



Clinical trial results:

Use of buspiron in chemioreflex modulation and central apnea treatment in heart failure patients (BREATH: BuspiRon for chEmoreflex modulation and central Apnea treatment in Heart failure patients). Phase II, monocentric, cross-over, duple dummy, randomized and controlled, pilot study.

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-005383-42 |
| Trial protocol | IT |
| Global end of trial date | 01 November 2018 |

Results information

| | |
|-----------------------------------|---------------------------------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2021 |
| First version publication date | 28 June 2021 |
| Summary attachment (see zip file) | Study Results (10.1002@ejhf.1854.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | BREATH |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Fondazione Toscana Gabriele Monasterio |
| Sponsor organisation address | Via trieste, Pisa, Italy, |
| Public contact | UOC Medicina Cardiovascolare, Fondazione Toscana Gabriele Monasterio, +39 0585493507, farmacisti@ftgm.it |
| Scientific contact | UOC Medicina Cardiovascolare, Fondazione Toscana Gabriele Monasterio, +39 0585493507, farmacisti@ftgm.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 | 01 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 November 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Evaluation of buspiron effects on chemoceptive sensitivity to carbon dioxide (CO₂) in heart failure patients with CO₂ hypersensitivity

Protection of trial subjects:

The study protocol and all its amendments have been assessed and approved by the local Ethics Committee and by the Competent Authority.

The study was performed in accordance with the Helsinki declaration.

The willingness of each individual patient to participate in the study was respected and informed consent was signed by each patient at the time of enrollment. The study was performed in accordance with the Good Clinical Practice (GCP). No discrimination in terms of ethnicity, sexual, religious or political orientation was applied when enrolling patients.

Sensitive data relating to enrolled patients will be kept for 7 years and will be used anonymously according to an alphanumeric coding.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 18 November 2016 |
| 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 | Italy: 16 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 16 |

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) | 8 |
| From 65 to 84 years | 8 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

16 patients of both sexes and with an age between 18 and 80 years, with a diagnosis of heart failure and central sleep apnea syndrome were enrolled. Patients were randomly treated with both buspiron and placebo, in addition to their previous therapeutic plan. Patients were enrolled in Pisa, from 18-nov-2016 to 01-nov-2018

Pre-assignment

Screening details:

All the patients respecting the following Inclusion criteria were evaluated:

- Age between 18 and 80 years;
- Heart failure (diagnosed according to Framingham criteria) with a left ventricular dysfunction, NYHA classes I-III;
- Chemoreflex activation to hypercapnia;
- Central apneas at the cardiorespiratory monitoring
- Informed consent signature

Period 1

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

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | No |
| Arm title | Buspirone |

Arm description: -

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Buspirone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

5 mg 1 cps x 3/die every 8h for 2 days, 10 mg (2 cps of 5 mg) x 3/die every 8h for 2 days, 15 mg (3 cps of 5 mg) x 3/die every 8h for 2 days

| | |
|-----------|---------|
| Arm title | Placebo |
|-----------|---------|

Arm description: -

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

1 cps x 3/die every 8h for 2 days, 2 cps x 3/die every 8h for 2 days, 13 cps x 3/die every 8h for 2 days

| Number of subjects in period 1 | Buspirone | Placebo |
|---------------------------------------|-----------|---------|
| Started | 16 | 16 |
| Completed | 16 | 16 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Treatment with buspirone |
|-----------------------|--------------------------|

Reporting group description: -

| Reporting group values | Treatment with buspirone | Total | |
|------------------------|--------------------------|-------|--|
| Number of subjects | 16 | 16 | |
| Age categorical | | | |
| Adults 18-80 | | | |
| Units: Subjects | | | |
| Adults 18-80 | 16 | 16 | |
| Gender categorical | | | |
| was enrolled only male | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 16 | 16 | |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Patients enrolled |
|----------------------------|-------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

A total of 16 consecutive HF patients were enrolled (age 71.3 ± 5.8 years, all males, 50% ischaemic aetiology, LVEF $29.8 \pm 7.8\%$, 38% in NYHA class III) and showed moderate-severe CA at nighttime, despite optimal treatment (Figure 1, Table 1). No patient withdrew from the study, two patients were intolerant to the chemoreflex test, while all other measurements were available in all patients.

| Reporting group values | Patients enrolled | | |
|------------------------|-------------------|--|--|
| Number of subjects | 16 | | |
| Age categorical | | | |
| Adults 18-80 | | | |
| Units: Subjects | | | |
| Adults 18-80 | 16 | | |
| Gender categorical | | | |
| was enrolled only male | | | |
| Units: Subjects | | | |
| Female | 0 | | |
| Male | 16 | | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | Buspirone |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Subject analysis set title | Patients enrolled |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| A total of 16 consecutive HF patients were enrolled (age 71.3 ± 5.8 years, all males, 50% ischaemic aetiology, LVEF $29.8 \pm 7.8\%$, 38% in NYHA class III) and showed moderate-severe CA at nighttime, despite optimal treatment (Figure 1, Table 1). No patient withdrew from the study, two patients were intolerant to the chemoreflex test, while all other measurements were available in all patients. | |

Primary: reduction in CO2 chemosensitivity or hypercapnic ventilatory response

| | |
|---------------------------|---|
| End point title | reduction in CO2 chemosensitivity or hypercapnic ventilatory response |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| after 1 week of treatment | |

| End point values | Buspirone | Placebo | Patients enrolled | |
|----------------------------------|--------------------|--------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 16 | 16 | 16 | |
| Units: L/min/mmHg | | | | |
| number (confidence interval 95%) | -0.6 (-1.1 to 0.2) | -0.1 (-0.2 to 0.3) | -0.6 (-1.1 to 0.2) | |

Statistical analyses

| | |
|--|--------------------------------|
| Statistical analysis title | Statistical analysis endpoints |
| Statistical analysis description: | |
| Statistical analysis was performed with the SPSS 21.0 program (1989–2012, LEAD Technologies Inc., Charlotte, NC, USA). Values are presented as mean \pm standard deviation (SD) or median and interquartile range (IQR) according to normal/skewed distribution. From pilot data, considering a SD of 0.36 L/min/mmHg (repeated intra-subject measures) and >0.5 L/min/mmHg ($>25\%$ reduction from baseline) as a clinically significant reduction in CO2 chemosensitivity. | |
| Comparison groups | Buspirone v Patients enrolled |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 32 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

none

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | No AE |
|-----------------------|-------|

Reporting group description:

NO AE reported

| Serious adverse events | No AE | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | No AE | | |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | | |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: the patients did not experience adverse events

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|----------------------------------|
| 26 September 2017 | number of patients from 10 to 20 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported