Clinical trial results:
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.

Summary

EudraCT number	2018-004145-16
Trial protocol	ES IT
Global end of trial date	05 January 2021

Results information

Result version number	v1 (current)
This version publication date	29 July 2021
First version publication date	29 July 2021

Trial information

Trial identification

Sponsor protocol code	Z7219K01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03753763
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon S.p.A.
Sponsor organisation address	Via Lillo del Duca 10, Bresso (MI), Italy, 20091
Public contact	Clinical Development Manager, Zambon S.p.A., +39 02665241, clinicaltrials@zambongroup.com
Scientific contact	Clinical Development Manager, Zambon S.p.A., +39 02665241, clinicaltrials@zambongroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 January 2021
Global end of trial reached?	Yes
Global end of trial date	05 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety: To evaluate the safety and tolerability of safinamide 200 mg once daily compared with placebo.
Efficacy: To evaluate the potential efficacy of safinamide 200 mg once daily, as add-on therapy, on motor function and/or quality of life.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions, Regulation (European Union) No 536/2014, Commission Directive 2005/28/EC, and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with International Council for Harmonisation (ICH) E6 Good Clinical Practice Guidelines.

Background therapy:

Oral daily Levodopa alone or in combination with other anti-parkinsonian drugs (such as dopamine agonist, anticholinergic, and/or amantadine) allowed for MSA treatment.

Evidence for comparator: -

Actual start date of recruitment	29 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Italy: 36
Worldwide total number of subjects	49
EEA total number of subjects	49

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28

From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 56 participants were planned to be screened in order to achieve 49 participants randomly assigned (2:1) to study drug and 42 evaluable participants, resulting in a planned estimated total of 32 evaluable participants receiving safinamide and 17 evaluable participants receiving matching placebo.

Pre-assignment

Screening details:

After providing written informed consent to participate in the study, participants entered a Screening period of up to 2 weeks. During the Screening period, participants underwent all of the evaluations necessary to establish their eligibility for the study and were assigned a unique screening number.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a double-blind study; therefore, the Sponsor, Investigator, and participant did not know the study drugs being administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	Safinamide

Arm description:

Safinamide methanesulfonate film-coated tablets once daily.
During the titration period of 2 weeks (Week 1 to Week 2) participants received 1 tablet (100 mg) safinamide, while during the treatment period (Week 3 to Week 12) they received 2 tablets (200 mg) safinamide once-a-day, taken in the morning, in addition to their daily levodopa dose.

Arm type	Experimental
Investigational medicinal product name	Safinamide
Investigational medicinal product code	
Other name	safinamide methanesulfonate
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

During the titration period of 2 weeks (Week 1 to Week 2) participants received 1 tablet (100 mg) safinamide once-daily.
During the treatment period (Week 3 to Week 12) they received 2 tablets (200 mg) safinamide once-a-day.
Tablets were taken in the morning, along with patients' first levodopa dose of the day.
Safinamide was supplied as 100 mg round, orange to copper, biconcave, film-coated tablets.

Arm title	Placebo

Arm description:

Safinamide methanesulfonate matching placebo film-coated tablets once daily.
Safinamide matching placebo was administered both during the titration period of 2 weeks (Week 1 to Week 2) and during the following period (Week 3 to Week 12), once daily, taken in the morning, in addition to their daily levodopa dose.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered both during the titration period of 2 weeks (Week 1 to Week 2) and during the following period (Week 3 to Week 12), once daily, taken in the morning, in addition to their daily levodopa dose.
Safinamide matching placebo was supplied as 100 mg round, orange to copper, biconcave, film-coated tablets.

Number of subjects in period 1	Safinamide	Placebo
Started	32	17
Completed	26	16
Not completed	6	1
Consent withdrawn by subject	3	1
Adverse event, non-fatal	2	-
clinical deterioration	1	-

Baseline characteristics

Reporting groups

Reporting group title	Safinamide

Reporting group description:

Safinamide methanesulfonate film-coated tablets once daily.
During the titration period of 2 weeks (Week 1 to Week 2) participants received 1 tablet (100 mg) safinamide, while during the treatment period (Week 3 to Week 12) they received 2 tablets (200 mg) safinamide once-a-day, taken in the morning, in addition to their daily levodopa dose.

Reporting group title	Placebo

Reporting group description:

Safinamide methanesulfonate matching placebo film-coated tablets once daily.
Safinamide matching placebo was administered both during the titration period of 2 weeks (Week 1 to Week 2) and during the following period (Week 3 to Week 12), once daily, taken in the morning, in addition to their daily levodopa dose.

Reporting group values	Safinamide	Placebo	Total
Number of subjects	32	17	49
Age categorical Units: Subjects			
Adults (18-64 years)	17	11	28
From 65-84 years	15	6	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.8	62.8	
standard deviation	± 8.23	± 10.27	-
Gender categorical Units: Subjects			
Female	20	6	26
Male	12	11	23

Subject analysis sets

Subject analysis set title	Safinamide - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all randomized participants. This population was used for describing all the demographic characteristics and all efficacy variables.

Subject analysis set title	Safinamide - PP
Subject analysis set type	Per protocol

Subject analysis set description:

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.

Subject analysis set title	Safinamide - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population included all randomized participants who took at least 1 dose of study drug. This population was used to summarize all safety data; participants were analyzed according to the drug they actually received.

Subject analysis set title	Placebo - ITT

Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all randomized participants. This population was used for all efficacy variables.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol (PP) Population included all randomized participants who did not have any entry criteria violations or protocol deviations that significantly impacted the assessment or interpretation of efficacy data.

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population included all randomized participants who took at least 1 dose of study drug. This population was used to summarize all safety data; participants were analyzed according to the drug they actually received.

Reporting group values	Safinamide - ITT	Safinamide - PP	Safinamide - Safety
Number of subjects	32	32	32
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	17
From 65-84 years	15	15	15
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.8	65.8	65.8
standard deviation	± 8.23	± 8.23	± 8.23
Gender categorical Units: Subjects			
Female	20	20	20
Male	12	12	12

Reporting group values	Placebo - ITT	Placebo - PP	Placebo - Safety
Number of subjects	17	17	17
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	11
From 65-84 years	6	6	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.8	62.8	62.8
standard deviation	± 10.27	± 10.27	± 10.27
Gender categorical Units: Subjects			
Female	6	6	6
Male	11	11	11

End points

End points reporting groups

Reporting group title	Safinamide

Reporting group description:

Safinamide methanesulfonate film-coated tablets once daily.
During the titration period of 2 weeks (Week 1 to Week 2) participants received 1 tablet (100 mg) safinamide, while during the treatment period (Week 3 to Week 12) they received 2 tablets (200 mg) safinamide once-a-day, taken in the morning, in addition to their daily levodopa dose.

Reporting group title	Placebo

Reporting group description:

Safinamide methanesulfonate matching placebo film-coated tablets once daily.
Safinamide matching placebo was administered both during the titration period of 2 weeks (Week 1 to Week 2) and during the following period (Week 3 to Week 12), once daily, taken in the morning, in addition to their daily levodopa dose.

Subject analysis set title	Safinamide - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all randomized participants. This population was used for describing all the demographic characteristics and all efficacy variables.

Subject analysis set title	Safinamide - PP
Subject analysis set type	Per protocol

Subject analysis set description:

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.

Subject analysis set title	Safinamide - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population included all randomized participants who took at least 1 dose of study drug. This population was used to summarize all safety data; participants were analyzed according to the drug they actually received.

Subject analysis set title	Placebo - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Population included all randomized participants. This population was used for all efficacy variables.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol (PP) Population included all randomized participants who did not have any entry criteria violations or protocol deviations that significantly impacted the assessment or interpretation of efficacy data.

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population included all randomized participants who took at least 1 dose of study drug. This population was used to summarize all safety data; participants were analyzed according to the drug they actually received.

Primary: TEAEs (treatment emergent adverse events) and SAEs (serious adverse events)

End point title	TEAEs (treatment emergent adverse events) and SAEs (serious adverse events)[1]

End point description:

While evaluating safety and tolerability of safinamide, 200 mg od, compared with placebo, severity of

TEAEs, their relationship to study drug, their seriousness and their consequences were assessed. TEAEs were defined as adverse events (AEs) that started after the first dose of study drug.

End point type	Primary

End point timeframe:

Throughout the study, from baseline (and at each interim visit) to telephone follow-up visit at 14 week.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Measure type "Number" related to adverse events can't have a statistical analysis

End point values	Safinamide - Safety	Placebo - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: events				
Any TEAEs	52	28		
Mild TEAEs	49	21		
Moderate TEAEs	4	5		
Severe TEAEs	3	4		
Serious TEAEs	2	0		
Study drug-related TEAEs	15	11		
TEAEs leading to study drug withdrawal	1	0		
AEs leading to death	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in the goniometric measurement for anterior displacement

End point title	Change from baseline to week 12 in the goniometric measurement for anterior displacement

End point description:

To evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on quality of life (change in anterior displacement). The goniometric measurement consists in the posture evaluation of the patient, measuring through a goniometer the angle of the flexion of the trunk. Goniometric measurement of “anterior” displacement was determined using a wall goniometer and expressing the value in degrees in the range of 0 to 90.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: degrees				
arithmetic mean (standard deviation)	1.3 (± 9.46)	0.9 (± 8.01)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Safinamide - ITT v Placebo - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.9697 [3]
Method	Mixed models analysis
Parameter estimate	least square mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	6.5

Notes:

[2] - The model included treatment, week of visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate.
[3] - A mixed-model repeated measures (MMRM) was used to analyze the change in anterior displacement from baseline.

Secondary: Change From Baseline to Week 12 in the Goniometric Measurement for lateral Displacement

End point title	Change From Baseline to Week 12 in the Goniometric Measurement for lateral Displacement

End point description:

To evaluate the potential efficacy of safinamide 200 mg od, as add-on therapy, on quality of life (change in anterior displacement). The goniometric measurement consists in the posture evaluation of the patient, measuring through a goniometer the angle of the flexion of the trunk. Goniometric measurement of "lateral" displacement was determined using a wall goniometer and expressing the value in degrees in the range of 0 to 90.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: degrees				
arithmetic mean (standard deviation)	1.3 (± 5.08)	-0.2 (± 4.47)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Safinamide - ITT v Placebo - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.7751 [5]
Method	Mixed models analysis
Parameter estimate	least square mean difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	4.1

Notes:

[4] - The model included treatment, week of visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate.
[5] - A mixed-model repeated measures (MMRM) was used to analyze the change in lateral displacement from baseline.

Secondary: Change From Baseline to Week 12 in Unified Multiple System Atrophy Rating Scale (UMSARS), Part II (ITT Population)

End point title	Change From Baseline to Week 12 in Unified Multiple System Atrophy Rating Scale (UMSARS), Part II (ITT Population)

End point description:

UMSARS is a validated, disease-specific scale representing the diverse signs and symptoms in MSA. Higher scores on the UMSARS scales mean poorer health.
UMSARS has the following domains:
Part I - Activities of Daily Living score (12 questions ranged in 0-4 [total score 0-48]) that evaluates motor including autonomic activities
Part II - Motor Examination score (14 questions, [total score 0-56])
Part III - Autonomic Examination
Part IV - Global disability scale ((1=completely independent; 2=not completely independent; 3=more dependent; 4=very dependent; 5=total
dependent and helpless).

Only UMSARS Part II total score is reported, which was obtained as the sum of the 14 items in the scale. If any of the items were missing, then the total score was considered missing. Higher scores indicate worse functional situation.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.1 (± 5.40)	-0.4 (± 5.85)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Safinamide - ITT v Placebo - ITT
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.9076 [7]
Method	Mixed models analysis
Parameter estimate	least square mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	3.7

Notes:

[6] - The model included treatment, week of visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate.
[7] - The MMRM analysis, specified in Section Goniometric measurement, was used to analyze the change in Part II total scores from baseline.

Secondary: Change From Baseline to Week 12 in Unified Multiple System Atrophy Rating Scale (UMSARS), Part II (PP Population)

End point title	Change From Baseline to Week 12 in Unified Multiple System Atrophy Rating Scale (UMSARS), Part II (PP Population)

End point description:

UMSARS is a validated, disease-specific scale representing the diverse signs and symptoms in MSA. Higher scores on the UMSARS scales mean poorer health.
UMSARS has the following domains:
Part I - Activities of Daily Living score (12 questions ranged in 0-4 [total score 0-48]) that evaluates motor including autonomic activities
Part II - Motor Examination score (14 questions, [total score 0-56])
Part III - Autonomic Examination
Part IV - Global disability scale ((1=completely independent; 2=not completely independent; 3=more dependent; 4=very dependent; 5=total
dependent and helpless).

Only UMSARS Part II total score is reported, which was obtained as the sum of the 14 items in the scale. If any of the items were missing, then the total score was considered missing. Higher scores indicate worse functional situation.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - PP	Placebo - PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	13		
Units: score on a scale				
arithmetic mean (standard deviation)	-1.1 (± 4.66)	-0.6 (± 6.17)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Placebo - PP v Safinamide - PP
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.5386 [9]
Method	Mixed models analysis
Parameter estimate	least square mean difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2.6

Notes:

[8] - The model included treatment, week of visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate.
[9] - A mixed-model repeated measures (MMRM) was used to analyze the change in from baseline in UMSARS Part II.

Secondary: Change From Baseline to Week 12 in Multiple System Atrophy Health-Related Quality of Life (MSA-QoL) Scale

End point title	Change From Baseline to Week 12 in Multiple System Atrophy Health-Related Quality of Life (MSA-QoL) Scale

End point description:

The MSA-QoL is a self-reported questionnaire focusing on MSA-specific symptoms and has a scale ranging from 0 to 160, with 0= 'no problem' and 160= "extreme problem".

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: units on a scale				
arithmetic mean (standard deviation)	5.6 (± 25.57)	-2.9 (± 14.37)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Safinamide - ITT v Placebo - ITT

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.3364 [11]
Method	Mixed models analysis
Parameter estimate	least square mean difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	18.6

Notes:

[10] - The model included treatment, week of visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate.
[11] - A mixed-model repeated measures (MMRM) was used to analyze the change in from baseline in MSA-QoL scale.

Secondary: Change From Baseline to Week 12 in Montreal Cognitive Assessment (MoCA) Scale

End point title	Change From Baseline to Week 12 in Montreal Cognitive Assessment (MoCA) Scale

End point description:

The Montreal Cognitive Assessment (MoCA) was designed as a tool for rapid screening for mild cognitive impairment. It evaluates different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructive skills, abstraction, calculation and orientation. The administration time of the MoCa is 10 minutes. The MoCA scale ranges from 0 to 30, with higher scores indicating better cognitive functioning.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: score on a scale				
arithmetic mean (standard deviation)	0.0 (± 2.01)	-0.3 (± 2.09)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Safinamide - ITT v Placebo - ITT

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.7574
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	1.5

Notes:

[12] - Change from Screening at Week 12 was analyzed by an analysis of covariance (ANCOVA). The ANCOVA included change from baseline as the response variable, treatment group as a factor, and baseline score as a covariate.

Secondary: Change From Baseline to Week 12 in Unified Dystonia Rating Scale (UDRS)

End point title	Change From Baseline to Week 12 in Unified Dystonia Rating Scale (UDRS)

End point description:

UDRS consists of a Historical Section, divided into questionnaires about 1) on-dyskinesia and 2) off - dystonia, and an Objective Section, divided into 3) impairment and 4) disability scales. The Historical Section is scored from 0-60, and the Objective section is scored 0-44, where higher scores reflect greater difficulty or impairment.
The Unified Dystonia Rating Scale (UDRS) assesses the motor severity and duration of dystonia in 14 body areas. The total score, obtained as the sum of the severity and duration factors, ranges from 0 to 112. Higher scores indicate worse dystonia.

End point type	Secondary

End point timeframe:

From baseline to week 12

End point values	Safinamide - ITT	Placebo - ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	17		
Units: units on a scale				
arithmetic mean (standard deviation)	1.0 (± 4.82)	0.3 (± 5.60)		

Statistical analyses

Statistical analysis title	Safinamide vs placebo
Comparison groups	Safinamide - ITT v Placebo - ITT

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.6393 [14]
Method	Mixed models analysis
Parameter estimate	least square mean difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	4

Notes:

[13] - The model included treatment, week of visit, and treatment-by-visit interaction as fixed effects and baseline score as a covariate.

[14] - A mixed-model repeated measures (MMRM) was used to analyze the change from baseline in UDRS.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At baseline, at interim visits (Weeks 2 - 8, and more precisely at days 14 ± 3, 28 ± 3, 56 ± 3), at End of Treatment visit (EOT) at Week 12 (84 ± 3 days), and at follow-up call at week 14 (98 ± 3).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Safinamide - safety

Reporting group description:

Safinamide methanesulfonate film-coated tablets once daily.
During the titration period of 2 weeks (Week 1 to Week 2) participants received 1 tablet (100 mg) safinamide, while during the treatment period (Week 3 to Week 12) they received 2 tablets (200 mg) safinamide once-a-day, taken in the morning, in addition to their daily levodopa dose.

Reporting group title	Placebo - safety

Reporting group description:

Safinamide methanesulfonate matching placebo film-coated tablets once daily.
Safinamide matching placebo was administered both during the titration period of 2 weeks (Week 1 to Week 2) and during the following period (Week 3 to Week 12), once daily, taken in the morning, in addition to their daily levodopa dose.

Serious adverse events	Safinamide - safety	Placebo - safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)	0 / 17 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac respiratory arrest			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safinamide - safety	Placebo - safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 32 (65.63%)	11 / 17 (64.71%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 32 (15.63%)	7 / 17 (41.18%)	
occurrences (all)	5	5	
Wound			
subjects affected / exposed	1 / 32 (3.13%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Chest injury			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)	2 / 17 (11.76%)	
occurrences (all)	2	4	
Dependent rubor			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dyskinesia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	2	0	

Hypoaesthesia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Nervous system disorder			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Parkinsonian gait			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Parkinsonism			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	2 / 32 (6.25%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Gait disturbance			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Peripheral swelling			

subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	1 / 32 (3.13%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Salivar hypersecretion			
subjects affected / exposed	0 / 32 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Abdominal discomfort			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hallucination			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	0 / 32 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nervousness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	3 / 32 (9.38%)	2 / 17 (11.76%)	
occurrences (all)	3	2	
Cystitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Escherichia infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Oral fungal infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pseudomonas infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2020	This amendment was developed to formally incorporate the administrative letter, to add details of measures taken during the COVID-19 pandemic, to clarify and correct inconsistencies in the original Protocol raised from the Italian Health Authority and/or Italian Coordinating Site, to address an inconsistency within the Protocol in regard to the number of evaluable participants, to provide additional clarifications on the sample size determination background, and to provide information on the benefit/risk assessment as outlined in the 09 August 2019 administrative letter.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations or caveats were applicable to this summary of the results

Notes: