APPENDIX 16.1.9: DOCUMENTATION OF STATISTICAL METHODS

MEDPACE

STATISTICAL ANALYSIS PLAN

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
Protocol Version/Date:	V2.0 / 13 July 2020
Investigational Product:	Safinamide
Sponsor:	Zambon SpA
SAP Version/Date:	V2.0 / 20 January 2021

CONFIDENTIAL

SIGNATURE 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
SAP Version/Date:	V2.0 / 20 January 2021

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature		**Date**
Miao Yang	*Electronically signed by: Miao Yang* *Reason: Approved* *Date: Jan 20, 2021 12:08 EST*	20-Jan-2021
Miao Yang, PhD Biostatistician, Biostatistics Medpace, Inc.		
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James Vornov, MD, PhD Vice-President, Medical Department Medpace, Inc.		
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Elena Tiberio Global Clinical Program Manager CNS Zambon SpA		

VERSION HISTORY

Version	Version Date	Description
1.0	13 November 2020	Original signed version
2.0	20 January 2021	Updated dictionary version to MedDRA v23.0

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
ANCOVA	Analysis of Covariance
AE	Adverse event
ATC	Anatomical therapeutic chemical
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case report form
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ICF	Informed consent form
ITT	Intent-to-Treat
IVRS/IWRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Model Repeated Measures
MoCA	Montreal Cognitive Assessment
MSA	Multiple System Atrophy
MSA-QoL	MSA Health-Related Quality of Life
PD	Protocol Deviation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
UDRS	Unified Dystonia Rating Scale
UMSARS	Unified MSA Rating Scale
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number Z7219K01. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

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

The other objective is to evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on motor function and/or quality of life.

2.2 Study Design

2.2.1 Overview

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 (MSA) 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 (week 3 – 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.

A study schema is depicted in Figure 1. The schedule of study assessments is described in Table 1.

FIGURE 1: SCHEMA

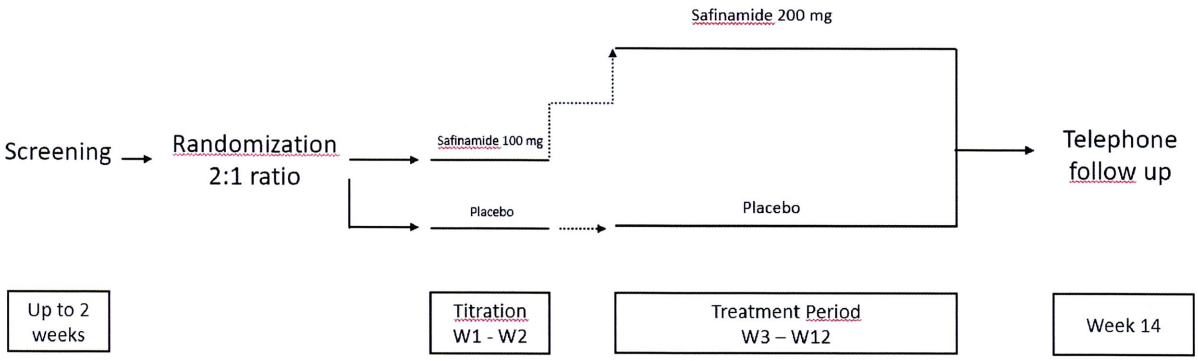

TABLE 1: SCHEDULE OF ACTIVITIES

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 of the protocol.
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**
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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.

2.2.2 Randomization and Blinding

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.

IVRS/IWRS	All participants will be centrally assigned to randomized study medication 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 medication will be dispensed at the study visits summarized in SoA. Returned study medication 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.

2.2.3 Sample Size Determination

As this is a pilot study with a focus on evaluating the safety of safinamide, no formal sample size has been calculated. Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1 active vs placebo) to study medication and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per group.

2.3 Study Endpoints

2.3.1 Efficacy Endpoints

Efficacy endpoints include the change from baseline to Weeks 4, 8 and 12 in the following parameters:

- 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 (Week 12 only)
- Unified Dystonia Rating Scale (UDRS)

2.3.1.1 Goniometric measurement

Goniometric measurement of "lateral" and "anterior" displacement is determined using a wall goniometer and expressing the value in degrees in the range of 0-90.

2.3.1.2 UMSARS

The Unified MSA Rating Scale (UMSARS) consists of four parts:

- Part I – Historical Review has 12 questions rated from 0 to 4, giving a range of 0-48 in the total score. Higher values indicate worse functional situation.
- Part II - Motor Examination Scale has 14 questions rated from 0 to 4, giving a range of 0-56 in the total score. Higher values indicate worse functional situation.
- Part III - Autonomic Examination has assessments of systolic blood pressure, diastolic blood pressure, heart rate and orthostatic symptoms (yes/no). Blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing.
- Part IV - Global Disability Scale ranges from 1 to 5 (1=completely independent; 2=not completely independent; 3=more dependent; 4=very dependent; 5=totally dependent and helpless).

2.3.1.3 MSA-QoL

The MSA Health-Related Quality of Life (MSA-QoL) scale has 40 questions on an ordinal scale of "no problem", "slight problem", "moderate problem", "marked problem", and "extreme problem". Additionally, patients were asked to indicate life satisfaction at the moment on a scale of 0 (extremely dissatisfied) to 100 (extremely satisfied).

2.3.1.4 MoCA

A score ranging from 0 to 30 will be recorded for each patient according to the Montreal Cognitive Assessment (MoCA) scale. Higher scores indicate better cognitive function.

2.3.1.5 UDRS

The Unified Dystonia Rating Scale (UDRS) assesses the severity and duration of dystonia in individual body areas. Each of 14 body area is evaluated via a 5-point ordinal scale of severity (0=none; 1=mild; 2=moderate; 3=severe; 4=extreme) and duration (0=none; 0.5=occasional, predominantly submaximal; 1.0= occasional, predominantly maximal; 1.5= intermittent, predominantly submaximal; 2.0= intermittent, predominantly maximal; 2.5= frequent, predominantly submaximal; 3.0= frequent, predominantly maximal; 3.5= constant, predominantly submaximal; 4.0=constant, predominantly maximal). A total score will be calculated as the sum of the severity and duration factors. If any of the factors is missing, then the total score is considered as missing. The total score ranges from 0 to 112.

2.3.2 Safety Endpoints

Safety endpoints include the following parameters:

- The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of TEAEs and SAEs.
    - Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The severity of AEs will be assessed using "mild", "moderate" and "severe". The degree of "relatedness" of the AE to the study treatment will be described using "related to study drug" and "not related to study drug".
    - Treatment-emergent adverse events (TEAEs) are defined as those AEs that have a start date on or after the first administration of study drug. AEs with unknown/unreported onset date will also be counted as TEAE.
- Physical and neurological examination findings.
    - Physical and neurological examinations will be performed at Screening and Week 12. Results will be recorded as "abnormal", "normal" and "not assessed".
- Vital sign (heart rate, systolic and diastolic blood pressure) values.
    - Vital signs will be assessed at Screening, Day 1, 14, 28, 56, and Day 84/Week 12.
- 12-lead Electrocardiogram (ECG) parameter measures.
    - 12-lead ECG will be performed at Screening and Week 12.
- Clinical chemistry and hematology values.
    - Clinical chemistry and haematology evaluations will be performed at Screening and Week 12.
- Number of withdrawals (and reason if given).
    - Subject withdrawals from the study will be recorded on the End of Study CRF with reasons provided.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Nominal visits (i.e., study visits captured on the CRF) will be used for all efficacy and safety analyses.

3.1.3 Definition of Baseline

Baseline measurements refer to data collected at Day 1. If a value at Day 1 is not available, the last measurement prior to the first dose of study medication will be used as the baseline value.

3.1.4 Summary Statistics

Categorical data will be summarized with counts and percentages of subjects. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.5 Hypothesis Testing

Efficacy endpoints will be tested with hypothesis of the form:

$$H_0: \mu_{test} = \mu_{placebo}$$

$$H_1: \mu_{test} \neq \mu_{placebo}$$

where μ is the mean value of any specified endpoint in the population.

3.2 Analysis Populations

3.2.1 Screened Population

The Screened Population will include all participants who sign the informed consent form (ICF). This population will be listed but not used for statistical analyses.

3.2.2 Intent-to-Treat (ITT) Population

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

3.2.3 Safety Population

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

3.2.4 Per-Protocol (PP) Population

The PP 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 PP Population. The list of participants to be excluded from the PP Population will be finalized prior to database unblinding. This population will be used for the analysis of the leading efficacy variable UMSARS if the number of subjects in the PP Population is less than 90% of that in the ITT Population.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will be provided for all screened subjects. The number and percentage of subjects in the following disposition categories will be presented by treatment and in total:

- Subjects who were screened (signed informed consent);
- Subjects who were screen failures;
- Subjects who were randomized;

- Subjects who completed Week 12, and the whole study (i.e., Week 14 follow-up);
- Subjects who terminated early

For subjects who failed screening and who did not complete the study, a summary will be provided for the reasons. Primary reason for screen failure or early termination due to Covid-19 will also be provided if available.

3.3.2 Protocol Deviations

Protocol deviations (PDs) will be defined in the Medpace Protocol Deviation Plan and captured in the Study Management System. The number and percentage of subjects with CSR-reportable PDs will be summarized for each deviation category and overall based on the ITT Population. PDs related to COVID-19 will be categorized and summarized separately.

CSR-reportable PDs and COVID-19 related non-reportable PDs will be listed.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all screened subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment and in total for all subjects in the ITT Population:

- Age (years)
- Sex
- Childbearing potential
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Continuous variables (age, height, weight, BMI) will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables (sex, race, ethnicity, childbearing potential) will be summarized with counts and percentages of subjects.

3.3.5 Medical History

General medical history and diagnosis of MSA for each subject will be provided in data listings for the ITT Population.

3.3.6 Prior and Concomitant Medications / Medical Procedures

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary Global B3, Sept 2019. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the ITT Population.

Prior and concomitant medical procedures and non-drug therapies will be listed.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <2 weeks (<14 days)
- 2 - <8 weeks (14 - 55 days)
- 8 - <12 weeks (56 – 83 days)
- ≥12 weeks (≥84 days)

Percent compliance to the study drug regimen will be calculated as

100 x (# of tablets dispensed - # of tables returned) / # of tablets expected to be taken.

If study drug is not returned, the number of tablets returned and lost will be considered 0 for the compliance calculation. The number of tablets expected will be calculated as

- Date of last visit – Date of randomization + 1, if subjects early terminated prior to Week 2 / Visit 3;
- (Date of last visit – Date of Visit 3 + 1) *2 + (Date of Visit 3 – Date of randomization), if subjects early terminated prior to Week 12 / Visit 6;
- (Date of Visit 6 – Date of Visit 3 + 1) *2 + (Date of Visit 3 – Date of randomization), if subjects completed the end of treatment visit (i.e., Visit 6);
- Any drug interruptions or temporary discontinuation will be taken into account.

Percent compliance to the study drug regimen will be summarized by treatment with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <80%
- 80-120%
- >120%

3.4 Efficacy Assessment

All efficacy analyses will be performed for the ITT Population. The analysis of UMSARS will be repeated for the PP Population if the number of subjects in the PP Population is less than 90% of that in the ITT Population.

3.4.1 Goniometric Measurement

At each visit, the actual value of goniometric measurement (including "lateral" and "anterior" displacement) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

A mixed-model repeated measures (MMRM) will be used to analyze the change in lateral displacement (and anterior displacement) from baseline. The model will include treatment, week of visit, treatment-by-visit interaction as fixed effects, and baseline score as a covariate. The unstructured covariance matrix will be assumed. Least squares means, standard errors, 95% confidence intervals and p-values for the differences between treatment groups at Weeks 4, 8 and 12 will be displayed. The treatment comparisons of most interest will be the LS means contrasts between the safinamide treated participants and the placebo treated participants at Week 12.

3.4.2 UMSARS

UMSARS Part I total scores, Part II total scores, Part III and Part IV will be respectively summarized by treatment group over time using descriptive statistics. If any of the items is missing in Part I or Part II, then the corresponding total score is considered missing.

The MMRM analysis specified in 3.4.1 will be used to analyze the change in Part I total scores from baseline, and the change in Part II total scores from baseline, respectively.

3.4.3 MSA-QoL

At each visit, life satisfaction and change from baseline will be summarized by treatment using descriptive statistics. The change in satisfaction from baseline will be analyzed by the MMRM specified in 3.4.1.

3.4.4 MoCA

MoCA scores will be summarized by treatment group using descriptive statistics at the Screening visit and Week 12. Change from Screening at Week 12 will also be summarized using descriptive statistics, and analyzed by an analysis of covariance (ANCOVA) model including treatment group as a factor, and baseline score as a covariate. P-values will be reported.

3.4.5 UDRS

At each visit, UDRS total scores and change from baseline will be summarized by treatment using descriptive statistics. The change in UDRS total score will be analyzed by the MMRM specified in 3.4.1.

3.5 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Population. Any abnormal laboratory test results or other safety assessments will be reported as AE and listed.

3.5.1 Adverse Events (AEs)

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs
- Any serious TEAEs (SAEs)
- Any TEAEs leading to dose interruption
- Any TEAEs leading to dose reduction
- Any TEAEs leading to discontinuation of study drug
- Any AEs leading to death

Counts and percentages of subjects will also be presented by system organ class and preferred term for TEAEs, SAEs, study drug related TEAEs, and TEAEs leading to discontinuation of study drug.

Listings will be presented for all TEAEs, SAEs, and study drug related TEAEs.

3.5.2 Clinical Laboratory Tests

Values and changes from baseline will be summarized using descriptive statistics for each treatment group by visit for protocol-required laboratory tests in Appendix A. All lab results will be listed.

3.5.3 Vital Signs

Vital signs parameters (heart rate, systolic and diastolic blood pressure) will be listed and summarized using descriptive statistics for each treatment group by visit.

3.5.4 12-Lead Electrocardiograms

The overall interpretation of ECG data will be summarized by counts and percentages by treatment group. All ECG findings will be listed.

3.5.5 Physical and Neurological Examinations

General physical examination and neurological examination results will be listed and summarized by counts and percentages for each treatment group at each scheduled visit.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned.

4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated.

4.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The "Enrolled Population" is redefined as "Screened Population"; the "Evaluable Population" is redefined as "Intent-to-Treat (ITT)" Population".

The analyses of efficacy endpoints other than MoCA will be conducted using MMRM instead of ANCOVA.

Shift tables will not be provided for safety assessments since any abnormal findings will be captured in AEs.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: PROTOCOL-REQUIRED LABORATORY TESTS

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	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	

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature		**Date**
Miao Yang	*Electronically signed by: Miao Yang* *Reason: Approved* *Date: Nov 16, 2020 10:27 EST*	16-Nov-2020
Miao Yang, PhD Biostatistician, Biostatistics Medpace, Inc.		
Mark Simmons	*Electronically signed by: Mark Simmons* *Reason: Approved* *Date: Nov 16, 2020 14:26 EST*	16-Nov-2020
Mark Simmons, PhD Sr. Biostatistician, Biostatistics Medpace, Inc.		
James Vornov	*Electronically signed by: James Vornov* *Reason: Approved* *Date: Nov 16, 2020 10:26 EST*	16-Nov-2020
James Vornov, MD, PhD Vice-President, Medical Department Medpace, Inc.		
	*Electronically signed by: Charlotte Keywood* *Reason: Approved* *Date: Nov 16, 2020 19:19 GMT+1*	16-Nov-2020
Charlotte Keywood Global Head Open R&D Zambon SpA		

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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 (MSA) 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 (week 3 – 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.

A study schema is depicted in Figure 1. The schedule of study assessments is described in Table 1.

FIGURE 1: SCHEMA

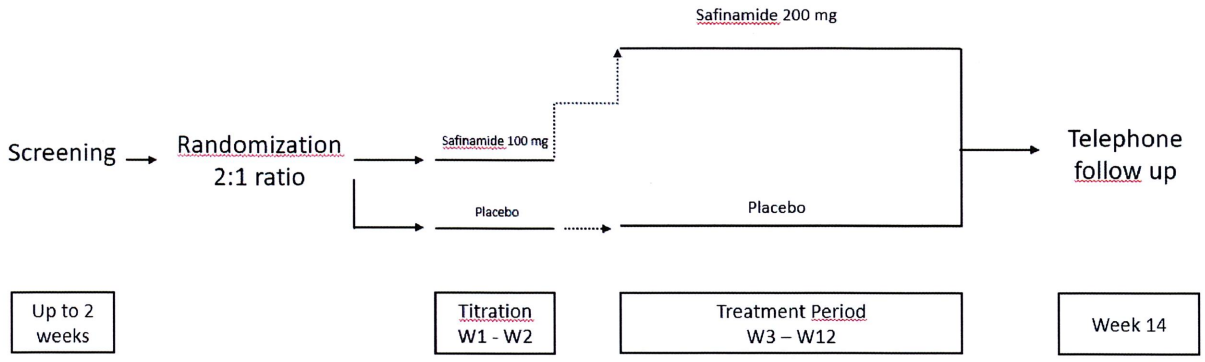

TABLE 1: SCHEDULE OF ACTIVITIES

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 of the protocol.
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.

2.2.2 Randomization and Blinding

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.

IVRS/IWRS	All participants will be centrally assigned to randomized study medication 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 medication will be dispensed at the study visits summarized in SoA. Returned study medication 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.

2.2.3 Sample Size Determination

As this is a pilot study with a focus on evaluating the safety of safinamide, no formal sample size has been calculated. Approximately 56 participants will be screened to achieve 48 randomly assigned (2:1 active vs placebo) to study medication and 40 evaluable participants for an estimated total of respectively 26 and 14 evaluable participants per group.

2.3 Study Endpoints

2.3.1 Efficacy Endpoints

Efficacy endpoints include the change from baseline to Weeks 4, 8 and 12 in the following parameters:

- 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 (Week 12 only)
- Unified Dystonia Rating Scale (UDRS)

2.3.1.1 Goniometric measurement

Goniometric measurement of "lateral" and "anterior" displacement is determined using a wall goniometer and expressing the value in degrees in the range of 0-90.

2.3.1.2 UMSARS

The Unified MSA Rating Scale (UMSARS) consists of four parts:

- Part I – Historical Review has 12 questions rated from 0 to 4, giving a range of 0-48 in the total score. Higher values indicate worse functional situation.
- Part II - Motor Examination Scale has 14 questions rated from 0 to 4, giving a range of 0-56 in the total score. Higher values indicate worse functional situation.
- Part III - Autonomic Examination has assessments of systolic blood pressure, diastolic blood pressure, heart rate and orthostatic symptoms (yes/no). Blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing.
- Part IV - Global Disability Scale ranges from 1 to 5 (1=completely independent; 2=not completely independent; 3=more dependent; 4=very dependent; 5=totally dependent and helpless).

2.3.1.3 MSA-QoL

The MSA Health-Related Quality of Life (MSA-QoL) scale has 40 questions on an ordinal scale of "no problem", "slight problem", "moderate problem", "marked problem", and "extreme problem". Additionally, patients were asked to indicate life satisfaction at the moment on a scale of 0 (extremely dissatisfied) to 100 (extremely satisfied).

2.3.1.4 MoCA

A score ranging from 0 to 30 will be recorded for each patient according to the Montreal Cognitive Assessment (MoCA) scale. Higher scores indicate better cognitive function.

2.3.1.5 UDRS

The Unified Dystonia Rating Scale (UDRS) assesses the severity and duration of dystonia in individual body areas. Each of 14 body area is evaluated via a 5-point ordinal scale of severity (0=none; 1=mild; 2=moderate; 3=severe; 4=extreme) and duration (0=none; 0.5=occasional, predominantly submaximal; 1.0= occasional, predominantly maximal; 1.5= intermittent, predominantly submaximal; 2.0= intermittent, predominantly maximal; 2.5= frequent, predominantly submaximal; 3.0= frequent, predominantly maximal; 3.5= constant, predominantly submaximal; 4.0=constant, predominantly maximal). A total score will be calculated as the sum of the severity and duration factors. If any of the factors is missing, then the total score is considered as missing. The total score ranges from 0 to 112.

2.3.2 Safety Endpoints

Safety endpoints include the following parameters:

- The nature, frequency, severity, relationship (to study drug), actions taken, and outcome of TEAEs and SAEs.
    - Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0. The severity of AEs will be assessed using "mild", "moderate" and "severe". The degree of "relatedness" of the AE to the study treatment will be described using "related to study drug" and "not related to study drug".
    - Treatment-emergent adverse events (TEAEs) are defined as those AEs that have a start date on or after the first administration of study drug. AEs with unknown/unreported onset date will also be counted as TEAE.
- Physical and neurological examination findings.
    - Physical and neurological examinations will be performed at Screening and Week 12. Results will be recorded as "abnormal", "normal" and "not assessed".
- Vital sign (heart rate, systolic and diastolic blood pressure) values.
    - Vital signs will be assessed at Screening, Day 1, 14, 28, 56, and Day 84/Week 12.
- 12-lead Electrocardiogram (ECG) parameter measures.
    - 12-lead ECG will be performed at Screening and Week 12.
- Clinical chemistry and hematology values.
    - Clinical chemistry and haematology evaluations will be performed at Screening and Week 12.
- Number of withdrawals (and reason if given).
    - Subject withdrawals from the study will be recorded on the End of Study CRF with reasons provided.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Nominal visits (i.e., study visits captured on the CRF) will be used for all efficacy and safety analyses.

3.1.3 Definition of Baseline

Baseline measurements refer to data collected at Day 1. If a value at Day 1 is not available, the last measurement prior to the first dose of study medication will be used as the baseline value.

3.1.4 Summary Statistics

Categorical data will be summarized with counts and percentages of subjects. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.5 Hypothesis Testing

Efficacy endpoints will be tested with hypothesis of the form:

$$H_0: \mu_{test} = \mu_{placebo}$$

$$H_1: \mu_{test} \neq \mu_{placebo}$$

where μ is the mean value of any specified endpoint in the population.

3.2 Analysis Populations

3.2.1 Screened Population

The Screened Population will include all participants who sign the informed consent form (ICF). This population will be listed but not used for statistical analyses.

3.2.2 Intent-to-Treat (ITT) Population

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

3.2.3 Safety Population

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

3.2.4 Per-Protocol (PP) Population

The PP 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 PP Population. The list of participants to be excluded from the PP Population will be finalized prior to database unblinding. This population will be used for the analysis of the leading efficacy variable UMSARS if the number of subjects in the PP Population is less than 90% of that in the ITT Population.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will be provided for all screened subjects. The number and percentage of subjects in the following disposition categories will be presented by treatment and in total:

- Subjects who were screened (signed informed consent);
- Subjects who were screen failures;
- Subjects who were randomized;

- Subjects who completed Week 12, and the whole study (i.e., Week 14 follow-up);
- Subjects who terminated early

For subjects who failed screening and who did not complete the study, a summary will be provided for the reasons. Primary reason for screen failure or early termination due to Covid-19 will also be provided if available.

3.3.2 Protocol Deviations

Protocol deviations (PDs) will be defined in the Medpace Protocol Deviation Plan and captured in the Study Management System. The number and percentage of subjects with CSR-reportable PDs will be summarized for each deviation category and overall based on the ITT Population. PDs related to COVID-19 will be categorized and summarized separately.

CSR-reportable PDs and COVID-19 related non-reportable PDs will be listed.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized by treatment and in total based on all screened subjects.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment and in total for all subjects in the ITT Population:

- Age (years)
- Sex
- Childbearing potential
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Continuous variables (age, height, weight, BMI) will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables (sex, race, ethnicity, childbearing potential) will be summarized with counts and percentages of subjects.

3.3.5 Medical History

General medical history and diagnosis of MSA for each subject will be provided in data listings for the ITT Population.

3.3.6 Prior and Concomitant Medications / Medical Procedures

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHODrug Dictionary Global B3, Sept 2019. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the ITT Population.

Prior and concomitant medical procedures and non-drug therapies will be listed.

3.3.7 Study Drug Exposure and Compliance

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- <2 weeks (<14 days)
- 2 - <8 weeks (14 - 55 days)
- 8 - <12 weeks (56 – 83 days)
- ≥12 weeks (≥84 days)

Percent compliance to the study drug regimen will be calculated as

100 x (# of tablets dispensed - # of tables returned) / # of tablets expected to be taken.

If study drug is not returned, the number of tablets returned and lost will be considered 0 for the compliance calculation. The number of tablets expected will be calculated as

- Date of last visit – Date of randomization + 1, if subjects early terminated prior to Week 2 / Visit 3;
- (Date of last visit – Date of Visit 3 + 1) *2 + (Date of Visit 3 – Date of randomization), if subjects early terminated prior to Week 12 / Visit 6;
- (Date of Visit 6 – Date of Visit 3 + 1) *2 + (Date of Visit 3 – Date of randomization), if subjects completed the end of treatment visit (i.e., Visit 6);
- Any drug interruptions or temporary discontinuation will be taken into account.

Percent compliance to the study drug regimen will be summarized by treatment with descriptive statistics and with counts and percentages of subjects with compliance in the following categories:

- <80%
- 80-120%
- >120%

3.4 Efficacy Assessment

All efficacy analyses will be performed for the ITT Population. The analysis of UMSARS will be repeated for the PP Population if the number of subjects in the PP Population is less than 90% of that in the ITT Population.

3.4.1 Goniometric Measurement

At each visit, the actual value of goniometric measurement (including "lateral" and "anterior" displacement) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

A mixed-model repeated measures (MMRM) will be used to analyze the change in lateral displacement (and anterior displacement) from baseline. The model will include treatment, week of visit, treatment-by-visit interaction as fixed effects, and baseline score as a covariate. The unstructured covariance matrix will be assumed. Least squares means, standard errors, 95% confidence intervals and p-values for the differences between treatment groups at Weeks 4, 8 and 12 will be displayed. The treatment comparisons of most interest will be the LS means contrasts between the safinamide treated participants and the placebo treated participants at Week 12.

3.4.2 UMSARS

UMSARS Part I total scores, Part II total scores, Part III and Part IV will be respectively summarized by treatment group over time using descriptive statistics. If any of the items is missing in Part I or Part II, then the corresponding total score is considered missing.

The MMRM analysis specified in 3.4.1 will be used to analyze the change in Part I total scores from baseline, and the change in Part II total scores from baseline, respectively.

3.4.3 MSA-QoL

At each visit, life satisfaction and change from baseline will be summarized by treatment using descriptive statistics. The change in satisfaction from baseline will be analyzed by the MMRM specified in 3.4.1.

3.4.4 MoCA

MoCA scores will be summarized by treatment group using descriptive statistics at the Screening visit and Week 12. Change from Screening at Week 12 will also be summarized using descriptive statistics, and analyzed by an analysis of covariance (ANCOVA) model including treatment group as a factor, and baseline score as a covariate. P-values will be reported.

3.4.5 UDRS

At each visit, UDRS total scores and change from baseline will be summarized by treatment using descriptive statistics. The change in UDRS total score will be analyzed by the MMRM specified in 3.4.1.

3.5 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Population. Any abnormal laboratory test results or other safety assessments will be reported as AE and listed.

3.5.1 Adverse Events (AEs)

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs
- Any serious TEAEs (SAEs)
- Any TEAEs leading to dose interruption
- Any TEAEs leading to dose reduction
- Any TEAEs leading to discontinuation of study drug
- Any AEs leading to death

Counts and percentages of subjects will also be presented by system organ class and preferred term for TEAEs, SAEs, study drug related TEAEs, and TEAEs leading to discontinuation of study drug.

Listings will be presented for all TEAEs, SAEs, and study drug related TEAEs.

3.5.2 Clinical Laboratory Tests

Values and changes from baseline will be summarized using descriptive statistics for each treatment group by visit for protocol-required laboratory tests in Appendix A. All lab results will be listed.

3.5.3 Vital Signs

Vital signs parameters (heart rate, systolic and diastolic blood pressure) will be listed and summarized using descriptive statistics for each treatment group by visit.

3.5.4 12-Lead Electrocardiograms

The overall interpretation of ECG data will be summarized by counts and percentages by treatment group. All ECG findings will be listed.

3.5.5 Physical and Neurological Examinations

General physical examination and neurological examination results will be listed and summarized by counts and percentages for each treatment group at each scheduled visit.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned.

4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated.

4.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The "Enrolled Population" is redefined as "Screened Population"; the "Evaluable Population" is redefined as "Intent-to-Treat (ITT)" Population".

The analyses of efficacy endpoints other than MoCA will be conducted using MMRM instead of ANCOVA.

Shift tables will not be provided for safety assessments since any abnormal findings will be captured in AEs.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: PROTOCOL-REQUIRED LABORATORY TESTS

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	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	