do not tolerate the study medication, they can withdraw from the study. MSA is a severe neurodegenerative disease for which there are limitations in existing therapy. There is a scientific rationale to assess the clinical benefit of safinamide in MSA patients in this proof of concept study. The existing clinical data on safinamide derived from post marketing surveillance, and clinical studies support an overall, favorable benefit/risk profile. More detailed information	

Section # and Name	Description of Change	Brief Rationale
	about the known and expected benefits and risks as well as reasonably expected adverse events of safinamide may be found in the Investigator's Brochure.	
4.1 Overall Design	Original text: Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1) to study intervention and 40 evaluable participants for an estimated total of respectively 30 and 10 evaluable participants per intervention group Amended text: Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1) to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group	Correction of an inconsistency between this section and the same information across other sections of the protocol
5.1 Inclusion Criteria	Original text: Participants who are diagnosed (with MRI confirmation) with possible or probable parkinsonian variant of Multiple System Atrophy less than 2 years ago. Amended text: Participants who are diagnosed with possible or probable parkinsonian variant of Multiple System Atrophy less than 2 years ago (calendar years), with MRI consistent with the diagnosis of MSA and not suggesting an alternative explanation to the clinical diagnosis of MSA (ie it should not have lesions that would suggest an alternative explanation for the symptoms that have been diagnosed as MSA such as subcortical infarctions, neoplasms, etc.).	The text "(with MRI confirmation)" was leading to misunderstandings since MSA patients might have "normal" MRI; the intention is to use MRI to exclude alternative explanation for the symptoms that have been diagnosed as MSA.
6.2 Preparation/Handling/Storage/ Accountability	Original text: 4.Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual. Amended text: ~~4.Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual~~. Original text: *Not applicable* Amended text: COVID-19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, two measures have been adopted where applicable: - IMP has been shipped direct to patient's home through sites' Pharmacy courier	- A Study Reference Manual has not been finalized for the study - Reference to the measures taken during COVID-19 outbreak

Section # and Name	Description of Change	Brief Rationale
	- Care giver/family member has been allowed to pick up the IMP at site and bring it to patient. Everything has been documented in the source data as per guidance distributed to the affected sites.	
8 Study Assessments and Procedures	Original text: *Not applicable* Amended text: COVID-19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, sites have been allowed: - to perform these visits using phone call and/or video – consultation - to manage study medication dispensation as described under section 6.2 Everything has been documented in the source data as per guidance distributed to the affected sites. Original text: Visit 6: End of Treatment Visit Following completion of 12 weeks (Day 84) of treatment or in the event of early termination, the following EOT assessments and procedures should be performed. Amended text: Visit 6: End of Treatment Visit Following completion of 12 weeks (Day 84) of treatment or in the event of early termination, the following EOT assessments and procedures should be performed. In case of EOT, the visit should be performed in the first day available.	- Reference to the measures taken during COVID-19 outbreak - Clarification of V6 timelines in case of End of Treatment
10.1.2. Financial Disclosure	Original text: Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study Amended text: ~~Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit~~	Not applicable for the study

Section # and Name	Description of Change	Brief Rationale
	~~complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study~~	

Title Page

Protocol Title:

A 12-WEEKS, MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EXPLORATORY, PILOT STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SAFINAMIDE 200 MG ONCE DAILY, AS ADD-ON THERAPY, IN PATIENTS WITH POSSIBLE OR PROBABLE PARKINSONIAN VARIANT OF MULTIPLE SYSTEM ATROPHY

Protocol Number: **Z7219K01**
Amendment Number: **01**

Compound Number: **Safinamide**

Short Title:

Safinamide for Multiple System Atrophy

Sponsor Name: **Zambon SpA**

Legal Registered Address: **Via Lillo del Duca 10**

20091 Bresso, Milan, Italy

Regulatory Agency Identifying Number(s):

EudraCT Number: 2018-004145-16

Approval Date: July 13, 2020

Sponsor Signatory:

13.7.2020

Charlotte Keywood
Global Head Open R&D

Date

Medical Monitor Name and Contact Information will be provided separately.

Investigator Signature Page

I have read this protocol.

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

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

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

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

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

Investigator Signatory:

_____ _____

Name: Date:

Title:

Affiliation:

_____

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 01	13 July 2020
Original Protocol	21 Feb 2019

Amendment 01, 13 July 2020:
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in this protocol amendment is to fix some inconsistencies of the original protocol raised from Italian Health Authority and/or Italian Coordinating Site and addressed in a first instance with a Protocol Administrative Letter with the willingness to consolidate everything in the first available protocol amendment. Furthermore some sentences have been rephrased in order to be more clear and details about measures taken during the COVID-19 outbreak have been added.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall design 8 Study assessments and procedures 8.2 Efficacy assessments 9.4.2 Efficacy analyses	"anterior" has been added	When taking goniometric measurements it's common practice to obtain data about both "lateral" and "anterior" displacement
1.1 Synopsis 4.1 Overall Design	"and/or dopamine agonist, anticholinergic and/or amantadine" has been added	Clarification in order to increase consistency with what is mentioned under the Exclusion Criteria #15
1.1 Synopsis 4.1 Overall Design	(and/or the above mentioned allowed MSA treatments)	Clarification in order to increase consistency with what is mentioned under the Exclusion Criteria #15

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	* added close to some visits and text under the table	Reference to the measures taken during COVID-19 outbreak
Throughout	Deletion of "five body areas" close to UDRS mention	The common practice is to complete the full questionnaire
1.3 Schedule of activities	"morning" dose of safinamide has been changed in "daily" dose of safinamide	This change avoid mistakes in the study drug administration which should be taken OD
2.3 Benefit/Risk assessment	Extended text added	As per Italian Health Authority request, the section has been modified adding a more detailed risk/assessment evaluation on the basis of the available safinamide data
4.1 Overall Design	Correction of the number of patients assigned to the two intervention groups	Correction of an inconsistency between this section and the same information across other sections of the protocol
5.1 Inclusion Criteria	Better explanation of the MRI requirement	The text "(with MRI confirmation)" was leading to misunderstandings since MSA patients might have "normal" MRI; the intention is to use MRI to exclude alternative explanation for the symptoms that have been diagnosed as MSA.
6.2 Preparation/Handling/Storage/Accountability	- Bullet point #4 has been removed - COVID-19 outbreak text has been added	- A Study Reference Manual has not been finalized for the study - Reference to the measures taken during COVID-19 outbreak
8 Study Assessments and Procedures	- COVID-19 outbreak text has been added - Timelines for Visit 6 in case of End of Treatment has been added	- Reference to the measures taken during COVID-19 outbreak - Clarification of V6 timelines in case of End of Treatment

Section # and Name	Description of Change	Brief Rationale
10.1.2 Financial Disclosure	Paragraph removed	Not applicable for this study

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A 12-weeks, multicentre, randomized, double-blind, placebo-controlled, exploratory, pilot study to evaluate the safety and efficacy of safinamide 200 mg once daily, as add-on therapy, in patients with possible or probable parkinsonian variant of multiple system atrophy.

Short Title:

Safinamide for Multiple System Atrophy

Rationale:

To establish the safety and tolerability of 200 mg of safinamide and to explore whether this dose may offer benefits to patients with the parkinsonian variant of MSA.

Objectives and Endpoints

Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of safinamide, 200 mg od, compared with placebo	• The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of TEAEs and SAEs. • Changes in physical and neurological examination findings. • Changes in vital sign (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities. • Changes in 12-lead ECG parameter measures, including occurrence of abnormalities. • Changes in clinical chemistry and hematology values, including shifts from Baseline and occurrence of abnormalities. • Number of withdrawals (and reason if given).

Efficacy	
To evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on motor function and/or quality of life	• The change from baseline to week 12 in the goniometric measurement for "lateral" and "anterior" displacement • Change from baseline at week 12 in Unified MSA Rating Scale, MSA Health-Related Quality of Life (MSA-QoL) scale, Montreal Cognitive Assessment (MoCA) scale, Unified Dystonia Rating Scale (UDRS).

Overall Design:

The study is a randomized placebo controlled double blind study, with two parallel arms, in which participants will be assigned in a 2:1 ratio to receive either safinamide or placebo. Study population is patients diagnosed, less than two years ago, with possible or probable parkinsonian variant of Multiple System Atrophy who are on a stable treatment of levodopa and/or dopamine agonist, anticholinergic and/or amantadine.

Outcome will be assessed after 12 weeks of treatment, when progression is unlikely to be a confounder of change. No Independent Data Monitoring Committee is foreseen.

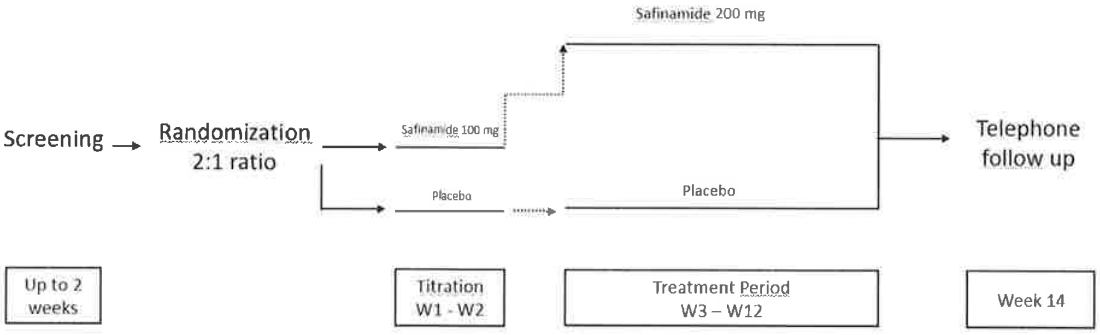
Number of Participants:

Approximately 56 participants will be screened to achieve 48 randomly assigned to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group (See section 9.2)

Intervention Groups and Duration:

Trial participation will be up to a maximum duration of 14 weeks and will comprise a screening period (up to 2 weeks), a 2-week run in period during which subjects will receive 1 tablet (either 100 mg safinamide or matching placebo), followed by a 10-week period, during which study participants will take 2 tablets of study medication (200 mg safinamide or placebo) once daily, taken in the morning in addition to their morning levodopa dose (and/or the above mentioned allowed MSA treatments). A telephone follow-up call will be performed 2 weeks after the end of treatment.

1.2. Schema



1.3. Schedule of Activities (SoA)

Study Period	**Screening period**	**Baseline**	**Interim Visits** Weeks 2 - 8			**EOT / ET** Week 12	**Telephone follow-up** Week 14	**Notes**
Day	**-14 to -0**	**1**	**14 ±3**	**28 ±3**	**56 ±3**	**84 ±3**	**98 ±3**	In the event of early termination (ET) participants should complete the End of Treatment (EoT) assessments
Visit	**1**	**2**	**3***	**4***	**5***	**6***	**7**	
Informed consent	X							
Eligibility criteria	X	X						
Randomization		X						
Demographics	X							
Medical history/diagnosis	X							
Prior and concomitant medications	X	X	X	X	X	X	X	Details of excluded and permitted concomitant treatments are presented in Section 6.5.
Vital signs	X	X	X	X	X	X		
12-lead ECG	X					X		
Physical & neurological examination	X					X		
UMSARS		X		X	X	X		
MSA-QoL		X		X	X	X		
MoCA	X					X		
UDRS		X		X	X	X		To be evaluated at approximately the same time of day as at the baseline visit, and this should be at least 1 hour after the patient has taken their daily dose of safinamide and is in the optimal "ON" state, where possible.
Goniometric assessment		X		X	X	X		

Study Period	**Screening period**	**Baseline**	**Interim Visits** Weeks 2 - 8			**EOT / ET** Week 12	**Telephone follow-up** Week 14	**Notes**
Day	**-14 to -0**	**1**	**14 ±3**	**28 ±3**	**56 ±3**	**84 ±3**	**98 ±3**	In the event of early termination (ET) participants should complete the End of Treatment (EoT) assessments
Visit	**1**	**2**	**3***	**4***	**5***	**6***	**7**	
Haematology/Clinical chemistry	X					X		
Pregnancy test (urine)		X				X		Only for WOCBP.
Adverse events		X	X	X	X	X	X	
Dispense randomized medication		X	X	X	X			The first dose of study medication will be administered at the study centre.
Drug accountability			X	X	X	X		

*= COVID-19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, sites have been allowed to perform these visits using phone call and/or video – consultation.

Everything has been documented in the source data as per guidance distributed to the affected sites.

2. Introduction

Safinamide (licensed with the commercial name Xadago) is approved as add-on therapy to levodopa for Parkinson's disease patients experiencing fluctuations. Safinamide has both dopaminergic and non-dopaminergic activities. It is a potent, selective and reversible monoamine oxidase type B (MAO-B) inhibitor, a mechanism associated with enhancement of dopaminergic transmission in the brain. Safinamide is also a state-dependent inhibitor of voltage-gated sodium channels, and inhibits calcium channels, dopamine transporters, and some other targets at higher concentrations in vitro. Safinamide has been shown to inhibit the stimulated release of glutamate (in vitro and in vivo studies) without affecting the basal glutamate levels.

These molecular mechanisms act in animal models of PD to increase brain dopamine, extend levodopa induced ON-time (dopaminergic actions) and reduce the severity of levodopa induced dyskinesia (non-dopaminergic action).

In addition, safinamide's state dependent sodium channel inhibiting activity has been shown to modulate microglia function (Black JA, 2009). Respectively, safinamide has shown neuroprotection in models of Parkinson's disease and multiple sclerosis that has been strongly associated with reduction of microglial activation (Morsali D, 2013).

Safinamide may also have neuroprotective effects. (Borgohain R, 2013) Safinamide inhibits α-1 receptors in the endoplasmic reticulum (Fariello RG, 1998). These receptors are believed to be multifunctional regulatory proteins with a role in CNS development, plasticity and neurodegeneration. Safinamide has been shown to completely prevent forebrain dopamine depletion and neuronal cell death in the gerbil substantia nigra when administered prior to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. (Vaghi F, 1997) In animal epilepsy models, safinamide was shown to counteract neuronal death that had been induced by excitotoxin.(Maj R, 1998) Possible mechanisms of action for safinamide's potential neuroprotective properties are MAO-B inhibition (Kupsch A, 2001) and reduction in glutamate release.(Caccia C, 2006, 2008)

Multiple System Atrophy (MSA) is a progressive and fatal neurodegenerative disease. MSA is characterized pathologically by glial cytoplasmic inclusions (GCIs) that consist of ectopic aggregates of hyperphosphorylated and insoluble filamentous α-synuclein in oligodendrocytes (Tu PH, 1998) and selective neurodegeneration in the striatonigral and olivopontocerebellar regions. Microglial activation parallels the neurodegeneration and GCI pathology in MSA (Ishizawa K, 2004).

Clinically, the cardinal features include autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs in any combination. Two major motor presentations can be distinguished clinically. Parkinsonian features predominate in 80% of patients (MSA-P subtype), whereas cerebellar ataxia predominates in the remaining 20% of patients (MSA-C subtype). MSA is a progressive disorder with early disability and shortened life expectancy.

No cures are available and treatment is symptomatic. Levodopa is used to manage the motor symptoms, but patients become rapidly irresponsive to this drug due to widespread glial and neuronal cell degeneration and shrinkage of some brain areas such as cerebellum, basal ganglia and brainstem with eventual death within 9-10 years after diagnosis. Pain is a common non-motor symptom both in PD and MSA (Kass-Iliyya, 2015).

2.1. Study Rationale

Post hoc analysis of data from previous safinamide studies in PD patients suggested effects on nonmotor symptoms such as mood and pain (Cattaneo et al, 2017 & 2018).

Given the pathophysiological overlap between PD and MSA the study aims to establish the safety and tolerability of a higher dose (200 mg) of safinamide, and whether this may offer benefit to patients with the parkinsonian variant of MSA.

2.2. Background

Multiple clinical trials of potential therapies, including riluzole, lithium, growth hormone, minocycline and rifampin (also called rifampicin) have shown no benefit over a placebo. With regard to the same class of compounds, Poewe and colleagues conducted a 48-week randomised, controlled, multicentre trial at 40 academic sites across 12 countries evaluating the potential disease modifying and symptomatic effects of 1 mg/day of another MAO-B inhibitor, rasagiline (n=84) versus placebo (n=90) in 174 patients with the parkinsonian subtype of multiple system atrophy. (Poewe W, 2015)

Eligible patients aged 30 years or older had <3 years from the time of documented diagnosis of multiple system atrophy to enrolment and, on the basis of investigators' clinical judgment, an anticipated survival of at least 3 years. Main exclusion criteria were severe orthostatic symptoms, speech/swallowing impairment, impairment in ambulation or falling more frequently than once per week.

The primary outcome was change from baseline to 48 weeks in the Unified Multiple System Atrophy Rating Scale (UMSARS) score (sum of parts I and II), and several secondary outcome measures were assessed, including putaminal mean diffusivity on MRI in a subset of patients.

The study did not show that this regimen was effective in the slowing of disease progression or improvement of symptoms in this population of patients with the parkinsonian variant of multiple system atrophy. 68 (81%) patients in the rasagiline group and 67 (74%) patients in the placebo group reported adverse events, and serious adverse events in 29 (35%) versus 23 (26%) patients. The most common adverse events in the rasagiline group were dizziness (n=10 [12%]), peripheral oedema (n=9 [11%]), urinary tract infections (n=9 [11%]), and orthostatic hypotension (n=8 [10%]).

Failure of the drug to show any effect could be due to several reasons, including the dose tested might have been too low compared to that used in an MSA preclinical model study, or that the treatment should have started earlier, i.e. within 2 years of diagnosis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of safinamide is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

Safinamide has been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of PD patients as add-on therapy to levodopa (alone or in combination with other antiparkinsonian drugs). At the current date, safinamide is on the market in 13 European countries and the USA, Canada, Australia, Brazil and Colombia. There are extensive post marketing surveillance data in PD patients for the 50mg and 100 mg doses.

With regards to the current trial in which a dose of 200 mg will be taken for 12 weeks, safety data are also derived from trials performed in over 3000 subjects, including 2019 with Parkinson's disease of whom 500 were treated for more than 2 years.

For the 200 mg dose, safety data are available for 134 PD patients who had repeated doses of safinamide ≥150mg daily. Of these, long term safety and tolerability data of up to 2 years for safinamide doses ≥ 150 mg/day are available in 89 patients who took part in Study NW-1015/015/III/2003 and in the 69 who continued treatment in the double-blind, placebo-controlled, extension Study NW-1015/017/III/2003.

Doses of ≥ 150 mg/day were generally well- tolerated and no safety concerns were observed. The tolerability was similar to the 50mg and 100 mg/day doses, although the proportion of patients experiencing severe TEAEs (approx. 10%) was somewhat higher in the 150 – 200 mg group. The proportion of patients discontinuing due to TEAEs and the number of SAEs was similar for all treatment groups. The most frequent treatment-emergent adverse events (TEAEs) reported in Studies 015 and 017 were in the CNS and GI systems and are consistent with those reported in the SmPC. All TEAEs resolved without sequelae.

From the available clinical data, the safety and tolerability of the 200 mg dose in MSA patients is expected to be acceptable. Should patients not tolerate this dose, they may de-escalate to a lower dose or if they still do not tolerate the study medication, they can withdraw from the study.

MSA is a severe neurodegenerative disease for which there are limitations in existing therapy. There is a scientific rationale to assess the clinical benefit of safinamide in MSA patients in this proof of concept study. The existing clinical data on safinamide derived from post marketing surveillance, and clinical studies support an overall, favorable benefit/risk profile. More detailed information about the known and expected benefits and risks as well as reasonably expected adverse events of safinamide may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of safinamide, 200 mg od, compared with placebo	• The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of TEAEs and SAEs. • Changes in physical and neurological examination findings. • Changes in vital sign (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities. • Changes in 12-lead ECG parameter measures, including occurrence of abnormalities. • Changes in clinical chemistry and hematology values, including shifts from Baseline and occurrence of abnormalities. • Number of withdrawals (and reason if given).
Efficacy	
• To evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on motor function and/or quality of life	• The change from baseline to week 12 in the goniometric measurement for "lateral" and "anterior" displacement • Change from baseline at week 12 in Unified MSA Rating Scale, MSA Health-Related Quality of Life (MSA-QoL) scale, Montreal Cognitive Assessment (MoCA) scale, Unified Dystonia Rating Scale (UDRS).

4. Study Design

4.1. Overall Design

The overall design is a parallel group, placebo controlled, double blind study.

The target population are participants diagnosed, less than two years ago, with possible or probable parkinsonian variant of Multiple System Atrophy (Gilman, 2008) who are on stable doses of levodopa and/or dopamine agonist, anticholinergic and/or amantadine.

Trial participation will be up to a maximum duration of 14 weeks and will comprise a screening period (up to 2 weeks), a run in period of 2 weeks (week 1 – week 2) during which study participants will receive 1 tablet (either 100 mg safinamide or matching placebo) followed by a treatment period (week3 – week 12), during which they will receive two tablets (200 mg safinamide or matching placebo) once daily, taken in the morning in addition to their daily levodopa dose (and/or the above mentioned allowed MSA treatments). In the event the study participant does not tolerate 2 tablets, they can drop down to 1 tablet per day and remain in the study at that dose level.

A telephone follow-up call will be performed 2 weeks after the end of treatment. The treatment duration is sufficiently long to evaluate the safety and tolerability of safinamide 200 mg od and potentially show symptomatic efficacy. Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1) to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group

The safety parameters will be assessed monitoring TEAEs and SAEs and changes (baseline – week 12) in physical and neurological examination findings, vital signs, 12-lead ECG and clinical chemistry and hematology values.

The efficacy parameters will be assessed looking at goniometric measurement for "lateral" and "anterior" displacement (Tinazzi, 2015) and assessing the changes (baseline – week 12) in the UMSARS (Wenning, 2004), the MSA-QoL (Schrag, 2007), the MoCA and the UDRS.

4.2. Scientific Rationale for Study Design

This study is a randomized, double blind, trial to provide scientific rigor to minimize the chance of bias in the results. The trial duration is sufficiently long to establish safety, tolerability, and possible symptomatic benefits, yet short enough for disease progression not to be a confounding factor.

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

The sponsor believes that placebo can be safely and ethically administered in this study based on the following rationale:

- All patients, whether in the active or placebo group, will continue using MSA treatment including levodopa; the investigational product will be added to the patient's standard therapy.

- Prior and concomitant medications which are considered necessary for the safety and well-being of the subject are permitted during the study at the discretion of the investigator provided the medication is not listed within the study exclusion criteria or in the excluded medication. If a subject is treated with a prohibited medication, a decision will be taken on whether or not the subject should continue in the study.

The treatment duration is sufficiently long to potentially show symptomatic efficacy, yet short enough that disease progression is unlikely to be a confounder.

4.3. Justification for Dose

The dose of 200 mg/day was selected based on the results of the previous studies, indicating that potentially a higher than the minimal effect dose for patients with PD would be needed.

The efficacy and safety of safinamide has been evaluated in clinical studies as add-on therapy to dopamine agonists (DA) in early-stage PD (Di Paolo T, 2011; Colombo E, 2006) and as add-on to LD in mid- to late-stage PD (Neliat G, 2008; Izzo E, 2005; Jolas T, 2009), and in PD patients at doses between 150 to 200 mg daily for 18 months (data on file).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 30 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are diagnosed with possible or probable parkinsonian variant of Multiple System Atrophy less than 2 years ago (calendar years), with MRI consistent with the diagnosis of MSA and not suggesting an alternative explanation to the clinical diagnosis of MSA (ie it should not have lesions that would suggest an alternative explanation for the symptoms that have been diagnosed as MSA such as subcortical infarctions, neoplasms, etc.)
3. Participants with an anticipated survival of at least 3 years in the opinion of the investigator.

Sex

4. Male or female

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

    i. Not a woman of childbearing potential (WOCBP)

    OR

    ii. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 30 days after the last dose of study intervention.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. History of neurosurgical procedure, including stereotactic surgery.
2. History of Deep Brain Stimulation (DBS)
3. History of bipolar disorder, severe depression, schizophrenia or other psychotic disorder.
4. History of drug and/or alcohol abuse within 12 months prior to screening as defined by the current edition of the Diagnostic and Statistical Manual of Mental Disorders
5. History of dementia (DSM-V criteria)
6. Ophthalmologic history including any of the following conditions: albinism, uveitis, retinitis pigmentosa, retinal degeneration, active retinopathy, severe progressive diabetic retinopathy, inherited retinopathy or family history of hereditary retinal disease.
7. Active hepatitis B or C
8. History of human immunodeficiency virus (HIV) infection
9. Subjects not able to swallow oral medications
10. Subjects with severe orthostatic symptoms
11. Impaired ambulation, i.e. falling more than once per week, bedridden patients or confined to a wheelchair during the whole day.
12. Subjects with active malignant neoplasms.
13. Movement disorders other than MSA (e.g. Parkinson Disease, dementia with Lewy bodies, essential tremor, progressive supranuclear palsy, pharmacological or post-encephalic parkinsonism).
14. Any clinically significant or unstable medical or surgical condition that, in the opinion of the investigator, might preclude safe completion of the study or might affect the results of the study.

Prior/Concomitant Therapy

15. Not on a stable regime, for at least 4 weeks prior to the randomization (baseline visit), of
    a. oral levodopa (including controlled release [CR], immediate release [IR] or a combination of CR/IR), with or without benserazide/carbidopa, with or without addition of a catechol O-methyltransferase (COMT) inhibitor or
    b. dopamine agonist, anticholinergic and/or amantadine.

Prior/Concurrent Clinical Study Experience

16. Patients should not have received treatment with monoamine oxidase inhibitors in the 2 weeks prior to the randomization visit, nor treatment with levodopa infusion, pethidine, opiates, opioids, fluoxetine, fluvoxamine in the 4 weeks prior to the randomization visit.
17. Patients should not have received treatment with an oral or depot neuroleptic within 12 weeks prior to the randomization visit.

18. Use of any investigational drug within 30 days prior to screening or 5 half-lives, whichever is the longest.

Diagnostic assessments

19. Montreal Cognitive Assessment (MoCA) ≤ 20
20. Laboratory assessments showing moderate or severe hepatic impairment (2x ULN)

Other Exclusions

21. Allergy/sensitivity or contraindications to the investigational medicinal products (IMPs) or their excipients, anticonvulsants, levodopa or other anti-parkinsonian drugs.
22. Any clinically significant condition which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for patients while in the study.

5.3. Lifestyle Considerations

No restriction regarding meals or activity. Safinamide does not affect L-type calcium channels (no effects in blood pressure and heart rate) and can be given without food restrictions related to tyramine.

5.4. Screen Failures

Potential subjects will be screened prior to entry into the study. Laboratory assessments may be repeated once for any laboratory parameter that falls outside the relevant exclusion criteria provided they are completed and reviewed within the 2-week screening period.

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

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

6. Study Intervention

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

6.1. Study Intervention(s) Administered

Study Intervention Name:	Active Safinamide methanesulfonate	Placebo
Dosage formulation:	Orange to copper, round, biconcave film-coated tablets	
Unit dose strength(s)/Dosage level(s):	100 mg (free base)	Only excipients: microcrystalline cellulose, crospovidone, colloidal silicone dioxide, magnesium stearate, and for the coating: purified water, hypromellose and polyethyleneglycole. Candurin® pigments are included for color modification.
Route of Administration	Oral	
Dosing instructions:	Once daily along with first levodopa dose of the day	
Packaging and Labeling	Study Intervention will be provided in PVC/PVDC60/Al blisters. Sufficient blisters of 10 tablets will be paced in cases, sufficient for each visit interval. Each case with blisters will be labeled as required per country requirement.	
Manufacturer	Catalent, Schorndorf, Germany in alternative Zambon Spa, Vicenza, Italy	Zambon Spa, Vicenza, Italy

Primary packaging	Zambon Spa, Vicenza, Italy in alternative Catalent, Schorndorf, Germany	Zambon Spa, Vicenza, Italy in alternative Catalent, Schorndorf, Germany
Secondary packaging & labeling	Almac, Craigavon, United Kingdom	Almac, Craigavon, United Kingdom

6.2. Preparation/Handling/Storage/Accountability

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

COVID-19 outbreak: in order to ensure the continuity of the study, limiting the subjects' exposure to infection and overcoming travel restriction imposed by governments, two measures have been adopted where applicable:

- IMP has been shipped direct to patient's home through sites' Pharmacy courier
- Care giver/family member has been allowed to pick up the IMP at site and bring it to patient

Everything has been documented in the source data as per guidance distributed to the affected sites.

6.3. Measures to Minimize Bias: Randomization and Blinding

IVRS/IWRS	*All participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site.* *Study intervention will be dispensed at the study visits summarized in SoA.* *Returned study intervention should not be re-dispensed to the participants.*
Blind Break (IVRS/IWRS)	*The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.*

6.4. Study Intervention Compliance

Compliance will be assessed based on drug accountability.

6.5. Concomitant Therapy

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

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

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

6.5.1. Excluded medication

Use of other monoamine oxidase inhibitors, including moclobemide, treatment with levodopa infusion, pethidine, opiates, opioids, fluoxetine, fluvoxamine are not permitted during the course of the study.

Use of serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics or tetracyclics, selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine or fluvoxamine is permitted, providing the dose is kept as low as possible and remains stable throughout the study.

Sympathomimetics, dextromethorphan, nasal and oral decongestants or cold remedies (e.g. ephedrine, pseudoephedrine, phenylephrine or phenylpropanolamine) are permitted if used for treating cough but must be used with caution.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.6. Dose Modification

In case, due to an AE, a dose reduction is necessary, the study participant can drop down from two (2) to one (1) tablet per day. Dose re-escalation is allowed once the AE is resolved.

6.7. Intervention after the End of the Study

No planned extension or continued access.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

If patient does not tolerate the dose, they may drop down to 1 tablet per day, but if that is not tolerated patient should be withdrawn.

7.1.2. Rechallenge

Investigator judgment should be applied to temporarily reduce dose and then rechallenge.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- The following assessments and procedures will be performed as detailed in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Visit 1: Screening Visit

After providing written informed consent to participate in the study, patients will enter a screening period of up to 2 weeks. During the screening period, patients will undergo all the evaluations necessary to establish their eligibility for the study and be assigned a unique screening number.

- Obtain written informed consent.
- Log in to IWRS for assignment of unique screening number; numbers will be allocated in sequence within each study center.
- Check of inclusion and exclusion criteria.
- Record demographic data, including age, sex, ethnicity, smoking and alcohol use.
- Record medical history and MSA diagnosis, including date (at least one MRI evidence).
- Perform physical examination including height and body weight.
- Perform neurological examination.
- Measure vital signs: pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position.
- Obtain 12-lead ECG in the supine position.

Obtain blood sample for clinical laboratory assessments (Appendix 2).

- Record prior medications, concomitant medications and therapies.
- Completion of MoCA

Please bear in mind when scheduling the next visit that UMSARS, MSA-QoL and UDRS evaluations should take place at approximately the same time of day at the baseline and subsequent visits, where possible.

Visit 2: Baseline Visit

At baseline (Day 1, Visit 2), eligible patients will enter the treatment period (2 titration weeks) and will be randomized to receive either safinamide or matching placebo, orally od in a 2:1 ratio.

- Verify that participant meets the eligibility criteria, including the laboratory assessments & urine pregnancy test for WOCBP.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of scales by rater/study participant:
  - UMSARS
  - MSA-QoL
  - UDRS
- Recording of prior medications, concomitant medications and therapies.
- Goniometric assessment for "lateral" and "anterior" displacement
- Recording of AEs.
- Randomization to treatment group.
- Following completion of the relevant assessments and procedures, patients will take their first dose of study intervention at the study center (safinamide 100mg or matching placebo)
- Dispense study medication for the next 14 days.

Study medication can be taken with or without food.

The dose of the concomitant anti-Parkinson drugs and of the treatments of orthostatic hypotension must be kept unchanged from the baseline to the end of the study (week 12 or early discontinuation).

Remind study participant not to take their dose on the morning of their Visit 3 appointment.

Visit 3: End of Titration Visit

At the end of titration period (Day 14, Visit 3), the following assessments should be done:

- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Perform drug accountability.
- Dispense study medication (safinamide 200mg or matching placebo) and take first dose under supervision in clinic.

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

- to perform these visits using phone call and/or video – consultation
- to manage study medication dispensation as described under section 6.2

Everything has been documented in the source data as per guidance distributed to the affected sites.

Visits 4 and 5: Interim Visits

At the interim visits (Day 28, Visit 4 & Day 56, Visit 5) the following assessments should be done.

- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of scales by rater/study participant:
  - UMSARS
  - MSA-QoL
  - UDRS
- Recording of concomitant medications and therapies.
- Goniometric assessment for "lateral" and "anterior" displacement
- Recording of AEs.
- Perform drug accountability.
- Dispense study medication.

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

- to perform these visits using phone call and/or video – consultation
- to manage study medication dispensation as described under section 6.2
- to take Vital Sign using patient's instruments

Everything has been documented in the source data as per guidance distributed to the affected sites.

Visit 6: End of Treatment Visit

Following completion of 12 weeks (Day 84) of treatment or in the event of early termination, the following EOT assessments and procedures should be performed.

In case of EOT, the visit should be performed in the first day available.

- Physical examination including body weight.

- Neurological examination.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- 12-lead ECG in the supine position.
- Completion of scales by rater/participant:
  - UMSARS
  - MSA-QoL
  - MoCA
  - UDRS
- Blood sampling for clinical laboratory assessments (hematology and clinical chemistry).
- Urine sampling for urine (dipstick) pregnancy test for women (only for WOCBP).
- Record concomitant medications and therapies.
- Goniometric assessment for "lateral" and "anterior" displacement
- Record AEs.
- Perform drug accountability.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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

- to perform these visits using phone call and/or video – consultation
- to manage study medication return at site through a care-giver/family member
- to take Vital Sign using patient's instruments

Everything has been documented in the source data as per guidance distributed to the affected sites.

Visit 7: Telephone Follow-up

After 2 weeks from the End of Treatment, a telephone follow-up with patient should be performed, questioning about:

- Concomitant medications and therapies
- AEs

8.1. Safety Assessments

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

8.1.1. Physical Examinations

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

8.1.2. Vital Signs

- Vital signs (to be taken before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed in the supine with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.1.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).
- ECGs will be reviewed locally, for safety findings, which should be documented by the Investigator. Paper ECGs will remain at site (as source documents).
- Results are to be documented in the eCRF as normal, or abnormal and whether clinically significant.

8.1.4. Clinical Safety Laboratory Assessments

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

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.1.5. Suicidal Risk Monitoring

Not done.

8.2. Efficacy Assessments

Goniometric measurement of "lateral" and "anterior" displacement is determined using a wall goniometer and expressing the value in degrees.

Site personnel who are to be involved in performing the efficacy assessments, UMSARS, the MSA-QoL, the MoCA, the UDRS must be experienced in the use of the various scales and questionnaires.

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

Wherever possible the MSA QoL should be completed by the participant. However, in the case of the participant's incapacity, the participant's caregiver may help complete it based on information reported by the participant.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies in female will be collected after the start of study intervention and until 1 month after the last dose of study drug

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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

Not applicable

8.4. Treatment of Overdose

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

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

In the event of an overdose, the Investigator should:

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

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

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Not applicable

9. Statistical Considerations

9.1. Statistical Hypotheses

Safety data will be presented descriptively, thus no formal hypothesis for safety will be tested.

Efficacy endpoints will be tested with hypothesis of the form:

H0: $\mu_{Test} = \mu_{Placebo}$

H1: $\mu_{Test} \neq \mu_{Placebo}$ for continuous variables

H0: $\pi_{Test} = \pi_{Placebo}$

H1: $\pi_{Test} \neq \pi_{Placebo}$ for categorical variables

where μ is the mean in the population and π is the proportion in the population

9.2. Sample Size Determination

As this is a pilot study, no formal sample size has been calculated.

The sample size was selected based on previous studies in this population and the safety profile of salfinamide in the marketed indication of Parkinson's Disease. The current study enrolls 26 active vs 14 placebo. While there are few recent efficacy studies of symptomatic therapy in MSA, there is a more recent study of the efficacy of rasagiline (Poewe, W., et al. (2015) that randomized 84 subjects to rasagiline and 90 to placebo. While this study failed to find a therapeutic effect of rasagiline, it demonstrated that this sample size would have been adequate to detect a clinically relevant change in symptoms. A study of that size was deemed too large as an initial safety study.

Previous studies of salfinamide in Parkinson's Disease showed Adverse Event rates in treated groups to be less than 10% in excess of placebo (Borgohain, R, et al. 2014). In that occasion, it was deemed reasonable to perform a trial with approximately 56 participants - randomized at a 2:1 ratio active : placebo - to achieve 48 randomly assigned to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group - and it was judged to be sufficient to provide an estimate as to whether AEs are likely to be within this range in the MSA patient population at this dose.

9.3. Populations for Analyses

9.3.1. Enrolled Population

The Enrolled Population will include all participants who sign the ICF.

9.3.2. Evaluable Population

The Evaluable Population will include all randomized participants. This population will be used for all efficacy variables.

9.3.3. Safety Population

The Safety Population will include all randomized participants who take at least one dose of study intervention. This population will be used to summarize all safety data; participants will be analyzed according to the intervention they actually received.

9.3.4. Per Protocol Population

The Per Protocol Population will include all randomized participants who do not have any entry criteria violations or protocol deviations that could significantly impact the assessment or interpretation of efficacy data. Participant data will be reviewed by the clinical team to identify exclusions from the Per Protocol Population. The list of participants to be excluded from the Per Protocol Population will be finalized prior to database unblinding. This population will be used for the analysis of the efficacy variables.

9.4. Statistical Analyses

All statistical summaries will be descriptive in nature. All results will be presented separately for each of the study intervention groups. All analyses, summaries and listings will be performed using SAS version 9.4 or later.

All continuous variables will be summarized by presenting the number of participants, mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be presented as frequencies and percentages.

A separate Statistical Analysis Plan (SAP) will be prepared to provide additional details on the definitions of the safety and efficacy variables, analysis approach, statistical justification

9.4.1. Safety Analyses

The primary objective of this study is to evaluate the safety and tolerability of safinamide, 200 mg od, compared with placebo.

9.4.1.1. Adverse events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be classified as Treatment Emergent Adverse Events (TEAEs) or pre-treatment AEs. An AE with an unknown/unreported onset date will also be counted as a TEAE.

An overview of adverse events categories will be summarized with counts and percentages. Categories will include:

- TEAEs
- Relationship to study intervention (*possibly, unrelated*)
- Action taken with study intervention (*categories)*
- Outcome (*categories)*
- Maximum severity of TEAE (*mild, moderate, severe*)
- Serious TEAEs

Treatment Emergent Adverse Events will also be summarized by System Organ Class (SOC) and Preferred Term (PT) within SOC with counts and percentages within each treatment group. Similar summaries will also be provided for Serious TEAEs and TEAEs related to study intervention.

A participant experiencing the same AE multiple times will be counted only once for the corresponding PT. Similarly, if a participant experiences multiple AEs within the same SOC, the participant will be counted only once for that SOC.

Analysis listings of serious TEAEs and study intervention-related TEAEs will be provided by study intervention group. The analysis listings will include a treatment-emergent flag, reported term, SOC, PT, start date, stop date, severity, relationship to study intervention, action taken with study intervention, outcome and seriousness.

9.4.1.2. Physical and Neurological Examinations

Physical exam findings will be summarized at baseline and at week 12 in terms of number and proportion of participants with normal/abnormal results per body system and treatment group. *Shift tables from baseline to week 12 will be presented.*

9.4.1.3. Vital Signs

Values and changes from baseline will be summarized using descriptive statistics for each vital sign parameter at each visit by study intervention group.

9.4.1.4. Electrocardiogram parameters

An analysis listing of subjects with ECG abnormalities will be provided by study intervention group.

9.4.1.5. Safety Laboratory Parameters

Descriptive statistics for each clinical laboratory test will be presented by study intervention group at each visit. Change from baseline to week 12 values will also be summarized.

According to laboratory normal ranges, laboratory test results will be categorized as low (< lower normal limit), normal (within normal range), and high (> upper normal limit). Shift tables

comparing the distributions of these three categories at baseline versus week 12 will be presented by treatment group for key safety laboratory evaluations.

9.4.2. Efficacy Analyses

The following are the efficacy endpoints for this study:

- Change from baseline to week 12 in:
  - Goniometric measurement for "lateral" and "anterior" displacement
  - Unified MSA Rating Scale (UMSARS) Part II
  - MSA Health-Related Quality of Life (MSA-QoL) scale
  - Montreal Cognitive Assessment (MoCA) scale
  - Unified Dystonia Rating Scale (UDRS)

At each visit, the actual value and change from baseline will be summarized using descriptive statistics. Analyses of the efficacy variables will be conducted using an analysis of covariance (ANCOVA) model with study intervention included as a fixed effect and the baseline score as a covariate.

9.4.3. Other Analyses

Other exploratory analyses will be described in the statistical analysis plan finalized before database lock.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.3. Data Protection

- 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, the operations of collection, storage, circulation of biological samples as well as 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.

10.1.4. Committees Structure

The study protocol is written by a coordinating author with input from various experts. Final draft, after review and input from the CRO, in particular the statistical sections, is reviewed by Sponsor Quality Assurance and Pharmacovigilance units, and approved by the Global Clinical Development Head and the Global Head of Open R&D. The study will be carried out by a CRO, and clinical laboratory tests will be done locally.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

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

10.1.8. Study and Site Closure

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

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

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

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

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings.
- 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. As a consequence hereof, investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 days 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 .
- Further, without any prejudice to Investigator's right to divulge and save information for what stated hereinabove, 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.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count		White blood cell (WBC) count with Differential:	
	Red blood cell (RBC) Count		Neutrophils	
	Hemoglobin		Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
		Calcium	Alkaline phosphatase	
NOTES : [1] All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured				

which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Investigators must document their review of each laboratory safety report.

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

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

Definition of SAE

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

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

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

Reporting of SAEs

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

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

Definitions:

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

Women in the following categories **are not considered WOCBP**

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

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

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

Contraception Guidance:

Female participants

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

Table 2: Highly Effective Contraceptive Methods

Table 2: Highly Effective Contraceptive Methods

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

Pregnancy Testing:

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

Collection of Pregnancy Information:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5. Appendix 5: Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
ET	Early Termination
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IR	Immediate Release
ITT	Intent-To-Treat
MAO-B	Monoamine Oxidase-B
mg	Milligrams
mL	Milliliters
MoCA	Montreal Cognitive Assessment scale
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
MSA-QoL	Multiple System Atrophy-Quality of Life scale

od	once daily
PD	Parkinson's disease
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
SAE	Serious Adverse Event
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SoC	Standard of Care
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent Adverse Event
UDRS	Unified Dystonia Rating Scale
UMSARS	Unified Multiple System Atrophy Rating Scale
WOCBP	Women of child bearing potential

10.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

11. References

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Protocol Administrative Letter #1

Protocol Title: A 12-WEEKS, MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EXPLORATORY, PILOT STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SAFINAMIDE 200 MG ONCE DAILY, AS ADD-ON THERAPY, IN PATIENTS WITH POSSIBLE OR PROBABLE PARKINSONIAN VARIANT OF MULTIPLE SYSTEM ATROPHY

Protocol Number:	**Z7219K01**
Amendment Number:	**0**
Compound Number:	**Safinamide**
Short Title:	**Safinamide for Multiple System Atrophy**
Sponsor Name:	**Zambon SpA**
Legal Registered Address:	**Via Lillo del Duca 10** **20091 Bresso, Milan, Italy**

Regulatory Agency Identifying Number(s):
EudraCT Number: 2018-004145-16

Approval Date: August 09, 2019

Purpose

The aim of this administrative change is to clarify an inconsistency within the study protocol in regards to the number of evaluable patients, to provide additional clarifications on the sample size determination background and to provide information on the benefit/risk assessment.

1. Number of Evaluable Patients

It has been noted that in section 4.1 "Overall design" is incorrectly reported the following: "Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1) to study intervention and 40 evaluable participants for an estimated total of respectively 30 and 10 evaluable participants per intervention group."

We confirm that, as correctly reported in all the other sections of the protocol, approximately 56 participants will be screened to achieve 48 randomly assigned to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group.

The inconsistency within the document will be corrected with the first protocol amendment.

2. Sample Size Determination Background

The primary objective of the current study is to evaluate safety of salfinamide 200 mg once daily compared to placebo. This is the first formal evaluation of salfinamide in this population in a double blind, placebo controlled study, so a pilot study was deemed advisable prior to an adequately powered efficacy study. As the primary objective of the study is evaluation of safety, no formal sample size calculations have been made to justify sample size.

The sample size was selected based on previous studies in this population and the safety profile of salfinamide in the marketed indication of Parkinson's Disease. The current study enrolls 26 active vs 14 placebo. While there are few recent efficacy studies of symptomatic therapy in MSA, there is a more recent study of the efficacy of rasagiline (Poewe, W., et al. (2015) "Efficacy of rasagiline in patients with the parkinsonian variant of multiple system atrophy : a randomised , placebo-controlled trial" published on *The Lancet Neurology*, *14*(2), 145–152. https://doi.org/10.1016/S1474-4422(14)70288-1) that randomized 84 subjects to rasagiline and 90 to placebo. While this study failed to find a therapeutic effect of rasagiline, it demonstrated that this sample size would have been adequate to detect a clinically relevant change in symptoms. A study of that size was deemed too large as an initial safety study.

Previous studies of salfinamide in Parkinson's Disease showed Adverse Event rates in treated groups to be less than 10% in excess of placebo (for example Borgohain, R, et al. (2014) "Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations" published on *Movement Disorders*, *29*(2), 229–237. https://doi.org/10.1002/mds.25751). In that occasion, it was deemed reasonable to perform a trial with approximately 40 subjects - randomized at a 2:1 ratio active : placebo – and it was judged to be sufficient to provide an estimate as to whether AEs are likely to be within this range in the MSA patient population at this dose.

3. Benefit/Risk Assessment

Safinamide has been approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of PD patients as add-on therapy to levodopa (alone or in combination with other antiparkinsonian drugs). At the current date, safinamide is on the market in 13 European countries and the USA, Canada, Australia, Brazil and Colombia. There are extensive post marketing surveillance data in PD patients for the 50mg and 100 mg doses.
With regards to the current trial in which a dose of 200 mg will be taken for 12 weeks, safety data are also derived from trials performed in over 3000 subjects, including 2019 with Parkinson's disease of whom 500 were treated for more than 2 years.
For the 200 mg dose, safety data are available for 134 PD patients who had repeated doses of safinamide ≥150mg daily. Of these, long term safety and tolerability data of up to 2 years for safinamide doses ≥ 150 mg/day are available in 89 patients who took part in Study NW-1015/015/III/2003 and in the 69 who continued treatment in the double-blind, placebo-controlled, extension Study NW-1015/017/III/2003.
Doses of ≥ 150 mg/day were generally well- tolerated and no safety concerns were observed. The tolerability was similar to the 50mg and 100 mg/day doses, although the proportion of patients experiencing severe TEAEs (approx. 10%) was somewhat higher in the 150 – 200 mg group. The proportion of patients discontinuing due to TEAEs and the number of SAEs was similar for all treatment groups. The most frequent treatment-emergent adverse events (TEAEs) reported in Studies 015 and 017 were in the CNS and GI systems and are consistent with those reported in the SmPC. All TEAEs resolved without sequelae.
From the available clinical data, the safety and tolerability of the 200 mg dose in MSA patients is expected to be acceptable. Should patients not tolerate this dose, they may de-escalate to a lower dose or if they still do not tolerate the study medication, they can withdraw from the study.
MSA is a severe neurodegenerative disease for which there are limitations in existing therapy. There is a scientific rationale to assess the clinical benefit of safinamide in MSA patients in this proof of concept study. The existing clinical data on safinamide derived from post marketing surveillance, and clinical studies support an overall, favourable benefit/risk profile. More detailed information about the known and expected benefits and risks as well as reasonably expected adverse events of safinamide may be found in the Investigator's Brochure.

These information will be included in the first protocol amendment.

Sponsor Signatory:

Charlotte Keywood
Global Head Open R&D

9-8-2019
Date

Title Page

Protocol Title:

A 12-WEEKS, MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, EXPLORATORY, PILOT STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SAFINAMIDE 200 MG ONCE DAILY, AS ADD-ON THERAPY, IN PATIENTS WITH POSSIBLE OR PROBABLE PARKINSONIAN VARIANT OF MULTIPLE SYSTEM ATROPHY

Protocol Number: Z7219K01
Amendment Number: 0

Compound Number: Safinamide

Short Title:

Safinamide for Multiple System Atrophy

Sponsor Name: Zambon SpA

Legal Registered Address: Via Lillo del Duca 10

20091 Bresso, Milan, Italy

Regulatory Agency Identifying Number(s):

EudraCT Number: 2018-004145-16

Approval Date: February 21, 2019

Sponsor Signatory:

Charlotte Keywood
Global Head Open R&D

21 Feb 2019
Date

Mark Wakefield
Head Global Clinical Development

21 Feb 2019
Date

Medical Monitor Name and Contact Information will be provided separately.

Investigator Signature Page

I have read this protocol.

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

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

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

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

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

Investigator Signatory:

Name: Date:

Title:

Affiliation:

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A 12-weeks, multicentre, randomized, double-blind, placebo-controlled, exploratory, pilot study to evaluate the safety and efficacy of safinamide 200 mg once daily, as add-on therapy, in patients with possible or probable parkinsonian variant of multiple system atrophy.

Short Title:

Safinamide for Multiple System Atrophy

Rationale:

To establish the safety and tolerability of 200 mg of safinamide and to explore whether this dose may offer benefits to patients with the parkinsonian variant of MSA.

Objectives and Endpoints

Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of safinamide, 200 mg od, compared with placebo	• The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of TEAEs and SAEs. • Changes in physical and neurological examination findings. • Changes in vital sign (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities. • Changes in 12-lead ECG parameter measures, including occurrence of abnormalities. • Changes in clinical chemistry and hematology values, including shifts from Baseline and occurrence of abnormalities. • Number of withdrawals (and reason if given).

Efficacy	
To evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on motor function and/or quality of life	• The change from baseline to week 12 in the goniometric measurement for "lateral" displacement • Change from baseline at week 12 in Unified MSA Rating Scale, MSA Health-Related Quality of Life (MSA-QoL) scale, Montreal Cognitive Assessment (MoCA) scale, Unified Dystonia Rating Scale (UDRS).

Overall Design:

The study is a randomized placebo controlled double blind study, with two parallel arms, in which participants will be assigned in a 2:1 ratio to receive either safinamide or placebo. Study population is patients diagnosed, less than two years ago, with possible or probable parkinsonian variant of Multiple System Atrophy who are on a stable treatment of levodopa.

Outcome will be assessed after 12 weeks of treatment, when progression is unlikely to be a confounder of change. No Independent Data Monitoring Committee is foreseen.

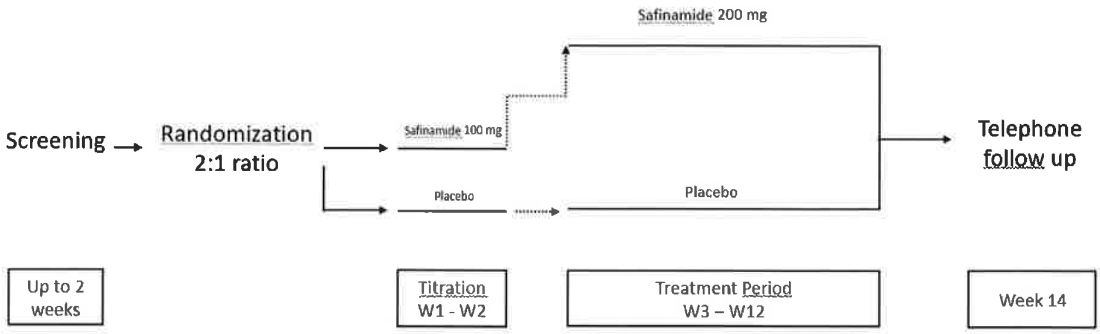
Number of Participants:

Approximately 56 participants will be screened to achieve 48 randomly assigned to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group (See section 9.2)

Intervention Groups and Duration:

Trial participation will be up to a maximum duration of 14 weeks and will comprise a screening period (up to 2 weeks), a 2-week run in period during which subjects will receive 1 tablet (either 100 mg safinamide or matching placebo), followed by a 10-week period, during which study participants will take 2 tablets of study medication (200 mg safinamide or placebo) once daily, taken in the morning in addition to their morning levodopa dose. A telephone follow-up call will be performed 2 weeks after the end of treatment.

1.2. Schema



1.3. Schedule of Activities (SoA)

Study Period	**Screening period**	**Baseline**	**Interim Visits** Weeks 2 - 8			**EOT / ET** Week 12	**Telephone follow-up** Week 14	**Notes**
Day	**-14 to -0**	**1**	**14 ±3**	**28 ±3**	**56 ±3**	**84 ±3**	**98 ±3**	In the event of early termination (ET) participants should complete the End of Treatment (EoT) assessments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Informed consent	X							
Eligibility criteria	X	X						
Randomization		X						
Demographics	X							
Medical history/diagnosis	X							
Prior and concomitant medications	X	X	X	X	X	X	X	Details of excluded and permitted concomitant treatments are presented in Section 6.5.
Vital signs	X	X	X	X	X	X		
12-lead ECG	X					X		
Physical & neurological examination	X					X		
UMSARS		X		X	X	X		
MSA-QoL		X		X	X	X		
MoCA	X					X		
UDRS (first five body areas)		X		X	X	X		To be evaluated at approximately the same time of day as at the baseline visit, and this should be at least 1 hour after the patient has taken their morning dose of safinamide and is in the optimal "ON" state, where possible.
Goniometric assessment		X		X	X	X		
Haematology/Clinical chemistry	X					X		

Study Period	**Screening period**	**Baseline**	**Interim Visits** Weeks 2 - 8			**EOT / ET** Week 12	**Telephone follow-up** Week 14	**Notes**
Day	**-14 to -0**	**1**	**14 ±3**	**28 ±3**	**56 ±3**	**84 ±3**	**98 ±3**	In the event of early termination (ET) participants should complete the End of Treatment (EoT) assessments
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Pregnancy test (urine)		X				X		Only for WOCBP.
Adverse events		X	X	X	X	X	X	
Dispense randomized medication		X	X	X	X			The first dose of study medication will be administered at the study centre.
Drug accountability			X	X	X	X		

2. Introduction

Safinamide (licensed with the commercial name Xadago) is approved as add-on therapy to levodopa for Parkinson's disease patients experiencing fluctuations. Safinamide has both dopaminergic and non-dopaminergic activities. It is a potent, selective and reversible monoamine oxidase type B (MAO-B) inhibitor, a mechanism associated with enhancement of dopaminergic transmission in the brain. Safinamide is also a state-dependent inhibitor of voltage-gated sodium channels, and inhibits calcium channels, dopamine transporters, and some other targets at higher concentrations in vitro. Safinamide has been shown to inhibit the stimulated release of glutamate (in vitro and in vivo studies) without affecting the basal glutamate levels.

These molecular mechanisms act in animal models of PD to increase brain dopamine, extend levodopa induced ON-time (dopaminergic actions) and reduce the severity of levodopa induced dyskinesia (non-dopaminergic action).

In addition, safinamide's state dependent sodium channel inhibiting activity has been shown to modulate microglia function (Black JA, 2009). Respectively, safinamide has shown neuroprotection in models of Parkinson's disease and multiple sclerosis that has been strongly associated with reduction of microglial activation (Morsali D, 2013).

Safinamide may also have neuroprotective effects. (Borgohain R, 2013) Safinamide inhibits α-1 receptors in the endoplasmic reticulum.(Fariello RG, 1998) These receptors are believed to be multifunctional regulatory proteins with a role in CNS development, plasticity and neurodegeneration. Safinamide has been shown to completely prevent forebrain dopamine depletion and neuronal cell death in the gerbil substantia nigra when administered prior to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. (Vaghi F, 1997) In animal epilepsy models, safinamide was shown to counteract neuronal death that had been induced by excitotoxin.(Maj R, 1998) Possible mechanisms of action for safinamide's potential neuroprotective properties are MAO-B inhibition (Kupsch A, 2001) and reduction in glutamate release.(Caccia C, 2006, 2008)

Multiple System Atrophy (MSA) is a progressive and fatal neurodegenerative disease. MSA is characterized pathologically by glial cytoplasmic inclusions (GCIs) that consist of ectopic aggregates of hyperphosphorylated and insoluble filamentous α-synuclein in oligodendrocytes (Tu PH, 1998) and selective neurodegeneration in the striatonigral and olivopontocerebellar regions. Microglial activation parallels the neurodegeneration and GCI pathology in MSA (Ishizawa K, 2004).

Clinically, the cardinal features include autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs in any combination. Two major motor presentations can be distinguished clinically. Parkinsonian features predominate in 80% of patients (MSA-P subtype), whereas cerebellar ataxia predominates in the remaining 20% of patients (MSA-C subtype). MSA is a progressive disorder with early disability and shortened life expectancy.

No cures are available and treatment is symptomatic. Levodopa is used to manage the motor symptoms, but patients become rapidly irresponsive to this drug due to widespread glial and neuronal cell degeneration and shrinkage of some brain areas such as cerebellum, basal ganglia and brainstem with eventual death within 9-10 years after diagnosis. Pain is a common non-motor symptom both in PD and MSA (Kass-Iliyya, 2015).

2.1. Study Rationale

Post hoc analysis of data from previous safinamide studies in PD patients suggested effects on nonmotor symptoms such as mood and pain (Cattaneo et al, 2017 & 2018).

Given the pathophysiological overlap between PD and MSA the study aims to establish the safety and tolerability of a higher dose (200 mg) of safinamide, and whether this may offer benefit to patients with the parkinsonian variant of MSA.

2.2. Background

Multiple clinical trials of potential therapies, including riluzole, lithium, growth hormone, minocycline and rifampin (also called rifampicin) have shown no benefit over a placebo. With regard to the same class of compounds, Poewe and colleagues conducted a 48-week randomised, controlled, multicentre trial at 40 academic sites across 12 countries evaluating the potential disease modifying and symptomatic effects of 1 mg/day of another MAO-B inhibitor, rasagiline (n=84) versus placebo (n=90) in 174 patients with the parkinsonian subtype of multiple system atrophy. (Poewe W, 2015)

Eligible patients aged 30 years or older had <3 years from the time of documented diagnosis of multiple system atrophy to enrolment and, on the basis of investigators' clinical judgment, an anticipated survival of at least 3 years. Main exclusion criteria were severe orthostatic symptoms, speech/swallowing impairment, impairment in ambulation or falling more frequently than once per week.

The primary outcome was change from baseline to 48 weeks in the Unified Multiple System Atrophy Rating Scale (UMSARS) score (sum of parts I and II), and several secondary outcome measures were assessed, including putaminal mean diffusivity on MRI in a subset of patients.

The study did not show that this regimen was effective in the slowing of disease progression or improvement of symptoms in this population of patients with the parkinsonian variant of multiple system atrophy. 68 (81%) patients in the rasagiline group and 67 (74%) patients in the placebo group reported adverse events, and serious adverse events in 29 (35%) versus 23 (26%) patients. The most common adverse events in the rasagiline group were dizziness (n=10 [12%]), peripheral oedema (n=9 [11%]), urinary tract infections (n=9 [11%]), and orthostatic hypotension (n=8 [10%]).

Failure of the drug to show any effect could be due to several reasons, including the dose tested might have been too low compared to that used in an MSA preclinical model study, or that the treatment should have started earlier, i.e. within 2 years of diagnosis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of safinamide is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

The existing clinical data on safinamide derived from studies supports an overall, favorable benefit/risk profile. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of safinamide may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of safinamide, 200 mg od, compared with placebo	• The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of TEAEs and SAEs. • Changes in physical and neurological examination findings. • Changes in vital sign (heart rate, systolic and diastolic blood pressure) values, including occurrence of abnormalities. • Changes in 12-lead ECG parameter measures, including occurrence of abnormalities. • Changes in clinical chemistry and hematology values, including shifts from Baseline and occurrence of abnormalities. • Number of withdrawals (and reason if given).
Efficacy	
• To evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on motor function and/or quality of life	• The change from baseline to week 12 in the goniometric measurement for "lateral" displacement • Change from baseline at week 12 in Unified MSA Rating Scale, MSA Health-Related Quality of Life (MSA-QoL) scale, Montreal Cognitive Assessment (MoCA) scale, Unified Dystonia Rating Scale (UDRS).

4. Study Design

4.1. Overall Design

The overall design is a parallel group, placebo controlled, double blind study.

The target population are participants diagnosed, less than two years ago, with possible or probable parkinsonian variant of Multiple System Atrophy (Gilman, 2008) who are on stable doses of levodopa.

Trial participation will be up to a maximum duration of 14 weeks and will comprise a screening period (up to 2 weeks), a run in period of 2 weeks (week 1 – week 2) during which study participants will receive 1 tablet (either 100 mg safinamide or matching placebo) followed by a treatment period (week3 – week 12), during which they will receive two tablets (200 mg safinamide or matching placebo) once daily, taken in the morning in addition to their morning levodopa dose. In the event the study participant does not tolerate 2 tablets, they can drop down to 1 tablet per day and remain in the study at that dose level.

A telephone follow-up call will be performed 2 weeks after the end of treatment. The treatment duration is sufficiently long to evaluate the safety and tolerability of safinamide 200 mg od and potentially show symptomatic efficacy. Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1) to study intervention and 40 evaluable participants for an estimated total of respectively 30 and 10 evaluable participants per intervention group

The safety parameters will be assessed monitoring TEAEs and SAEs and changes (baseline – week 12) in physical and neurological examination findings, vital signs, 12-lead ECG and clinical chemistry and hematology values.

The efficacy parameters will be assessed looking at goniometric measurement for "lateral" displacement (Tinazzi, 2015) and assessing the changes (baseline – week 12) in the UMSARS (Wenning, 2004), the MSA-QoL (Schrag, 2007), the MoCA and the UDRS (first five body areas).

4.2. Scientific Rationale for Study Design

This study is a randomized, double blind, trial to provide scientific rigor to minimize the chance of bias in the results. The trial duration is sufficiently long to establish safety, tolerability, and possible symptomatic benefits, yet short enough for disease progression not to be a confounding factor.

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

The sponsor believes that placebo can be safely and ethically administered in this study based on the following rationale:

- All patients, whether in the active or placebo group, will continue using MSA treatment including levodopa; the investigational product will be added to the patient's standard therapy.

- Prior and concomitant medications which are considered necessary for the safety and well-being of the subject are permitted during the study at the discretion of the investigator provided the medication is not listed within the study exclusion criteria or in the excluded medication. If a subject is treated with a prohibited medication, a decision will be taken on whether or not the subject should continue in the study.

The treatment duration is sufficiently long to potentially show symptomatic efficacy, yet short enough that disease progression is unlikely to be a confounder.

4.3. Justification for Dose

The dose of 200 mg/day was selected based on the results of the previous studies, indicating that potentially a higher than the minimal effect dose for patients with PD would be needed.

The efficacy and safety of safinamide has been evaluated in clinical studies as add-on therapy to dopamine agonists (DA) in early-stage PD (Di Paolo T, 2011; Colombo E, 2006) and as add-on to LD in mid- to late-stage PD (Neliat G, 2008; Izzo E, 2005; Jolas T, 2009), and in PD patients at doses between 150 to 200 mg daily for 18 months (data on file).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 30 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are diagnosed (with MRI confirmation) with possible or probable parkinsonian variant of Multiple System Atrophy less than 2 years ago.
3. Participants with an anticipated survival of at least 3 years in the opinion of the investigator.

Sex

4. Male or female

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

    i. Not a woman of childbearing potential (WOCBP)

    OR

    ii. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 30 days after the last dose of study intervention.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. History of neurosurgical procedure, including stereotactic surgery.
2. History of Deep Brain Stimulation (DBS)
3. History of bipolar disorder, severe depression, schizophrenia or other psychotic disorder.

4. History of drug and/or alcohol abuse within 12 months prior to screening as defined by the current edition of the Diagnostic and Statistical Manual of Mental Disorders
5. History of dementia (DSM-V criteria)
6. Ophthalmologic history including any of the following conditions: albinism, uveitis, retinitis pigmentosa, retinal degeneration, active retinopathy, severe progressive diabetic retinopathy, inherited retinopathy or family history of hereditary retinal disease.
7. Active hepatitis B or C
8. History of human immunodeficiency virus (HIV) infection
9. Subjects not able to swallow oral medications
10. Subjects with severe orthostatic symptoms
11. Impaired ambulation, i.e. falling more than once per week, bedridden patients or confined to a wheelchair during the whole day.
12. Subjects with active malignant neoplasms.
13. Movement disorders other than MSA (e.g. Parkinson Disease, dementia with Lewy bodies, essential tremor, progressive supranuclear palsy, pharmacological or post-encephalic parkinsonism).
14. Any clinically significant or unstable medical or surgical condition that, in the opinion of the investigator, might preclude safe completion of the study or might affect the results of the study.

Prior/Concomitant Therapy

15. Not on a stable regime, for at least 4 weeks prior to the randomization (baseline visit), of
    a. oral levodopa (including controlled release [CR], immediate release [IR] or a combination of CR/IR), with or without benserazide/carbidopa, with or without addition of a catechol O-methyltransferase (COMT) inhibitor
    or
    b. dopamine agonist, anticholinergic and/or amantadine.

Prior/Concurrent Clinical Study Experience

16. Patients should not have received treatment with monoamine oxidase inhibitors in the 2 weeks prior to the randomization visit, nor treatment with levodopa infusion, pethidine, opiates, opioids, fluoxetine, fluvoxamine in the 4 weeks prior to the randomization visit.
17. Patients should not have received treatment with an oral or depot neuroleptic within 12 weeks prior to the randomization visit.
18. Use of any investigational drug within 30 days prior to screening or 5 half-lives, whichever is the longest.

Diagnostic assessments

19. Montreal Cognitive Assessment (MoCA) ≤ 20
20. Laboratory assessments showing moderate or severe hepatic impairment (2x ULN)

Other Exclusions

21. Allergy/sensitivity or contraindications to the investigational medicinal products (IMPs) or their excipients, anticonvulsants, levodopa or other anti-parkinsonian drugs.
22. Any clinically significant condition which, in the opinion of the Investigator, would not be compatible with study participation or represent a risk for patients while in the study.

5.3. Lifestyle Considerations

No restriction regarding meals or activity. Safinamide does not affect L-type calcium channels (no effects in blood pressure and heart rate) and can be given without food restrictions related to tyramine.

5.4. Screen Failures

Potential subjects will be screened prior to entry into the study. Laboratory assessments may be repeated once for any laboratory parameter that falls outside the relevant exclusion criteria provided they are completed and reviewed within the 2-week screening period.

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

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

6. Study Intervention

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

6.1. Study Intervention(s) Administered

Study Intervention Name:	Active Safinamide methanesulfonate	Placebo
Dosage formulation:	Orange to copper, round, biconcave film-coated tablets	
Unit dose strength(s)/Dosage level(s):	100 mg (free base)	Only excipients: microcrystalline cellulose, crospovidone, colloidal silicone dioxide, magnesium stearate, and for the coating: purified water, hypromellose and polyethyleneglycole. Candurin® pigments are included for color modification.
Route of Administration	Oral	
Dosing instructions:	Once daily along with first levodopa dose of the day	
Packaging and Labeling	Study Intervention will be provided in PVC/PVDC60/Al blisters. Sufficient blisters of 10 tablets will be paced in cases, sufficient for each visit interval. Each case with blisters will be labeled as required per country requirement.	
Manufacturer	Catalent, Schorndorf, Germany in alternative Zambon Spa, Vicenza, Italy	Zambon Spa, Vicenza, Italy

Primary packaging	Zambon Spa, Vicenza, Italy in alternative Catalent, Schorndorf, Germany	Zambon Spa, Vicenza, Italy in alternative Catalent, Schorndorf, Germany
Secondary packaging & labeling	Almac, Craigavon, United Kingdom	Almac, Craigavon, United Kingdom

6.2. Preparation/Handling/Storage/Accountability

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

6.3. Measures to Minimize Bias: Randomization and Blinding

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

Blind Break (IVRS/IWRS)	*The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.*

6.4. Study Intervention Compliance

Compliance will be assessed based on drug accountability.

6.5. Concomitant Therapy

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

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

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

6.5.1. Excluded medication

Use of other monoamine oxidase inhibitors, including moclobemide, treatment with levodopa infusion, pethidine, opiates, opioids, fluoxetine, fluvoxamine are not permitted during the course of the study.

Use of serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics or tetracyclics, selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine or fluvoxamine is permitted, providing the dose is kept as low as possible and remains stable throughout the study.

Sympathomimetics, dextromethorphan, nasal and oral decongestants or cold remedies (e.g. ephedrine, pseudoephedrine, phenylephrine or phenylpropanolamine) are permitted if used for treating cough but must be used with caution.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.6. Dose Modification

In case, due to an AE, a dose reduction is necessary, the study participant can drop down from two (2) to one (1) tablet per day. Dose re-escalation is allowed once the AE is resolved.

6.7. Intervention after the End of the Study

No planned extension or continued access.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

If patient does not tolerate the dose, they may drop down to 1 tablet per day, but if that is not tolerated patient should be withdrawn.

7.1.2. Rechallenge

Investigator judgment should be applied to temporarily reduce dose and then rechallenge.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- The following assessments and procedures will be performed as detailed in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Visit 1: Screening Visit

After providing written informed consent to participate in the study, patients will enter a screening period of up to 2 weeks. During the screening period, patients will undergo all the evaluations necessary to establish their eligibility for the study and be assigned a unique screening number.

- Obtain written informed consent.
- Log in to IWRS for assignment of unique screening number; numbers will be allocated in sequence within each study center.
- Check of inclusion and exclusion criteria.
- Record demographic data, including age, sex, ethnicity, smoking and alcohol use.
- Record medical history and MSA diagnosis, including date (at least one MRI evidence).
- Perform physical examination including height and body weight.
- Perform neurological examination.
- Measure vital signs: pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position.
- Obtain 12-lead ECG in the supine position.
- Obtain blood sample for clinical laboratory assessments (Appendix 2).
- Record prior medications, concomitant medications and therapies.
- Completion of MoCA

Please bear in mind when scheduling the next visit that UMSARS, MSA-QoL and UDRS (first five body areas) evaluations should take place at approximately the same time of day at the baseline and subsequent visits, where possible.

Visit 2: Baseline Visit

At baseline (Day 1, Visit 2), eligible patients will enter the treatment period (2 titration weeks) and will be randomized to receive either safinamide or matching placebo, orally od in a 2:1 ratio.

- Verify that participant meets the eligibility criteria, including the laboratory assessments & urine pregnancy test for WOCBP.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of scales by rater/study participant:
  - UMSARS
  - MSA-QoL
  - UDRS (first five body areas)
- Recording of prior medications, concomitant medications and therapies.
- Goniometric assessment for "lateral" displacement
- Recording of AEs.
- Randomization to treatment group.
- Following completion of the relevant assessments and procedures, patients will take their first dose of study intervention at the study center (safinamide 100mg or matching placebo)
- Dispense study medication for the next 14 days.

Study medication can be taken with or without food.

The dose of the concomitant anti-Parkinson drugs and of the treatments of orthostatic hypotension must be kept unchanged from the baseline to the end of the study (week 12 or early discontinuation).

Remind study participant not to take their dose on the morning of their Visit 3 appointment.

Visit 3: End of Titration Visit

At the end of titration period (Day 14, Visit 3), the following assessments should be done:

- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Recording of concomitant medications and therapies.
- Recording of AEs.
- Perform drug accountability.
- Dispense study medication (safinamide 200mg or matching placebo) and take first dose under supervision in clinic.

Visits 4 and 5: Interim Visits

At the interim visits (Day 28, Visit 4 & Day 56, Visit 5) the following assessments should be done.

- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- Completion of scales by rater/study participant:
    - UMSARS
    - MSA-QoL
    - UDRS (first five body areas)
- Recording of concomitant medications and therapies.
- Goniometric assessment for "lateral" displacement
- Recording of AEs.
- Perform drug accountability.
- Dispense study medication.

Visit 6: End of Treatment Visit

Following completion of 12 weeks (Day 84) of treatment or in the event of early termination, the following EOT assessments and procedures should be performed.

- Physical examination including body weight.
- Neurological examination.
- Vital signs (pulse rate, systolic and diastolic blood pressure measured after at least 5 minutes in the supine position).
- 12-lead ECG in the supine position.
- Completion of scales by rater/participant:
    - UMSARS
    - MSA-QoL
    - MoCA
    - UDRS (first five body areas)
- Blood sampling for clinical laboratory assessments (hematology and clinical chemistry).
- Urine sampling for urine (dipstick) pregnancy test for women (only for WOCBP).
- Record concomitant medications and therapies.
- Goniometric assessment for "lateral" displacement
- Record AEs.
- Perform drug accountability.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Visit 7: Telephone Follow-up

After 2 weeks from the End of Treatment, a telephone follow-up with patient should be performed, questioning about:

- Concomitant medications and therapies
- AEs

8.1. Safety Assessments

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

8.1.1. Physical Examinations

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

8.1.2. Vital Signs

- Vital signs (to be taken before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed in the supine with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.1.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).
- ECGs will be reviewed locally, for safety findings, which should be documented by the Investigator. Paper ECGs will remain at site (as source documents).
- Results are to be documented in the eCRF as normal, or abnormal and whether clinically significant.

8.1.4. Clinical Safety Laboratory Assessments

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

8.1.5. Suicidal Risk Monitoring

Not done.

8.2. Efficacy Assessments

Goniometric measurement of "lateral" displacement is determined using a wall goniometer and expressing the value in degrees.

Site personnel who are to be involved in performing the efficacy assessments, UMSARS, the MSA-QoL, the MoCA, the UDRS (first five body areas) must be experienced in the use of the various scales and questionnaires.

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

Wherever possible the MSA QoL should be completed by the participant. However, in the case of the participant's incapacity, the participant's caregiver may help complete it based on information reported by the participant.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

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

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

Not applicable

8.4. Treatment of Overdose

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

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

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE or laboratory abnormalities
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).

- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Not applicable

9. Statistical Considerations

9.1. Statistical Hypotheses

Safety data will be presented descriptively, thus no formal hypothesis for safety will be tested.

Efficacy endpoints will be tested with hypothesis of the form:

$H0: \mu_{Test} = \mu_{Placebo}$

$H1: \mu_{Test} \neq \mu_{Placebo}$ for continuous variables

$H0: \pi_{Test} = \pi_{Placebo}$

$H1: \pi_{Test} \neq \pi_{Placebo}$ for categorical variables

where μ is the mean in the population and π is the proportion in the population

9.2. Sample Size Determination

As this is a pilot study, no formal sample size has been calculated. The sample size is based on clinical considerations and is deemed sufficient to provide initial safety and tolerability information.

Approximately 56 participants will be screened to achieve 48 randomly assigned to study intervention and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per intervention group.

9.3. Populations for Analyses

9.3.1. Enrolled Population

The Enrolled Population will include all participants who sign the ICF.

9.3.2. Evaluable Population

The Evaluable Population will include all randomized participants. This population will be used for all efficacy variables.

9.3.3. Safety Population

The Safety Population will include all randomized participants who take at least one dose of study intervention. This population will be used to summarize all safety data; participants will be analyzed according to the intervention they actually received.

9.3.4. Per Protocol Population

The Per Protocol Population will include all randomized participants who do not have any entry criteria violations or protocol deviations that could significantly impact the assessment or interpretation of efficacy data. Participant data will be reviewed by the clinical team to identify exclusions from the Per Protocol Population. The list of participants to be excluded from the Per Protocol Population will be finalized prior to database unblinding. This population will be used for the analysis of the efficacy variables.

9.4. Statistical Analyses

All statistical summaries will be descriptive in nature. All results will be presented separately for each of the study intervention groups. All analyses, summaries and listings will be performed using SAS version 9.4 or later.

All continuous variables will be summarized by presenting the number of participants, mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be presented as frequencies and percentages.

A separate Statistical Analysis Plan (SAP) will be prepared to provide additional details on the definitions of the safety and efficacy variables, analysis approach, statistical justification

9.4.1. Safety Analyses

The primary objective of this study is to evaluate the safety and tolerability of safinamide, 200 mg od, compared with placebo.

9.4.1.1. Adverse events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be classified as Treatment Emergent Adverse Events (TEAEs) or pre-treatment AEs. An AE with an unknown/unreported onset date will also be counted as a TEAE.

An overview of adverse events categories will be summarized with counts and percentages. Categories will include:

- TEAEs
- Relationship to study intervention (*possibly, unrelated*)
- Action taken with study intervention (*categories)*
- Outcome (*categories)*
- Maximum severity of TEAE (*mild, moderate, severe*)
- Serious TEAEs

Treatment Emergent Adverse Events will also be summarized by System Organ Class (SOC) and Preferred Term (PT) within SOC with counts and percentages within each treatment group. Similar summaries will also be provided for Serious TEAEs and TEAEs related to study intervention.

A participant experiencing the same AE multiple times will be counted only once for the corresponding PT. Similarly, if a participant experiences multiple AEs within the same SOC, the participant will be counted only once for that SOC.

Analysis listings of serious TEAEs and study intervention-related TEAEs will be provided by study intervention group. The analysis listings will include a treatment-emergent flag, reported term, SOC, PT, start date, stop date, severity, relationship to study intervention, action taken with study intervention, outcome and seriousness.

9.4.1.2. Physical and Neurological Examinations

Physical exam findings will be summarized at baseline and at week 12 in terms of number and proportion of participants with normal/abnormal results per body system and treatment group. *Shift tables from baseline to week 12 will be presented.*

9.4.1.3. Vital Signs

Values and changes from baseline will be summarized using descriptive statistics for each vital sign parameter at each visit by study intervention group.

9.4.1.4. Electrocardiogram parameters

An analysis listing of subjects with ECG abnormalities will be provided by study intervention group.

9.4.1.5. Safety Laboratory Parameters

Descriptive statistics for each clinical laboratory test will be presented by study intervention group at each visit. Change from baseline to week 12 values will also be summarized.

According to laboratory normal ranges, laboratory test results will be categorized as low (< lower normal limit), normal (within normal range), and high (> upper normal limit). Shift tables comparing the distributions of these three categories at baseline versus week 12 will be presented by treatment group for key safety laboratory evaluations.

9.4.2. Efficacy Analyses

The following are the efficacy endpoints for this study:

- Change from baseline to week 12 in:
  - Goniometric measurement for "lateral" displacement
  - Unified MSA Rating Scale (UMSARS) Part II
  - MSA Health-Related Quality of Life (MSA-QoL) scale
  - Montreal Cognitive Assessment (MoCA) scale
  - Unified Dystonia Rating Scale (UDRS)

At each visit, the actual value and change from baseline will be summarized using descriptive statistics. Analyses of the efficacy variables will be conducted using an analysis of covariance (ANCOVA) model with study intervention included as a fixed effect and the baseline score as a covariate.

9.4.3. Other Analyses

Other exploratory analyses will be described in the statistical analysis plan finalized before database lock.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

10.1.4. Data Protection

- 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, the operations of collection, storage, circulation of biological samples as well as 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.

10.1.5. Committees Structure

The study protocol is written by a coordinating author with input from various experts. Final draft, after review and input from the CRO, in particular the statistical sections, is reviewed by Sponsor Quality Assurance and Pharmacovigilance units, and approved by the Global Clinical

Development Head and the Global Head of Open R&D. The study will be carried out by a CRO, and clinical laboratory tests will be done locally.

10.1.6. Dissemination of Clinical Study Data

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

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

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

microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

10.1.9. Study and Site Closure

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

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

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

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

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings.
- 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. As a consequence hereof, investigator hereby undertakes to submit to Zambon, at least with a sixty (60) days (30 days 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 .
- Further, without any prejudice to Investigator's right to divulge and save information for what stated hereinabove, 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.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 1: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count			White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
		Calcium	Alkaline phosphatase	
NOTES : [1] All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured				

which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Investigators must document their review of each laboratory safety report.

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

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

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

Definition of SAE

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

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

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

Reporting of SAEs

SAE Reporting to Pharmacovigilance via an Electronic Data Collection Tool

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

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

Definitions:

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

Women in the following categories are not considered WOCBP

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

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

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

Contraception Guidance:

Female participants

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

Table 2: Highly Effective Contraceptive Methods

Table 2: Highly Effective Contraceptive Methods

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

Pregnancy Testing:

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

Collection of Pregnancy Information:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator

will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5. Appendix 5: Abbreviations

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment
ET	Early Termination
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IR	Immediate Release
ITT	Intent-To-Treat
MAO-B	Monoamine Oxidase-B
mg	Milligrams
mL	Milliliters
MoCA	Montreal Cognitive Assessment scale
MRI	Magnetic Risonance Imaging
MSA	Multiple System Atrophy
MSA-QoL	Multiple System Atrophy-Quality of Life scale
od	once daily

PD	Parkinson's disease
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
SAE	Serious Adverse Event
SNRI	Serotonin-norepinephrine Reuptake Inhibitor
SOC	System Organ Class
SoC	Standard of Care
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent Adverse Event
UDRS	Unified Dystonia Rating Scale
UMSARS	Unified Multiple System Atrophy Rating Scale
WOCBP	Women of child bearing potential

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