Clinical trial results:
A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of safinamide 100 mg once daily, as add-on therapy, in idiopathic Parkinson's Disease (IPD) patients with motor fluctuations and PD related chronic pain

Summary

EudraCT number	2017-002426-20
Trial protocol	ES FR AT IT
Global end of trial date	03 May 2021

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	Z7219M01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03841604
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon SpA
Sponsor organisation address	Via Antonio Meucci, 3, Bresso (Milan), Italy, 20091
Public contact	Clinical Development Manager , Zambon SpA, clinicaltrials@zambongroup.com
Scientific contact	Clinical Development Manager , Zambon SpA, 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	18 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
• The change from baseline to Week 16 in pain severity, as assessed with an 11-point NRS.
Secondary:
• Subjects with reduction in pain severity of ≥2 points at Week 16, as assessed with an 11-point NRS, compared to baseline.
• The Clinical Global Impression of Severity (CGI-S) score for pain at Week 16.
• The change from baseline to Week 16 in the Clinical Global Impression of Change (CGI-C) score for pain.
• The change from baseline to Week 16 in the Patient Global Impression of Change (PGI-C) score for pain.
• The percentage of reduction in number of concomitant pain drugs from baseline to Week 16.
• The number of patients with at least one intake of PRN pain medication.
• Amount of PRN pain medication.
• The change from baseline to Week 16 in the Hospital Anxiety and Depression Scale (HADS) score.
• The change from baseline to Week 16 in the Movement Disorder Society–Unified Parkinson's Disease Rating Scale during the "ON" phase.

Protection of trial subjects:

Written consent was obtained from the patient before he/she could participate in the study. The content and process of obtaining informed consent was in accordance with all applicable regulatory requirements.
Prior to the initiation of any procedures relating to the study, a patient's consent was obtained using a consent form written in the patient's native language that was approved by the institutional review boards (IRBs)/independent ethics committee (IEC) and that was signed and personally dated by the patient at the time of consent. The person who conducted the informed consent discussion signed and personally dated the consent form. A copy of the signed and dated informed consent was given to the patient. The Investigator kept each patient's original, signed and dated consent form on file for inspection by a regulatory authority or authorized party at any time.
Depending on national regulations, an authorized person other than the Investigator could inform the patient, sign and date the consent form.
During the patient's participation in the study, whenever important new information became available that was relevant to the patient's consent, the consent form was updated accordingly for IRB/IEC approval. The patient was informed in a timely manner if new information became available that was relevant to the patient's willingness to continue participation in the study. The communication of this information was documented. The approved revised consent form was signed and dated by the patient.

Background therapy:

All patients were on a stable therapy with Levodopa (L-DOPA), alone or in combination with other anti Parkinson drugs. PRN PD pain medications were used as needed from Day 1 onwards, subjects recorded the use of as needed (PRN) medications along with indicating the worst pain they experienced on a daily basis.

Evidence for comparator:

There is no comparator. It is a placebo-controlled study.

Actual start date of recruitment	15 November 2018
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: 21
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 25
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	30
From 65 to 84 years	38
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A total of 94 subjects were enrolled in the study. 47 subjects were randomly assigned to safinamide and 25 subjects to placebo for a treatment period of 16 weeks. A screening period of up to 1 to 2 weeks was completed and reviewed to confirm each subject's eligibility criteria. Overall, 23 subjects (24.5%) were screen failures.

Pre-assignment

Screening details:

About 132 participants were screened, 105 were enrolled Study participation with up to a maximum duration of 19 weeks, comprising a screening period (1 to 2 weeks) and a treatment period (16 weeks). A telephone call was performed 1 week after the end of treatment.

Period 1

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

Blinding implementation details:

This was a double-blind study. The IWRS was programmed with blind-breaking instructions. In case of an emergency, the investigator had the sole responsibility for determining whether unblinding of a subject's treatment assignment was warranted. Subject safety was always the first consideration in making such a determination.

Arms

Are arms mutually exclusive?	Yes
Arm title	Safinamide (50 mg and 100mg)

Arm description:

Eligible subjects were randomly assigned in a double-blind manner in a 2:1 ratio to receive treatment with safinamide at Visit 2 (Day 1),

Arm type	Experimental
Investigational medicinal product name	Safinamide methanesulfonate 50mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Safinamide methanesulfonate 50 mg tablets was administered orally, OD, with or without food, at breakfast time when the subject was taking their morning dose of L-DOPA.

Investigational medicinal product name	Safinamide methanesulfonate 100mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Safinamide methanesulfonate 50 mg tablets was administered orally, OD, with or without food, at breakfast time when the subject was taking their morning dose of L-DOPA.

Arm title	Placebo (50mg and 100 mg)

Arm description:

Eligible subjects were randomly assigned in a double-blind manner in a 2:1 ratio to receive treatment with placebo at Visit 2 (Day 1).

Arm type	Placebo

Investigational medicinal product name	Placebo (50mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo (50 mg tablets) was administered orally, OD, with or without food, at breakfast time when the subject was taking their morning dose of L-DOPA.

Investigational medicinal product name	Placebo (100mg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo (100 mg tablets) was administered orally, OD, with or without food, at breakfast time when the subject was taking their morning dose of L-DOPA.

Number of subjects in period 1	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)
Started	46	25
Completed	38	22
Not completed	8	3
Consent withdrawn by subject	3	1
Physician decision	1	-
Adverse event, non-fatal	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Safinamide (50 mg and 100mg)
Reporting group description:	
Eligible subjects were randomly assigned in a double-blind manner in a 2:1 ratio to receive treatment with safinamide at Visit 2 (Day 1),	
Reporting group title	Placebo (50mg and 100 mg)
Reporting group description:	
Eligible subjects were randomly assigned in a double-blind manner in a 2:1 ratio to receive treatment with placebo at Visit 2 (Day 1).	

Reporting group values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)	Total
Number of subjects	46	25	71
Age categorical Units: Subjects			
Adults (18-64 years)	19	11	30
From 65-84 years	25	13	38
85 years and over	2	1	3
Age continuous Units: years			
median	65.5	67.0	
full range (min-max)	40 to 85	43 to 87	-
Gender categorical Units: Subjects			
Female	25	13	38
Male	21	12	33

Subject analysis sets	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects in the study, with at least one measurement of the primary efficacy variable following at least one dose of study drug, were included in the full analysis set (FAS). Summaries on the FAS were performed for all efficacy endpoints. Subjects in this analysis set were summarized according to the treatment to which they were randomly assigned.	
Subject analysis set title	Per-protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) set was a subset of subjects in the FAS who completed the study and for whom no relevant protocol deviations were documented. Identification of relevant protocol deviations occurred during a blinded review meeting that preceded database lock. A second analysis of the primary efficacy endpoint was based on the PP set. All subjects in the PP set were summarized according to the treatment to which they were assigned.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety set included all randomized subjects assigned to study drug who took at least 1 dose of study drug. The safety set was used for the analysis of all safety endpoints.	

Reporting group values	Full analysis set (FAS)	Per-protocol Set (PPS)	Safety Set
Number of subjects	68	54	71
Age categorical Units: Subjects			
Adults (18-64 years)	21	29	30
From 65-84 years	30	36	38
85 years and over	3	3	3
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female	37	30	38
Male	31	24	33

End points

End points reporting groups

Reporting group title	Safinamide (50 mg and 100mg)

Reporting group description:

Eligible subjects were randomly assigned in a double-blind manner in a 2:1 ratio to receive treatment with safinamide at Visit 2 (Day 1),

Reporting group title	Placebo (50mg and 100 mg)

Reporting group description:

Eligible subjects were randomly assigned in a double-blind manner in a 2:1 ratio to receive treatment with placebo at Visit 2 (Day 1).

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects in the study, with at least one measurement of the primary efficacy variable following at least one dose of study drug, were included in the full analysis set (FAS). Summaries on the FAS were performed for all efficacy endpoints. Subjects in this analysis set were summarized according to the treatment to which they were randomly assigned.

Subject analysis set title	Per-protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) set was a subset of subjects in the FAS who completed the study and for whom no relevant protocol deviations were documented. Identification of relevant protocol deviations occurred during a blinded review meeting that preceded database lock. A second analysis of the primary efficacy endpoint was based on the PP set. All subjects in the PP set were summarized according to the treatment to which they were assigned.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set included all randomized subjects assigned to study drug who took at least 1 dose of study drug. The safety set was used for the analysis of all safety endpoints.

Primary: Change from baseline to week 16 in pain severity (FAS)

End point title	Change from baseline to week 16 in pain severity (FAS)

End point description:

The primary endpoint evaluated in this study was the mean change in pain severity ("average worst pain experienced in the last 7 days", ie, average of the worst pain score on each of the 7 days preceding the site visit), as assessed by an 11-point NRS, from baseline to Week 16

End point type	Primary

End point timeframe:

From baseline to Week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	23		
Units: unit(s)				
arithmetic mean (standard deviation)				
Week 16	-1.6 (± 2.01)	-0.8 (± 1.29)		

Statistical analyses

Statistical analysis title	Difference in Change from Baseline at week 16

Statistical analysis description:

The primary efficacy endpoint was analyzed with a mixed model for repeated measures (MMRM), using visit on subject ID as the repeated factor with an unstructured covariance term. The model included fixed effects terms for treatment, country, visit, and regular pain medication use at baseline (yes or no) and a covariate term for pain severity score at baseline.

Comparison groups	Safinamide (50 mg and 100mg) v Placebo (50mg and 100 mg)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1695 [1]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares (LS) Means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	0.32
Variability estimate	Standard error of the mean
Dispersion value	0.52

Notes:

[1] - p-value at Week 16 is used for testing the null hypothesis for the primary endpoint that safinamide is no better than placebo in managing pain. p-value derived for the difference between treatment groups at each visit.

Primary: Change from baseline to week 16 in pain severity (PP set)

End point title	Change from baseline to week 16 in pain severity (PP set)

End point description:

The Per Protocol (PP) Set is a subset of subjects in the FAS who signed the ICF, completed the study i.e. follow-up visit after Week 16, received the treatment as per IVRS, had more than 80% study medication compliance at all visit-to-visit interval, had at least 4 out of 7 pain score available at baseline and Week 16 and for whom no major protocol deviations were documented.
Average worst Pain Score is calculated using 11-point NRS Scale by taking average of scores obtained in last 7 days before each visit.
At least 4 out of 7 daily pain scores are needed to calculate a valid average over 7 days.

End point type	Primary

End point timeframe:

From baseline until Week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	19		
Units: unit(s)				
arithmetic mean (standard deviation)				
Week 16	-1.6 (± 2.05)	-0.8 (± 1.33)		

Statistical analyses

Statistical analysis title	Difference in Change from Baseline at week 16

Statistical analysis description:

The primary efficacy endpoint was analyzed with a mixed model for repeated measures (MMRM), using visit on subject ID as the repeated factor with an unstructured covariance term. The model included fixed effects terms for treatment, country, visit, and regular pain medication use at baseline (yes or no) and a covariate term for pain severity score at baseline.

Comparison groups	Safinamide (50 mg and 100mg) v Placebo (50mg and 100 mg)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0784 [2]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares (LS) Mean
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.55

Notes:

[2] - p-value derived for the difference between treatment groups at each visit.

Secondary: Subjects with reduction in pain severity of ≥2 points at Week 16

End point title	Subjects with reduction in pain severity of ≥2 points at Week 16

End point description:

Subjects with reduction in pain severity of ≥2 points (“average worst pain experienced in the last 7 days”) at Week 16, as assessed with an 11-point NRS, compared to baseline.
Missing values at each visit for Observed Responder are not used in CMH calculation.

End point type	Secondary

End point timeframe:

At week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	23		
Units: percent				
number (not applicable)				
Responder	33.3	13.0		

Statistical analyses

Statistical analysis title	Percentages of Pain Responders

Statistical analysis description:

Percentage of pain responders, defined as subjects with reduction in pain severity of ≥2 points from baseline ("average worst pain experienced in the last 7 days"), as assessed with an 11-point NRS, was analyzed at Week 16 using a Cochran-Mantel-Haenszel (CMH) adjusted test of the difference in proportions between the 2 treatment groups. Country was used as the stratification factor.

Comparison groups	Placebo (50mg and 100 mg) v Safinamide (50 mg and 100mg)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0744 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.01

Notes:

[3] - p-value derived from the 2-sided Cochran-Mantel-Haenszel (CMH) test to test the null hypothesis of no difference between treatment groups in percentage of pain responder rates adjusted for country as stratification factor

Secondary: The Clinical Global Impression of Severity (CGI-S) score for pain at Week 16

End point title	The Clinical Global Impression of Severity (CGI-S) score for pain at Week 16

End point description:

The CGI-S was analyzed using the same statistical methods, ie, MMRM as for the primary efficacy parameter by replacing the covariate of pain severity at baseline with the respective efficacy parameter.

End point type	Secondary

End point timeframe:

From baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	20		
Units: unit(s)				
arithmetic mean (standard deviation)				
Baseline	3.8 (± 0.65)	3.8 (± 0.66)		
Week 16	3.4 (± 0.76)	3.5 (± 0.76)		

Statistical analyses

Statistical analysis title	Analysis of Clinical Global Impression of Severity

Statistical analysis description:

The Clinical Global Impression of Severity (CGI-S) score for pain was analyzed with a mixed model for repeated measures (MMRM). The model included fixed effects terms for treatment, country, visit, and regular pain medication use at baseline (yes or no) and a covariate term for pain severity score at baseline.

Comparison groups	Safinamide (50 mg and 100mg) v Placebo (50mg and 100 mg)
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9052 [4]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares (LS) Mean
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[4] - p-value derived for the difference between treatment groups at each visit.

Secondary: The change from baseline to Week 16 in the Clinical Global Impression of Change (CGI-C) score for pain.

End point title	The change from baseline to Week 16 in the Clinical Global Impression of Change (CGI-C) score for pain.

End point description:

The CGI-C was analyzed using the same statistical methods, ie, MMRM as for the primary efficacy parameter by replacing the covariate of pain severity at baseline with the respective efficacy parameter.

End point type	Secondary

End point timeframe:

From baseline to Week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	20		
Units: unit(s)				
arithmetic mean (standard deviation)				
Week 16	3.4 (± 1.09)	3.5 (± 1.00)		

Statistical analyses

Statistical analysis title	Analysis of Clinical Global Impression of Change

Statistical analysis description:

The change from baseline to Week 16 in the Clinical Global Impression of Change (CGI-C) score for pain was analyzed with a mixed model for repeated measures (MMRM). The model included fixed effects terms for treatment, country, visit, and regular pain medication use at baseline (yes or no) and a covariate term for pain severity score at baseline.

Comparison groups	Placebo (50mg and 100 mg) v Safinamide (50 mg and 100mg)
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7247 [5]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares (LS) Mean
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[5] - p-value derived for the difference between treatment groups at each visit.

Secondary: The change from baseline to Week 16 in the Patient Global Impression of Change (PGI-C) score for pain.

End point title	The change from baseline to Week 16 in the Patient Global Impression of Change (PGI-C) score for pain.

End point description:

The PGI-C was analyzed using the same statistical methods, ie, MMRM as for the primary efficacy parameter by replacing the covariate of pain severity at baseline with the respective efficacy parameter.

End point type	Secondary

End point timeframe:

From baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	20		
Units: unit(s)				
arithmetic mean (standard deviation)				
Week 16	2.7 (± 1.33)	2.5 (± 1.28)		

Statistical analyses

Statistical analysis title	Analysis of Patient Global Impression of Change

Statistical analysis description:

The change from baseline to Week 16 in the Patient Global Impression of Change (PGI-C) score for pain was analyzed with a mixed model for repeated measures (MMRM). The model included fixed effects terms for treatment, country, visit, and regular pain medication use at baseline (yes or no) and a covariate term for pain severity score at baseline.

Comparison groups	Placebo (50mg and 100 mg) v Safinamide (50 mg and 100mg)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7115 [6]
Method	Mixed model for repeated measures
Parameter estimate	Least Squares (LS) Mean
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.88
Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[6] - p-value derived for the difference between treatment groups at each visit.

Secondary: The percentage of reduction in number of concomitant pain drugs from baseline to Week 16.

End point title	The percentage of reduction in number of concomitant pain drugs from baseline to Week 16.

End point description:

The analysis of concomitant pain drugs (as reported on the concomitant medications page in the eCRF) were summarized in the number of subjects who were taking pain medication in the 7 days preceding visits.
The statistical analysis is not estimable.

End point type	Secondary

End point timeframe:

From baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	23		
Units: percent				
number (not applicable)				
Subjects with Concomitant Pain Drug	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The number of patients with at least one intake of PRN pain medication.

End point title	The number of patients with at least one intake of PRN pain medication.

End point description:

The analysis of amount of concomitant PRN PD pain medications (as reported in the subject diary) was summarized in the number of days on which pain medication was taken in the number of subjects who were taking pain medication in the 7 days preceding visits.
Missing values at each visit for subjects with no data are not used in CMH calculation.

End point type	Secondary

End point timeframe:

From baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	23		
Units: percent				
number (not applicable)				
Subjects with PRN PD Pain Medication	33.3	43.5		

Statistical analyses

Statistical analysis title	Analysis of the Amount of PRN PD Pain Medication

Statistical analysis description:

95% CI and p-value for number of subjects with PRN PD Pain medication derived from the 2-sided Cohran-Mantel-Haenszel (CMH) test to test the null hypothesis of no difference between treatment groups in percentage of subjects who has taken and not taken PRN PD pain medication adjusted for country as stratification factor.

Comparison groups	Placebo (50mg and 100 mg) v Safinamide (50 mg and 100mg)

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5215 [7]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Risk difference (RD)
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.34

Notes:

[7] - p-value for number of days on which PRN PD pain medication was taken, are calculated using a two-sided Mann Whitney test to test the null hypothesis of no difference between the two treatments.

Secondary: Number of subjects using PRN

End point title	Number of subjects using PRN

End point description:

The analysis of amount of concomitant PRN PD pain medications (as reported in the subject diary) was summarized in the number of days on which pain medication was taken in the number of subjects who were taking pain medication in the 7 days preceding visits.
Missing values at each visit for subjects with no data are not used in CMH calculation.

End point type	Secondary

End point timeframe:

From baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	23		
Units: percent				
number (not applicable)				
Baseline - With PRN PD Pain Medication	26.7	30.4		
Baseline - with no PRN PD Pain Medication	73.3	69.6		
Baseline - with no data	0	0		
Week 16 - With PRN PD Pain Medication	11.1	17.4		
Week 16 - with no PRN PD Pain Medication	82.2	78.3		
Week 16 - with no data	6.7	4.3		

Statistical analyses

Statistical analysis title	Analysis of the Amount of PRN PD Pain Medication

Statistical analysis description:

95% CI and p-value for number of subjects with PRN PD Pain medication derived from the 2-sided Cohran-Mantel-Haenszel (CMH) test to test the null hypothesis of no difference between treatment

groups in percentage of subjects who has taken and not taken PRN PD pain medication adjusted for country as stratification factor.

Comparison groups	Safinamide (50 mg and 100mg) v Placebo (50mg and 100 mg)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5122 [8]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Risk difference (RD)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.26

Notes:

[8] - p-value for number of days on which PRN PD pain medication was taken, are calculated using a two-sided Mann Whitney test to test the null hypothesis of no difference between the two treatments

Secondary: The change from baseline to Week 16 in the Hospital Anxiety and Depression Scale (HADS) score.

End point title	The change from baseline to Week 16 in the Hospital Anxiety and Depression Scale (HADS) score.

End point description:

Change from baseline in HADS score at Week 16 was analyzed using an ANCOVA model. The model included treatment, baseline HADS, and country as fixed effects.

End point type	Secondary

End point timeframe:

From baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	20		
Units: unit(s)				
arithmetic mean (standard deviation)				
Week 16	-1.5 (± 6.03)	-2.0 (± 4.36)		

Statistical analyses

Statistical analysis title	ANCOVA Analysis of HADS Score

Statistical analysis description:

The analysis of covariance (ANCOVA) model for sensitivity analysis of the primary efficacy endpoint included fixed effects terms for treatment, country, and visit and a covariate term for pain severity score at baseline. The ANCOVA model for the secondary efficacy endpoint (change from baseline in HADS at Week 16) included treatment, baseline HADS, and country as fixed effects.

Comparison groups	Safinamide (50 mg and 100mg) v Placebo (50mg and 100 mg)

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7376 [9]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.03
upper limit	2.16
Variability estimate	Standard error of the mean
Dispersion value	1.29

Notes:

[9] - p-value derived for the difference between treatment groups at Week 16.

Secondary: The change from baseline to Week 16 in the Movement Disorder Society–Unified Parkinson's Disease Rating Scale during the "ON" phase.

End point title	The change from baseline to Week 16 in the Movement Disorder Society–Unified Parkinson's Disease Rating Scale during the "ON" phase.

End point description:

The change from baseline to Week 16 in the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS; total score and subscores) during the "ON" phase.

End point type	Secondary

End point timeframe:

From Baseline to week 16

End point values	Safinamide (50 mg and 100mg)	Placebo (50mg and 100 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	19		
Units: unit(s)				
arithmetic mean (standard deviation)				
Week 16	-6.8 (± 13.79)	-4.8 (± 11.68)		

Statistical analyses

Statistical analysis title	MMRM Analysis of MDS-UPDRS

Statistical analysis description:

The MDS-UPDRS was analyzed with a mixed model for repeated measures (MMRM). The model included fixed effects terms for treatment, country, visit, and regular pain medication use at baseline (yes or no) and a covariate term for pain severity score at baseline.

Comparison groups	Safinamide (50 mg and 100mg) v Placebo (50mg and 100 mg)

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5349 [10]
Method	Mixed Model Repeated Measures
Parameter estimate	Least Squares (LS) Mean
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.33
upper limit	5.43
Variability estimate	Standard error of the mean
Dispersion value	3.92

Notes:

[10] - p-value derived for the difference between treatment groups at each visit.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-Emergent Adverse Events (TEAEs) were summarized for the on-treatment period (Day 1 to Week 16)

Adverse event reporting additional description:

Overall, 43.7% of subjects had TEAEs, and the incidence was higher in the placebo group than in the safinamide group (48.0% versus 41.3%). Overall, 11.3% of subjects had TEAEs that led to treatment discontinuation and 7.0% to study discontinuation/early withdrawal, and no subjects died during the study. Overall, safinamide was found well tolerated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Safinamide

Reporting group description:

The study drugs administered to subjects in this study were safinamide 50 mg or 100 mg tablets.

Reporting group title	Placebo

Reporting group description:

The study drugs administered to subjects in this study were placebo 50 mg or 100 mg tablets.

Serious adverse events	Safinamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safinamide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 46 (41.30%)	12 / 25 (48.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 46 (2.17%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Hallucination			
subjects affected / exposed	1 / 46 (2.17%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Hallucination, visual			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 46 (2.17%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Dyskinesia			
subjects affected / exposed	2 / 46 (4.35%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Hyperkinesia			
subjects affected / exposed	2 / 46 (4.35%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Lacunar infarction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Motor dysfunction			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Paraesthesia			

subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Parkinson's disease			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Eye disorders			
Pterygium			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 46 (6.52%)	0 / 25 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	2 / 46 (4.35%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 46 (4.35%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Dental caries			
subjects affected / exposed	0 / 46 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Paraesthesia oral			

subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Salivary hypersecretion			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Tongue ulceration			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 46 (4.35%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 46 (2.17%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1	0 / 25 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2019	The first protocol amendment (dated 10 Oct 2019) was applicable to all countries where the study was conducted, except France. Amendment 1 was effective before the first subject was screened for the study. The major changes to the protocol amendment 1 are the following: - Rewording - to better reflect the endpoint data collected. - Inclusion Criteria - updated to reflect the SmPC and to better clarify the criteria - Exclusion Criteria - updated to grater clarity and to expand eligibility of patients without compromising the quality of the trial. - Screen Failure - Sentence rephrased to allow rescreening, defining times and time frame. - Study Intervention(s) Administered - updated to match with the update of IMPD - Concomitant Therapy and Excluded Medicine - Wording was added to better clarify the use of combination analgesic therapy. - Time Period and Frequency for Collecting AE and SAE Information - Paragraph 2 was deleted to conform with standard reporting AEs. - Regulatory Reporting Requirements for SAEs - Reference Safety Information added to specify the reference safety information for this study. - Appendix 3 Subsection "Assessment of Causality" and References - modified to delete Investigator's Brochure and left only SmPC, since SmPC was the reference safety information for this study.
27 October 2020	A France-specific Protocol Amendment 1 and Protocol Amendment 2 for other countries were made on 27 Oct 2020. The major Changes in France-specific Protocol Amendment 1 and Protocol Amendment 2 for Other Countries are the following: - Study Synopsis - Paragraph "number of participant" and Overall Design - Sample size was recalculated based on blind data review performed as recommended by FDA guidelines for studies conducted during COVID-19 emergency. - Schedules of Activities - Cross-reference to contingency plan (Appendix 10) was added. A contingency plan was developed to mitigate impact of COVID-19 emergency on the study visits; it described the measures to be adopted to keep patients in the study and mitigate countries' restrictions. Contingency plan was notified to sites when needed, but now it was attached to protocol for a quicker access and consultation. - Preparation / handling / storage / accountability ; Study Assessments and Procedures and Appendix 10, Contingency Plan - updated based on the above defined for contingency plan. - Sample Size Determination - Since Mar 2020, COVID-19 emergency impacted the feasibility of trial that were conducted in a vulnerable group of patients. FDA released guidelines with the aim of helping sponsors ensure that trials conducted during the COVID-19 emergency continue, where appropriate, to provide interpretable findings with correct statistical quantification of uncertainty. - Population of Analyses and Statistical Analyses - Wording was aligned with SAP to achieve consistency across the study documents. - References - FDA guideline was listed among the references as it was adopted for the sample size re-calculation

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.

None reported

Notes: