



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 intervention 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 prolongation | 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 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.

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