Clinical trial results:
Efficacy and safety of low doses of trazodone in patients affected by painful diabetic neuropathy: randomized, controlled, pilot study.

Summary

EudraCT number	2016-002772-27
Trial protocol	CZ HU PL
Global end of trial date	09 August 2018

Results information

Result version number	v1 (current)
This version publication date	30 August 2019
First version publication date	30 August 2019

Trial information

Trial identification

Sponsor protocol code	039(B)PO16143

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	A.C.R.A.F. SpA (Angelini SpA)
Sponsor organisation address	Piazzale della Stazione s.n.c., S.Palomba-Pomezia (Rome), Italy, 00071
Public contact	Study Manager, A.C.R.A.F. SpA (Angelini SpA), 0039 0691045349 , p.lipone@angelini.it
Scientific contact	Study Manager, A.C.R.A.F. SpA (Angelini SpA), 0039 0691045349 , p.lipone@angelini.it

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	29 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2018
Global end of trial reached?	Yes
Global end of trial date	09 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To collect preliminary information on the effect of low doses of trazodone on pain intensity in patients with painful diabetic neuropathy after 8-week treatment period.

Protection of trial subjects:

No specific measures are provided. In case of ineffective treatment the Investigator can administer alternative drugs and the patients discontinue study.

Background therapy:

Gabapentin was used in this study as "background therapy" in order to assure an effective pharmacological treatment, recommended as first line in painful diabetic neuropathy, to all patients which were enrolled in the trial. It was administered in open-label conditions to all patients enrolled in the study together with the investigational drug. A slow titration scheduling - 100 mg, 300 mg, 400 mg capsule (Neurontin®, Pfizer - was applied in order to better control the possible side effects when co-administered with trazodone. The increasing of dosage was implemented at each visit in accordance with the scheduling regimen.

Evidence for comparator:

A placebo arm was foreseen by the study protocol in order to facilitate a clear assessment of the clinical relevance of the efficacy and safety of trazodone when coadministered with gabapentin [EMA/CHMP/970057/2011]

Actual start date of recruitment	16 May 2017
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: 73
Country: Number of subjects enrolled	Czech Republic: 50
Country: Number of subjects enrolled	Hungary: 19
Worldwide total number of subjects	142
EEA total number of subjects	142

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	76
From 65 to 84 years	66
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of 120 patients per treatment group (trazodone 30 mg, trazodone 60 and placebo) was planned.
142 patients were randomised and received allocated interventation from 16 May 2017 to 09 August 2018.

Pre-assignment

Screening details:

214 patients were enrolled. 72 patients were excluded: 64 for screening failure, 7 for PT requests to be excluded from the study and 1 for other reasons.

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, Data analyst, Assessor

Blinding implementation details:

The study was performed in double-blind conditions. In order to maintain the study double-blind conditions, the double-dummy technique was used. Thus, patients randomized in group 2 were co-administered with active oral solution and placebo oral solution.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trazodone hydrochloride 6% oral solution - 60 mg

Arm description:

Trazodone 20 mg (corresponding to 10 drops of trazodone hydrochloride 6% oral solution), three times a day for 8 weeks. The total daily dose of trazodone administered to this group was 60 mg.

Arm type	Experimental
Investigational medicinal product name	Trazodone hydrochloride 6% oral solution - 60 mg
Investigational medicinal product code	039
Other name	Trittico®
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

trazodone 20 mg (corresponding to 10 drops of trazodone hydrochloride 6% oral solution), three times a day, for 8-week treatment period. The total daily dose of trazodone administered to this group was 60 mg.

Arm title	Trazodone hydrochloride 6% oral solution - 30 mg

Arm description:

Trazodone 10 mg (corresponding to 5 drops of trazodone hydrochloride 6% oral solution), three times a day for 8 weeks. The total daily dose of trazodone administered to this group was 30 mg. less

Arm type	Experimental
Investigational medicinal product name	Trazodone hydrochloride 6% oral solution - 30 mg
Investigational medicinal product code	039
Other name	Trittico®
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

trazodone 10 mg (corresponding to 5 drops of trazodone hydrochloride 6% oral solution), three times a day, for 8-week treatment period. The total daily dose of trazodone administered to this group was 30

mg.

Arm title	Placebo
Arm description:	
Placebo, oral solution 10 drops three times a day, for 8-week treatment period.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use
Dosage and administration details:	
Placebo, oral solution 10 drops three times a day, for 8-week treatment period.	

Number of subjects in period 1	Trazodone hydrochloride 6% oral solution - 60 mg	Trazodone hydrochloride 6% oral solution - 30 mg	Placebo
Started	51	43	48
Completed	36	33	35
Not completed	15	10	13
Consent withdrawn by subject	5	6	2
Adverse event, non-fatal	-	-	3
QTcF prolungation	5	3	5
Prohibited medication	-	-	1
Other reasons	5	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Trazodone hydrochloride 6% oral solution - 60 mg
Reporting group description:	
Trazodone 20 mg (corresponding to 10 drops of trazodone hydrochloride 6% oral solution), three times a day for 8 weeks. The total daily dose of trazodone administered to this group was 60 mg.	
Reporting group title	Trazodone hydrochloride 6% oral solution - 30 mg
Reporting group description:	
Trazodone 10 mg (corresponding to 5 drops of trazodone hydrochloride 6% oral solution), three times a day for 8 weeks. The total daily dose of trazodone administered to this group was 30 mg. less	
Reporting group title	Placebo
Reporting group description:	
Placebo, oral solution 10 drops three times a day, for 8-week treatment period.	

Reporting group values	Trazodone hydrochloride 6% oral solution - 60 mg	Trazodone hydrochloride 6% oral solution - 30 mg	Placebo
Number of subjects	51	43	48
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	26	23	27
From 65-84 years	25	20	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.2	62.1	62.3
standard deviation	± 8.45	± 8.55	± 7.19
Gender categorical Units: Subjects			
Female	25	18	25
Male	26	25	23

Reporting group values	Total		
Number of subjects	142		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	76		
From 65-84 years	66		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	68		
Male	74		

Subject analysis sets

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 were included in the Safety population: 43 in the Trazodone 30 mg group, 51 in the Trazodone 60 mg group and 48 in the placebo group.

Subject analysis set title	Intention-to treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consisted of 141 patients (43 in the Trazodone 30 mg group, 50 in the Trazodone 60 mg group and 48 in the placebo group) who received allocated intervention and had baseline and at least one post-baseline BPI-SF evaluation.

Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of 96 patients (31 in the Trazodone 30 mg group, 34 in the Trazodone 60 mg group and 31 in the placebo group) who completed the study period with no major protocol deviations and had baseline and V8 BPI-SF evaluation.

Reporting group values	Safety population	Intention-to treat (ITT) population	Per Protocol (PP) population
Number of subjects	142	141	96
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			

standard deviation	±	±	±

Gender categorical Units: Subjects			
Female	68	67	53
Male	74	74	43

End points

End points reporting groups

Reporting group title	Trazodone hydrochloride 6% oral solution - 60 mg
Reporting group description:	
Trazodone 20 mg (corresponding to 10 drops of trazodone hydrochloride 6% oral solution), three times a day for 8 weeks. The total daily dose of trazodone administered to this group was 60 mg.	
Reporting group title	Trazodone hydrochloride 6% oral solution - 30 mg
Reporting group description:	
Trazodone 10 mg (corresponding to 5 drops of trazodone hydrochloride 6% oral solution), three times a day for 8 weeks. The total daily dose of trazodone administered to this group was 30 mg. less	
Reporting group title	Placebo
Reporting group description:	
Placebo, oral solution 10 drops three times a day, for 8-week treatment period.	
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 were included in the Safety population: 43 in the Trazodone 30 mg group, 51 in the Trazodone 60 mg group and 48 in the placebo group.	
Subject analysis set title	Intention-to treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population consisted of 141 patients (43 in the Trazodone 30 mg group, 50 in the Trazodone 60 mg group and 48 in the placebo group) who received allocated intervention and had baseline and at least one post-baseline BPI-SF evaluation.	
Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population consisted of 96 patients (31 in the Trazodone 30 mg group, 34 in the Trazodone 60 mg group and 31 in the placebo group) who completed the study period with no major protocol deviations and had baseline and V8 BPI-SF evaluation.	

Primary: Change from baseline of the BPI-SF (item 5) at Visit 8 (day 56 ±2)

End point title	Change from baseline of the BPI-SF (item 5) at Visit 8 (day 56 ±2)
End point description:	
The primary endpoint of the study was the efficacy of low doses of trazodone on pain intensity assessed as change from baseline of the BPI-SF 24-hour average pain score (item 5) at Visit 8 (day 56 ±2).	
End point type	Primary
End point timeframe:	
The end point was evaluated at Visit 8 (day 56 ±2).	

End point values	Trazodone hydrochloride 6% oral solution - 60 mg	Trazodone hydrochloride 6% oral solution - 30 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	43	48	
Units: pain score				
arithmetic mean (standard deviation)	-2.6 (± 1.99)	-3.1 (± 1.74)	-2.5 (± 1.77)	

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

An analysis of covariance (ANCOVA) model including treatment as main effect and baseline as covariate was applied and the relevant least-square mean change from baseline to endpoint was estimated and compared between treatment groups.

Comparison groups	Trazodone hydrochloride 6% oral solution - 60 mg v Placebo
Number of subjects included in analysis	98
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.6272
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.52

Statistical analysis title	ANCOVA

Statistical analysis description:

An analysis of covariance (ANCOVA) model including treatment as main effect and baseline as covariate was applied and the relevant least-square mean change from baseline to endpoint was estimated and compared between treatment groups.

Comparison groups	Trazodone hydrochloride 6% oral solution - 30 mg v Placebo
Number of subjects included in analysis	91
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.1179
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.15

Statistical analysis title	ANCOVA

Statistical analysis description:

An analysis of covariance (ANCOVA) model including treatment as main effect and baseline as covariate was applied and the relevant least-square mean change from baseline to endpoint was estimated and compared between treatment groups.

Comparison groups	Trazodone hydrochloride 6% oral solution - 60 mg v Trazodone hydrochloride 6% oral solution - 30 mg
Number of subjects included in analysis	93
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.267
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	0.31

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored throughout the whole study period from the signature of the informed consent form up to the last visit scheduled in the protocol or ETV (if applicable).

Adverse event reporting additional description:

After initiation of the study treatments, 133 AEs (TEAEs) were recorded: 53 TEAEs were reported by 27 patients in the trazodone 30 mg group, 35 TEAEs by 21 patients in the trazodone 60 mg group and 45 TEAEs by 20 patients in the placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Trazodone hydrochloride 6% oral solution - 60 mg

Reporting group description:

Trazodone 20 mg (corresponding to 10 drops of trazodone hydrochloride 6% oral solution) three times a day for 8 weeks. The toatl daily dose of trazodone administered to this group was 60 mg.

Reporting group title	Trazodone hydrochloride 6% oral solution - 30 mg

Reporting group description:

Trazodone 10 mg (corresponding to5 drops of trazodone hydrochloride 6% oral solution) three times a day for 8 weeks. The toatl daily dose of trazodone administered to this group was 30 mg.

Reporting group title	Placebo

Reporting group description:

Placebo, oral solution 10 drops three times a day, for 8-week treatment period.

Serious adverse events	Trazodone hydrochloride 6% oral solution - 60 mg	Trazodone hydrochloride 6% oral solution - 30 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 51 (0.00%)	0 / 43 (0.00%)	0 / 48 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Trazodone hydrochloride 6% oral solution - 60 mg	Trazodone hydrochloride 6% oral solution - 30 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 51 (41.18%)	27 / 43 (62.79%)	20 / 48 (41.67%)
Investigations			

Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 51 (9.80%)	4 / 43 (9.30%)	8 / 48 (16.67%)
occurrences (all)	5	4	8
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	3 / 51 (5.88%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	4	0	0
Dizziness			
subjects affected / exposed	0 / 51 (0.00%)	0 / 43 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	5
Somnolence			
subjects affected / exposed	2 / 51 (3.92%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Peripheral swelling			
subjects affected / exposed	2 / 51 (3.92%)	0 / 43 (0.00%)	3 / 48 (6.25%)
occurrences (all)	2	0	3
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 51 (3.92%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 51 (0.00%)	3 / 43 (6.98%)	2 / 48 (4.17%)
occurrences (all)	0	3	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 43 (4.65%)	0 / 48 (0.00%)
occurrences (all)	2	3	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 43 (0.00%)	1 / 48 (2.08%)
occurrences (all)	0	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported