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, duble 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±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±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±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