EU Clinical Trials Register

Clinical trial results:
Efficacy and safety of Fixed-Dose Combination (FDC) products containing trazodone and gabapentin in patients affected by painful diabetic neuropathy: randomized, controlled, dose finding study.

Summary

EudraCT number	2018-000133-12
Trial protocol	CZ GB PL
Global end of trial date	06 June 2020

Results information

Result version number	v1 (current)
This version publication date	22 June 2021
First version publication date	22 June 2021

Trial information

Trial identification

Sponsor protocol code	039(1)PO16357

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03749642
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Angelini Pharma S.p.A
Sponsor organisation address	Viale Amelia, 70, Rome, Italy, 00181
Public contact	Study Manager, Angelini Pharma S.p.A, +39 0691045349, paola.lipone@angelinipharma.com
Scientific contact	Study Manager, Angelini Pharma S.p.A, +39 0691045349, paola.lipone@angelinipharma.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	06 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2020
Global end of trial reached?	Yes
Global end of trial date	06 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to collect preliminary information on the effect of three doses of trazodone/gabapentin FDC products on pain intensity in patients with painful diabetic neuropathy after 8-week treatment period.

Protection of trial subjects:

During the study the following treatment were allowed: paracetamol (acetaminophen) in case of need for analgesics and aspirin for prophylaxis for myocardial infarction or transient ischemic attacks.

Background therapy:

Not Applicable

Evidence for comparator:

Gabapentin, recommended as first line drug in PDN, was used in this study as active comparator of known effectiveness to give context to the measured differences from placebo and to facilitate an evaluation of the clinical relevance of those differences.

Actual start date of recruitment	22 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	Poland: 153
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Czechia: 72
Country: Number of subjects enrolled	France: 6
Worldwide total number of subjects	240
EEA total number of subjects	231

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)	125
From 65 to 84 years	115
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Before entering the study, patients were fully informed about the purposes of the research, possible benefits, any potential personal reasonable risk or discomfort, the expected duration of their participation, as well as procedures and laboratory tests to undergo. A copy of the ICF including the information sheet was given to the patient.

Pre-assignment

Screening details:

At Screening Visit (10-15 days before Visit -1) potentially eligible patients were selected for the enrolment in the trial.

Period 1

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

Blinding implementation details:

In case of medical emergency, the Investigator was able to unblind the treatment code through the blinded labels provided by the Sponsor. The reason for unblinding was properly documented and notified to the Sponsor. In order to maintain the study double-blind conditions, the double-dummy technique was used. Thus, patients randomized in Arms 1, 2, 3 and 5 were co-administered with placebo capsules, in order to balance the number of capsules taken by the patient each time during.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trazo/Gaba 2.5/25 mg

Arm description:

Trazodone/gabapentin FDC (Fixed-Dose Combination) 2.5/25 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 7.5/75 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.

Arm type	Experimental
Investigational medicinal product name	Trazo/Gaba 2.5/25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 7.5/75 mg.

Arm title	Trazo/Gaba 5/50 mg

Arm description:

Trazodone/gabapentin FDC 5/50 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 15/150 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.

Arm type	Experimental
Investigational medicinal product name	Trazo/Gaba 5/50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 15/150 mg.

Arm title	Trazo/Gaba 10/100 mg

Arm description:

Trazodone/gabapentin FDC 10/100 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 30/300 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.

Arm type	Experimental
Investigational medicinal product name	Trazo/Gaba 10/100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 30/300 mg.

Arm title	Placebo

Arm description:

Placebo, capsules. Two capsules, three times a day, for 8 weeks. Capsules contained lactose anhydrous, talc, magnesium stearate vegetal.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two capsules, three times a day, for 8 weeks.

Arm title	Gabapentin

Arm description:

Gabapentin, capsules (Neurontin®, Pfizer), according to the following scheduling dosage regimen:

Arm type	Active comparator
Investigational medicinal product name	Gabapentin
Investigational medicinal product code	
Other name	Neurontin® (Pfizer)
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Gabapentin 100 mg 2 capsules 3 times a day from day 0 to day 6 (±1).Total daily dosage: 600 mg
Gabapentin 300 mg 1 capsule 3 times a dayfrom day 7 (±1) to day 13 (±1). Total daily dosage: 900 mg
Gabapentin 400 mg 1 capsule 3 times a day   from day 14 (±1) to day 20 (±1). Total daily dosage:1200 mg
Gabapentin 300 mg 2 capsules 3 times a day   from day 21 (±1) to day 56 (±2)   . Total daily dosage:1800 mg

Number of subjects in period 1	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg
Started	39	38	37
Completed	35	35	32
Not completed	4	3	5
Consent withdrawn by subject	1	1	1
PT showing QTcF prolongation	2	2	4
Adverse event, non-fatal	-	-	-
PT erroneously enrolled	-	-	-
Prohibited medication	-	-	-
Other reasons	1	-	-

Number of subjects in period 1	Placebo	Gabapentin
Started	83	43
Completed	62	35
Not completed	21	8
Consent withdrawn by subject	8	2
PT showing QTcF prolongation	8	3
Adverse event, non-fatal	1	2
PT erroneously enrolled	2	1
Prohibited medication	1	-
Other reasons	1	-

Baseline characteristics

Reporting groups

Reporting group title	Trazo/Gaba 2.5/25 mg
Reporting group description:	
Trazodone/gabapentin FDC (Fixed-Dose Combination) 2.5/25 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 7.5/75 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.	
Reporting group title	Trazo/Gaba 5/50 mg
Reporting group description:	
Trazodone/gabapentin FDC 5/50 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 15/150 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.	
Reporting group title	Trazo/Gaba 10/100 mg
Reporting group description:	
Trazodone/gabapentin FDC 10/100 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 30/300 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.	
Reporting group title	Placebo
Reporting group description:	
Placebo, capsules. Two capsules, three times a day, for 8 weeks. Capsules contained lactose anhydrous, talc, magnesium stearate vegetal.	
Reporting group title	Gabapentin
Reporting group description:	
Gabapentin, capsules (Neurontin®, Pfizer), according to the following scheduling dosage regimen:	

Reporting group values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg
Number of subjects	39	38	37
Age categorical			
Units: Subjects			
Adults 18-64 years	24	23	21
Adults 65-84 years	15	15	16
Age continuous			
Demographic data - Age (years) in Safety Population			
Units: years			
arithmetic mean	61.74	61.29	61.62
standard deviation	± 8.54	± 8.53	± 9.17
Gender categorical			
Units: Subjects			
Female	15	18	19
Male	24	20	18

Reporting group values	Placebo	Gabapentin	Total
Number of subjects	83	43	240
Age categorical			
Units: Subjects			
Adults 18-64 years	39	18	125
Adults 65-84 years	44	25	115

Age continuous			
Demographic data - Age (years) in Safety Population			
Units: years			
arithmetic mean	63.02	63.74	
standard deviation	± 8.84	± 8.38	-
Gender categorical			
Units: Subjects			
Female	40	21	113
Male	43	22	127

Subject analysis sets

Subject analysis set title	m-ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized patients who took at least one dose of the study medication, having a baseline and at least one post-baselineNumeric Rating Scale (NRS) evaluation.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized patients with at least 80% of compliance to the treatment, having no major protocol violations, and having Numering Rating Scale (NRS) baseline and Visit 6 evaluations.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized patients who took at least one dose of the study medication;

Reporting group values	m-ITT population	PP population	Safety population
Number of subjects	236	201	240
Age categorical			
Units: Subjects			
Adults 18-64 years			
Adults 65-84 years			
Age continuous			
Demographic data - Age (years) in Safety Population			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female	101	98	113
Male	125	103	127

End points

End points reporting groups

Reporting group title	Trazo/Gaba 2.5/25 mg

Reporting group description:

Trazodone/gabapentin FDC (Fixed-Dose Combination) 2.5/25 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 7.5/75 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.

Reporting group title	Trazo/Gaba 5/50 mg

Reporting group description:

Trazodone/gabapentin FDC 5/50 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 15/150 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.

Reporting group title	Trazo/Gaba 10/100 mg

Reporting group description:

Trazodone/gabapentin FDC 10/100 mg, capsules. One capsule, three times a day, for 8 weeks. The total daily dose of trazodone/gabapentin administered was 30/300 mg. Capsules contained trazodone hydrochloride, gabapentin, lactose anhydrous, talc, magnesium stearate vegetal.

Reporting group title	Placebo

Reporting group description:

Placebo, capsules. Two capsules, three times a day, for 8 weeks. Capsules contained lactose anhydrous, talc, magnesium stearate vegetal.

Reporting group title	Gabapentin

Reporting group description:

Gabapentin, capsules (Neurontin®, Pfizer), according to the following scheduling dosage regimen:

Subject analysis set title	m-ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized patients who took at least one dose of the study medication, having a baseline and at least one post-baselineNumeric Rating Scale (NRS) evaluation.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized patients with at least 80% of compliance to the treatment, having no major protocol violations, and having Numering Rating Scale (NRS) baseline and Visit 6 evaluations.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized patients who took at least one dose of the study medication;

Primary: Change from baseline of the average daily pain score - V6

End point title	Change from baseline of the average daily pain score - V6[1]

End point description:

The primary endpoint of the study was the change from baseline of the average daily pain score based on the 11-point NRS to Visit 6 (Day 56 ±2) in the m-ITT with LOCF population. At the end-point time, scores were averaged from the last seven on-treatment entries in subjects' daily electronic device, calculated from a minimum of four pain ratings in daily electronic device entries.

End point type	Primary

End point timeframe:

Visit 6 (Day 56 ±2)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This study is a Phase II dose-finding study. Primary endpoint was evaluated on the 3 trazo-gaba doses combo versus placebo, excluding the active treatment (Gabapentin).

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	38	37	80
Units: mean change				
arithmetic mean (standard deviation)				
Mean change from baseline	-2.52 (± 2.31)	-2.24 (± 1.96)	-2.46 (± 2.12)	-2.02 (± 1.95)

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA)

Statistical analysis description:

Primary endpoint was evaluated using an analysis of covariance (ANCOVA), including treatment and center as factors and baseline as covariate and applying linear contrast test, excluding the active treatment (Gabapentin). Only if the linear contrast test was significant ($p<0.05$), the step down Dunnett test is used to determine the Minimum Effective Dose (MED). If linearity was not verified ($p>0.05$) an ANCOVA model is performed (m-ITT with LOCF and PP).

Comparison groups	Placebo v Trazo/Gaba 2.5/25 mg
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3729
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5356
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.274
upper limit	0.2026
Variability estimate	Standard deviation

Statistical analysis title	Analysis of covariance (ANCOVA)

Statistical analysis description:

Primary endpoint was evaluated using an analysis of covariance (ANCOVA), including treatment and center as factors and baseline as covariate and applying linear contrast test, excluding the active treatment (Gabapentin). Only if the linear contrast test was significant ($p<0.05$), the step down Dunnett test is used to determine the Minimum Effective Dose (MED). If linearity was not verified ($p>0.05$) an ANCOVA model is performed (m-ITT with LOCF and PP).

Comparison groups	Trazo/Gaba 5/50 mg v Placebo

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9239
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.2005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9401
upper limit	0.539
Variability estimate	Standard deviation

Statistical analysis title	Analysis of covariance (ANCOVA)

Statistical analysis description:

Primary endpoint was evaluated using an analysis of covariance (ANCOVA), including treatment and center as factors and baseline as covariate and applying linear contrast test, excluding the active treatment (Gabapentin). Only if the linear contrast test was significant ($p<0.05$), the step down Dunnett test is used to determine the Minimum Effective Dose (MED). If linearity was not verified ($p>0.05$) an ANCOVA model is performed (m-ITT with LOCF and PP).

Comparison groups	Trazo/Gaba 10/100 mg v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8135
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.288
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0342
upper limit	0.4582
Variability estimate	Standard deviation

Secondary: Change from baseline of the average daily pain score - V5

End point title	Change from baseline of the average daily pain score - V5[2]

End point description:

Change from baseline of the average daily pain score based on the 11-point NRS to V5. At the end-point times, scores were averaged from the last seven on-treatment entries in subjects' daily electronic device, calculated from a minimum of four pain ratings in daily electronic device entries.

End point type	Secondary

End point timeframe:

V5

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This study is a Phase II dose-finding study. This endpoint was evaluated on the 3 trazo-gaba doses combo versus placebo, excluding the active treatment (Gabapentin).

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	38	37	80
Units: mean change form baseline				
arithmetic mean (standard deviation)	-2.55 (± 2.33)	-2.09 (± 1.81)	-2.23 (± 1.93)	-1.67 (± 1.73)

Statistical analyses

Statistical analysis title	Analysis of covariance (ANCOVA)
Statistical analysis description:	
Analysis of variance between the Trazo/gaba_2.5/25mg and Placebo.	
Comparison groups	Trazo/Gaba 2.5/25 mg v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0116
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.9387
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.665
upper limit	-0.213
Variability estimate	Standard deviation

Statistical analysis title	Analysis of covariance (ANCOVA)
Statistical analysis description:	
Analysis of variance between the Trazo/gaba_5/50 mg and Placebo.	
Comparison groups	Trazo/Gaba 5/50 mg v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.4564

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1882
upper limit	0.2753
Variability estimate	Standard deviation

Statistical analysis title	Analysis of covariance (ANCOVA)
Statistical analysis description:	
Analysis of variance between the Trazo/gaba_10/100 mg and Placebo.	
Comparison groups	Trazo/Gaba 10/100 mg v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1046
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.6108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3496
upper limit	0.1281
Variability estimate	Standard deviation

Secondary: Percentage of responder patients at Visit 6 (30%)

End point title	Percentage of responder patients at Visit 6 (30%)
End point description:	
The proportions of responder patients was defined as subjects who achieved at least 30% of reduction in the 11-point NRS pain score from baseline to Visit 6 evaluated in m-ITT population.	
End point type	Secondary
End point timeframe:	
Visit 6	

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	38	37	80
Units: Percentage				
number (not applicable)				
Percentage	51.3	47.4	51.4	42.5

End point values	Gabapentin			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Percentage				
number (not applicable)				
Percentage	33.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of the average daily pain score as assay sensitivity

End point title	Change from baseline of the average daily pain score as assay sensitivity[3]
End point description:	

Change from baseline of the average daily pain score based on the 11-point NRS to V6 between Gabapentin and Placeb as assay sensitivity.

End point type	Secondary
End point timeframe:	

Visit 6

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This study is a Phase II dose-finding study. This endpoint was evaluated on the 3 trazo-gaba doses combo versus placebo, excluding the active treatment (Gabapentin).

End point values	Placebo	Gabapentin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	42		
Units: Mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	-2.02 (± 1.95)	-1.92 (± 2.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 4 of NPSI

End point title	Change from baseline to Visit 4 of NPSI
End point description:	

Change from baseline to Visit 4 of NPSI Total score in m-ITT. The Neuropathic Pain Symptom Inventory (NPSI) questionnaire evaluates the several symptoms of neuropathic pain.

End point type	Secondary
End point timeframe:	

Visit 4

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	38	36	78
Units: mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	-27.39 (± 18.85)	-19.24 (± 19.63)	-23.42 (± 20.99)	-19.26 (± 22.54)

End point values	Gabapentin			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	-20.02 (± 23.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: BDI-II score change V6-V0

End point title	BDI-II score change V6-V0

End point description:

Change in BDI-II total score from baseline were evaluated at Visit 6. The Beck Depression Inventory-II (BDI-II) questionnaire specifically evaluates the intensity of depression.

End point type	Secondary

End point timeframe:

Visit 6

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	38	36	78
Units: mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	-2.79 (± 4.76)	-1.82 (± 3.78)	-1.06 (± 3.67)	-0.78 (± 3.84)

End point values	Gabapentin			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	0.36 (± 8.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 6 of ISI Total score

End point title	Change from baseline to Visit 6 of ISI Total score
End point description:	
Change from baseline to Visit 6 of Insomnia Severity Index (ISI) - Total score	
End point type	Secondary
End point timeframe:	
Visit 6	

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	38	36	78
Units: mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	-2.97 (± 4.72)	-2.82 (± 4.16)	-1.92 (± 5.76)	-2.44 (± 4.80)

End point values	Gabapentin			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	-2.64 (± 5.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to Visit 6 of EQ-5D-5L Health Today score

End point title	Change from baseline to Visit 6 of EQ-5D-5L Health Today score

End point description:

Change from baseline to Visit 6 of EQ-5D-5L Health Today score. The EQEuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire specifically evaluates 5 dimensions of patient's quality of life, like mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This scale also assesses the patient's self-rated health.

End point type	Secondary

End point timeframe:

Visit 6

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	38	36	78
Units: Mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	12.76 (± 16.22)	7.63 (± 18.84)	7.00 (± 19.07)	5.76 (± 23.12)

End point values	Gabapentin			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Mean change from baseline				
arithmetic mean (standard deviation)				
Mean change from baseline	4.79 (± 27.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responder patients at Visit 6 (50%)

End point title	Percentage of responder patients at Visit 6 (50%)

End point description:

The proportions of responder patients was defined as subjects who achieved at least 50% of reduction in the 11-point NRS pain score from baseline to Visit 6 evaluated in m-ITT population.

End point type	Secondary

End point timeframe:

Visit 6

End point values	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	38	37	80
Units: Percentage				
number (not applicable)				
Percentage of responsers	35.9	26.3	35.1	28.8

End point values	Gabapentin			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Percentage				
number (not applicable)				
Percentage of responsers	19.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe for reporting adverse events was from Informed Consent signature to last visit as per protocol.

Adverse event reporting additional description:

One hundred ninety-two (192) AEs were reported during the study. Four SAEs recorded in 4 patients in the study did not report a fatal outcome, but only 2 events occurred after the start of the investigational treatment (1 in Trazo/Gaba 5/50 mg group and 1 in placebo group).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	ver. 21.1

Reporting groups

Reporting group title	Trazo/Gaba 2.5/25 mg

Reporting group description:

Patient allocated to Trazodone/gabapentin FDC 2.5/25 mg capsules

Reporting group title	Trazo/Gaba 5/50 mg

Reporting group description:

Patient allocated to Trazodone/gabapentin FDC 5/50 mg capsules.

Reporting group title	Trazo/Gaba 10/100 mg

Reporting group description:

Patient allocated to Trazodone/gabapentin FDC 10/100 mg capsules.

Reporting group title	Placebo

Reporting group description:

Patient allocated to Placebo capsules.

Reporting group title	Gabapentin

Reporting group description:

Patient allocated to Gabapentin capsules.

Serious adverse events	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
PT inflammation wound			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 39 (0.00%)	0 / 38 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	Gabapentin	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 83 (1.20%)	0 / 43 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
PT inflammation wound			
subjects affected / exposed	0 / 83 (0.00%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 43 (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: 5 %

Non-serious adverse events	Trazo/Gaba 2.5/25 mg	Trazo/Gaba 5/50 mg	Trazo/Gaba 10/100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 39 (15.38%)	13 / 38 (34.21%)	5 / 37 (13.51%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 39 (5.13%)	3 / 38 (7.89%)	4 / 37 (10.81%)
occurrences (all)	2	3	4
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 39 (0.00%)	2 / 38 (5.26%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 39 (7.69%)	2 / 38 (5.26%)	0 / 37 (0.00%)
occurrences (all)	3	2	0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 39 (0.00%)	2 / 38 (5.26%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	2 / 38 (5.26%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Nasopharyngitis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 38 (5.26%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Hypoglycaemia			
subjects affected / exposed	1 / 39 (2.56%)	2 / 38 (5.26%)	0 / 37 (0.00%)
occurrences (all)	1	2	0

Non-serious adverse events	Placebo	Gabapentin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 83 (14.46%)	5 / 43 (11.63%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	9 / 83 (10.84%)	3 / 43 (6.98%)	
occurrences (all)	9	3	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 83 (1.20%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 83 (1.20%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Peripheral swelling			

subjects affected / exposed	0 / 83 (0.00%)	0 / 43 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 83 (0.00%)	0 / 43 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Nasopharyngitis			
subjects affected / exposed	1 / 83 (1.20%)	2 / 43 (4.65%)	
occurrences (all)	1	2	
Hypoglycaemia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 43 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2019	The substantial Study Amendment no. 1 dated April 04th, 2019 proposed an update of the Investigational Medicinal Product Dossier (IMPD) of the present clinical trial. The new version of the IMPD was prepared in order to include the long term positive stability data reached at 24 months for placebo capsules; the long term positive stability data reached at 24 months for gabapentin 100 mg, 300 mg, 400 mg capsules; a new water content analytical method developed and validated by Angelini S.p.A; and to declare Angelini S.p.A. as the company responsible for performing the water content analysis. The Study Amendment no. 1 was approved by the applicable Ethics Committees and Competent Authorities in accordance with the local regulations.

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.

Not applicable

Notes: