



Clinical trial results:

Multicenter parallel-group, concealed and randomized allocation and blinded-endpoint study, to evaluate the effects of Torasemide PR versus furosemide on a biochemical marker of collagen synthesis and deposition, in hypertensive patients with heart failure

Summary

EudraCT number	2006-001446-14
Trial protocol	ES
Global end of trial date	24 February 2010

Results information

Result version number	v1 (current)
This version publication date	09 September 2021
First version publication date	09 September 2021

Trial information

Trial identification

Sponsor protocol code	N/GF-TORAFIC-06
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	NOVAG S.A., FERRER GRUPO
Sponsor organisation address	CALLE GRAN VIA CARLES III, 94, Barcelona, Spain,
Public contact	Medical Advisor, Dpto. Médico, NOVAG S.A., FERRER GRUPO, 34 93600 37 28, efernandez@ferrergrupo.com
Scientific contact	Medical Advisor, Dpto. Médico, NOVAG S.A., FERRER GRUPO, 34 93600 37 28, efernandez@ferrergrupo.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	16 October 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2009
Global end of trial reached?	Yes
Global end of trial date	24 February 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of Torasemide-LP over Furosemide in reducing myocardial fibrosis in patients with heart failure, in grades II, III and IV, according to the New York Heart Association (NYHA) classification.

Protection of trial subjects:

Patients could discontinue study treatment at any time, without having to give any explanation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 155
Worldwide total number of subjects	155
EEA total number of subjects	155

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)	47
From 65 to 84 years	103
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Twenty-five centers throughout Spain participated in the present study. A total of 169 patients were included, of which 155 were randomized. The recruitment period lasted for 21 months (February 26, 2007 to November 18, 2008) and the duration of each patient in the study was 8 months.

Pre-assignment

Screening details:

169 patients were screened, 14 of them were not included for breaching any inclusion or exclusion criteria. Main inclusion criteria: adult patients with grade II-IV heart failure and with clinically stable heart failure. Main exclusion criteria: patients diagnosed with heart failure whose etiology was aortic stenosis or hypertrophic cardiomyopathy.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

At visit 0, and after obtaining the informed consent from the patient, each patient was assigned a four-digit selection number; the first two digits indicated the research center and the last two followed a sequential numbering that identified the patient during the study. If the patient was randomized, a randomization number was assigned according to the distribution of the medication by blocks, which consisted of three digits, which had been assigned sequentially to each center.

Arms

Are arms mutually exclusive?	Yes
Arm title	Toraseamide-PR Group
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Toraseamide prolonged release
Investigational medicinal product code	
Other name	Sutril Neo®
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were randomized at a dosage of 10 mg/day (orally) of toraseamide-prolonged release. After 4 weeks, in patients who did not respond to treatment, the dose was doubled to 20 mg/day. After 12-24 weeks, patients on toraseamide at 10 mg/day who showed no response to treatment, were switched to a dose of 20 mg/day. Patients who already received a dose 20 mg/day and who did not respond to treatment, increased the dose (at investigator's decision) to 30 mg/day or to 40 mg/day. Patients who had reached treatment doses of 40 mg/day of toraseamide-prolonged release and who were not responding to treatment, dropped out of the study.

Arm title	Furosemide Group
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Furosemide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

Patients were randomized at a dosage of 40 mg/day (orally) of furosemide.

After 4 weeks, in patients who did not respond to treatment, the dose was doubled to 80 mg/day. After 12-24 weeks, patients on furosemide at 40 mg/day who showed no response to treatment, were switched to a dose of 80 mg/day. Patients who already received a dose 80 mg/day and who did not respond to treatment, increased the dose (at investigator's decision) to 120 mg/day or to 160 mg/day. Patients who had reached treatment doses of 160 mg/day of furosemide and who were not responding to treatment, dropped out of the study.

Number of subjects in period 1	Torasemide-PR Group	Furosemide Group
Started	77	78
Completed	63	64
Not completed	14	14
Adverse event, serious fatal	2	4
Consent withdrawn by subject	3	3
Adverse event, non-fatal	-	1
Lost to follow-up	-	1
Protocol deviation	9	5

Baseline characteristics

Reporting groups

Reporting group title	Toraseamide-PR Group
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Reporting group description: -

Reporting group title	Furosemide Group
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Reporting group description: -

Reporting group values	Toraseamide-PR Group	Furosemide Group	Total
Number of subjects	77	78	155
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)	28	19	47
From 65-84 years	46	57	103
85 years and over	3	2	5
Age continuous Units: years			
arithmetic mean	68.05	69.63	
standard deviation	± 11.38	± 9.84	-
Gender categorical Units: Subjects			
Female	35	30	65
Male	42	48	90
Race Units: Subjects			
Caucasian	77	77	154
Other: Latin American	0	1	1
Heart failure Units: Subjects			
Yes	77	78	155
No	0	0	0
Arterial hypertension Units: Subjects			
Yes	77	77	154
No	0	1	1
Myocardial infarction Units: Subjects			
Yes	13	13	26
No	64	65	129
Coronary heart disease Units: Subjects			

Yes	14	13	27
No	63	65	128
Stroke Units: Subjects			
Yes	5	8	13
No	72	70	142
Peripheral vascular disease Units: Subjects			
Yes	4	9	13
No	73	69	142
Non-severe arrhythmia Units: Subjects			
Yes	22	24	46
No	55	54	109
Severe arrhythmia Units: Subjects			
Yes	0	0	0
No	77	78	155
Valvular disease Units: Subjects			
Yes	8	14	22
No	69	64	133
Aortic stenosis Units: Subjects			
Yes	1	1	2
No	76	77	153
Hypertrophic cardiomyopathy Units: Subjects			
Yes	0	0	0
No	77	78	155
Stable angina pectoris Units: Subjects			
Yes	7	11	18
No	70	67	137
Unstable angina pectoris Units: Subjects			
Yes	0	0	0
No	77	78	155
Metabolism and nutrition disorders Units: Subjects			
Yes	44	51	95
No	33	27	60
Musculoskeletal and connective tissue disorders Units: Subjects			
Yes	19	23	42
No	58	55	113
Psychiatric disorders Units: Subjects			
Yes	10	18	28
No	67	60	127

Total cholesterol			
Units: Subjects			
Clinically significant value	1	0	1
Non-clinically significant value	76	78	154
cHDL			
Units: Subjects			
Clinically significant value	0	1	1
Non-clinically significant value	77	77	154
cLDL			
Units: Subjects			
Clinically significant value	4	4	8
Non-clinically significant value	73	74	147
Triglycerides			
Units: Subjects			
Clinically significant value	2	0	2
Non-clinically significant value	75	78	153
GGT			
Units: Subjects			
Clinically significant value	0	1	1
Non-clinically significant value	77	77	154
Glucose			
Units: Subjects			
Clinically significant value	1	1	2
Non-clinically significant value	76	77	153
Uric acid			
Units: Subjects			
Clinically significant value	3	2	5
Non-clinically significant value	74	76	150
Global valuation			
Units: Subjects			
Normal	23	20	43
Abnormal not clinically relevant	53	56	109
Abnormal clinically relevant	0	1	1
Not available	1	1	2
Signs of pulmonary congestion			
Units: Subjects			
Presence of signs	12	11	23
Absence of signs	59	53	112
Not available	6	14	20
Presence of gallop S3			
Units: Subjects			
Yes	1	1	2
No	75	77	152
Not available	1	0	1
Hepatojugular reflux			
Units: Subjects			
Yes	1	3	4
No	75	75	150
Not available	1	0	1
Jugular venous distention			
Units: Subjects			

Yes	2	1	3
No	74	77	151
Not available	1	0	1
Dyspnea at rest			
Units: Subjects			
Yes	2	0	2
No	74	78	152
Not available	1	0	1
Dyspnea on exertion			
Units: Subjects			
Yes	55	61	116
No	21	17	38
Not available	1	0	1
Type of edema			
Units: Subjects			
Absence of edema	61	61	122
Pedic edema	5	5	10
Edema of feet and ankles	9	11	20
Edema up to half legs	2	1	3
Edema to the knees	0	0	0
Edema above the knees	0	0	0
Evaluation of heart failure functional class			
Units: Subjects			
Class I	0	0	0
Class II	74	70	144
Class III	3	8	11
Class IV	0	0	0
Current medication: antithrombotic agents			
Units: Subjects			
Yes	23	24	47
No	54	54	108
Current medication: beta-blocking agents			
Units: Subjects			
Yes	50	51	101
No	27	27	54
Current medication: lipid modifying agents			
Units: Subjects			
Yes	0	3	3
No	77	75	152
Current medication: agents acting in the renin-angiotensin system			
Units: Subjects			
Yes	58	57	115
No	19	21	40
Current medication: antihypertensive			
Units: Subjects			
Yes	1	4	5
No	76	74	150
Current medication: calcium channel			

blockers Units: Subjects			
Yes	12	12	24
No	65	66	131
Current medication: diuretics Units: Subjects			
Yes	72	71	143
No	5	7	12
Current medication: antianemic preparations Units: Subjects			
Yes	0	1	1
No	77	77	154
Current medication: mineral supplements Units: Subjects			
Yes	3	2	5
No	74	76	150
Current medication: cardiac therapy Units: Subjects			
Yes	14	14	28
No	63	64	127
Concomitant medication: antithrombotic agents Units: Subjects			
Yes	29	29	58
No	48	49	97
Concomitant medication: lipid modifying agents Units: Subjects			
Yes	38	39	77
No	39	39	78
Concomitant medication: agents for the treatment of alterations caused by acids Units: Subjects			
Yes	33	26	59
No	44	52	96
Concomitant medication: atorvastatin Units: Subjects			
Yes	19	23	42
No	58	55	113
Concomitant medication: omeprazole Units: Subjects			
Yes	21	19	40
No	56	59	115
Concomitant medication: acetylsalicylic acid Units: Subjects			
Yes	20	12	32
No	57	66	123
Weight (kg) Units: kilogram(s) arithmetic mean	82.30	80.41	

standard deviation	± 15.50	± 15.75	-
Size (cm)			
Units: centimeter			
arithmetic mean	161.25	162.67	
standard deviation	± 10.38	± 9.62	-
BMI			
Units: kilogram(s)/cubic meter			
arithmetic mean	31.59	30.42	
standard deviation	± 5.47	± 6.32	-
Systolic blood pressure (mmHg)			
Units: millimeter(s) of mercury			
arithmetic mean	133.51	137.64	
standard deviation	± 18.24	± 19.08	-
Diastolic blood pressure (mmHg)			
Units: millimeter(s) of mercury			
arithmetic mean	78.03	78.00	
standard deviation	± 11.89	± 12.28	-
Heart rate (bpm)			
Units: beats per minute			
arithmetic mean	68.19	70.85	
standard deviation	± 11.48	± 13.78	-
Hemoglobin (g/dL)			
Units: gram(s)/decilitre			
arithmetic mean	13.81	13.84	
standard deviation	± 1.57	± 1.58	-
Hematocrit (%)			
Units: percent			
arithmetic mean	41.24	41.54	
standard deviation	± 4.52	± 4.41	-
Total leukocytes (10*3/μL)			
Units: microlitre(s)			
arithmetic mean	7.05	7.51	
standard deviation	± 1.86	± 2.08	-
Platelets (10*3/μL)			
Units: microlitre(s)			
arithmetic mean	224.07	222.85	
standard deviation	± 56.90	± 65.10	-
Sodium (mEq/L)			
Units: milliequivalent(s)/litre			
arithmetic mean	141.49	140.73	
standard deviation	± 3.12	± 3.23	-
Potassium (mEq/L)			
Units: milliequivalent(s)/litre			
arithmetic mean	4.38	4.46	
standard deviation	± 0.49	± 0.56	-
Chlorine (mEq/L)			
Units: milliequivalent(s)/litre			
arithmetic mean	102.63	102.75	
standard deviation	± 3.40	± 3.82	-
Serum creatinine (mg/dL)			
Units: milligram(s)/decilitre			
arithmetic mean	1.03	1.08	

standard deviation	± 0.46	± 0.31	-
Ejection fraction (%)			
Units: percent			
arithmetic mean	54.39	50.72	
standard deviation	± 15.29	± 17.37	-
Left ventricular mass (g)			
Units: gram(s)			
arithmetic mean	340.77	359.36	
standard deviation	± 103.88	± 128.96	-
Body surface (m2)			
Units: square meter			
arithmetic mean	1.86	1.85	
standard deviation	± 0.21	± 0.19	-
Left ventricular mass index (g/m2)			
Units: gram(s)/square meter			
arithmetic mean	182.30	193.80	
standard deviation	± 50.49	± 65.54	-
Diastolic septal thickness (cm)			
Units: centimeter			
arithmetic mean	1.25	1.24	
standard deviation	± 0.19	± 0.25	-
Diastolic posterior wall thickness (cm)			
Units: centimeter			
arithmetic mean	1.18	1.14	
standard deviation	± 0.21	± 0.20	-
Diastolic diameter of the left ventricle (cm)			
Units: centimeter			
arithmetic mean	5.34	5.57	
standard deviation	± 0.86	± 1.05	-
Relative wall thickness (cm)			
Units: centimeter			
arithmetic mean	1.47	1.44	
standard deviation	± 0.23	± 0.29	-
Cardiac frequency beats/min.			
Units: beats per minute			
arithmetic mean	68.55	69.75	
standard deviation	± 12.82	± 13.26	-
Carboxyterminal peptide of procollagen type I (µg/l)			
Units: microgram(s)/litre			
arithmetic mean	102.72	108.65	
standard deviation	± 31.16	± 27.54	-
Brain natriuretic peptide (pg/ml)			
Units: picogram(s)/milliliter			
arithmetic mean	1638.14	1875.41	
standard deviation	± 884.95	± 1043.94	-

End points

End points reporting groups

Reporting group title	Toraseamide-PR Group
Reporting group description: -	
Reporting group title	Furosemide Group
Reporting group description: -	

Primary: Serum concentrations of the carboxy-terminal peptide of procollagen type I (ITT population)

End point title	Serum concentrations of the carboxy-terminal peptide of procollagen type I (ITT population)
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End point description:

This variable was analyzed both in the intention to treat (ITT) population and in the per protocol (PP) population with the intention of assessing the stability of the conclusions. The ITT population (n=155) included all patients who had taken at least one dose of study medication (randomized patients). The PP population (n=122) included all the randomized patients who concluded the study in accordance with the provisions of the protocol, who met all the inclusion criteria and none of the exclusion criteria and had made the final study visit. Those subjects judged as unanalyzable due to serious deviations from the protocol do not fall into this group.

End point type	Primary
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End point timeframe:

Primary efficacy endpoint of the study was the evaluation of the changes in plasma levels of carboxy-terminal peptide of procollagen type I (PICP) between the baseline visit and the final visit between the two treatment groups.

End point values	Toraseamide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: microgram(s)/litre				
arithmetic mean (standard deviation)				
PICP basal	102.72 (± 29.69)	108.65 (± 26.82)		
PICP final	97.73 (± 25.73)	98.60 (± 26.12)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Furosemide Group v Toraseamide-PR Group

Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7505 ^[1]
Method	ANCOVA

Notes:

[1] - A statistically significant model ($p < 0.0001$) was obtained between the baseline PIcP value and the final PIcP value in both treatment groups.

Primary: Serum concentrations of the carboxy-terminal peptide of procollagen type I (PP population)

End point title	Serum concentrations of the carboxy-terminal peptide of procollagen type I (PP population)
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End point description:

This variable was analyzed both in the intention to treat (ITT) population and in the per protocol (PP) population with the intention of assessing the stability of the conclusions. The ITT population (n=155) included all patients who had taken at least one dose of study medication (randomized patients). The PP population (n=122) included all the randomized patients who concluded the study in accordance with the provisions of the protocol, who met all the inclusion criteria and none of the exclusion criteria and had made the final study visit. Those subjects judged as unanalyzable due to serious deviations from the protocol do not fall into this group.

End point type	Primary
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End point timeframe:

Primary efficacy endpoint of the study was the evaluation of the changes in plasma levels of carboxy-terminal peptide of procollagen type I (PICP) between the baseline visit and the final visit between the two treatment groups.

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: microgram(s)				
arithmetic mean (standard deviation)				
PIcP basal	104.07 (\pm 32.79)	109.28 (\pm 29.34)		
PIcP final	99.07 (\pm 27.92)	98.74 (\pm 27.89)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Furosemide Group v Torasemide-PR Group
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6754 ^[2]
Method	ANCOVA

Notes:

[2] - A statistically significant model ($p < 0.0001$) was obtained between the baseline PIcP value and the final PIcP value in both treatment groups.

Secondary: Signs and symptoms derived from heart failure: Weight

End point title	Signs and symptoms derived from heart failure: Weight
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End point description:

End point type	Secondary
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End point timeframe:

The change in weight between the baseline and the final visit was calculated as: Weight change = basal weight - final weight. Positive values indicate a decrease and negative values an increase in the final visit compared to the baseline visit.

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	71		
Units: kilogram(s)				
arithmetic mean (standard deviation)				
Weight change (Kg)	-0.86 (± 4.13)	-0.47 (± 4.71)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6834
Method	Wilcoxon (Mann-Whitney)

Secondary: Signs and symptoms derived from heart failure: Edema

End point title	Signs and symptoms derived from heart failure: Edema
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End point description:

End point type	Secondary
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End point timeframe:

Changes in the presence of edema between the baseline visit and the final visit.

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	8	12		
Maintenance	52	55		
Deterioration	5	4		
Not available	12	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7341
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Gallop S3

End point title	Signs and symptoms derived from heart failure: Gallop S3
End point description:	
End point type	Secondary
End point timeframe:	
Changes in the presence of gallop S3 between baseline visit and final visit	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	0	0		
Maintenance	65	69		
Deterioration	0	2		
Not available	12	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torsemide-PR Group v Furosemide Group

Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4973
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Hepatojugular reflux

End point title	Signs and symptoms derived from heart failure: Hepatojugular reflux
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End point description:

End point type	Secondary
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End point timeframe:

Changes in hepatojugular reflux between baseline visit and final visit

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	1	2		
Maintenance	64	69		
Deterioration	0	0		
Not available	12	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Signs and symptoms derived from heart failure: Jugular venous distention

End point title	Signs and symptoms derived from heart failure: Jugular venous distention
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End point description:

End point type	Secondary
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End point timeframe:

Changes in jugular venous distention between baseline visit and final visit

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	2	1		
Maintenance	63	65		
Deterioration	0	5		
Not available	12	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0585
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Dyspnea at rest

End point title	Signs and symptoms derived from heart failure: Dyspnea at rest
End point description:	
End point type	Secondary
End point timeframe:	
Changes in dyspnea at rest between baseline visit and final visit	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	2	0		
Maintenance	62	71		
Deterioration	1	0		
Not available	12	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Furosemide Group v Torasemide-PR Group
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1065
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Dyspnea on exertion

End point title	Signs and symptoms derived from heart failure: Dyspnea on exertion
End point description:	
End point type	Secondary
End point timeframe:	
Changes in dyspnea on exertion between baseline visit and final visit	

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	10	10		
Maintenance	52	53		
Deterioration	3	8		
Not available	12	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3639
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Heart failure functional class

End point title	Signs and symptoms derived from heart failure: Heart failure functional class
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End point description:

End point type	Secondary
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End point timeframe:

Changes in New York Heart Association classification between baseline visit and final visit

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	14	13		
Maintenance	49	56		
Deterioration	2	2		
Not available	12	7		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.875
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Electrocardiogram I

End point title	Signs and symptoms derived from heart failure: Electrocardiogram I
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End point description:

End point type	Secondary
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End point timeframe:

Changes in heart rate between baseline visit and final visit

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	70		
Units: heartbeat per minute				
arithmetic mean (standard deviation)				
Changes in heart rate	1.87 (± 10.36)	0.34 (± 17.52)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5982
Method	Wilcoxon (Mann-Whitney)

Secondary: Signs and symptoms derived from heart failure: Electrocardiogram II

End point title	Signs and symptoms derived from heart failure: Electrocardiogram II
End point description:	
End point type	Secondary
End point timeframe:	
Changes in global assessment between baseline visit and final visit	

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	7	10		
Maintenance	49	53		
Deterioration	6	7		
Not available	15	8		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torasemide-PR Group v Furosemide Group

Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8696
Method	Chi-squared

Secondary: Signs and symptoms derived from heart failure: Echocardiogram I

End point title	Signs and symptoms derived from heart failure: Echocardiogram I
End point description:	
End point type	Secondary
End point timeframe:	
Changes in ejection fraction between baseline visit and final visit	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	69		
Units: percent				
arithmetic mean (standard deviation)				
Ejection fraction change	-1.47 (± 8.06)	-2.93 (± 11.42)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Signs and symptoms derived from heart failure: Echocardiogram II

End point title	Signs and symptoms derived from heart failure: Echocardiogram II
End point description:	
End point type	Secondary
End point timeframe:	
Changes in left ventricular mass between baseline visit and final visit	

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	70		
Units: gram(s)				
arithmetic mean (standard deviation)				
Left ventricular mass change	9.23 (\pm 77.85)	24.64 (\pm 92.05)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Signs and symptoms derived from heart failure: Echocardiogram III

End point title	Signs and symptoms derived from heart failure: Echocardiogram III
End point description:	
End point type	Secondary
End point timeframe:	
Changes in left ventricular mass index between baseline visit and final visit	

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	70		
Units: gram(s)/square meter				
arithmetic mean (standard deviation)				
LVMI change	5.48 (\pm 41.60)	14.38 (\pm 50.02)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Signs and symptoms derived from heart failure: Brain Natriuretic Peptide

End point title	Signs and symptoms derived from heart failure: Brain Natriuretic Peptide
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End point description:

End point type	Secondary
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End point timeframe:

Changes in NT-proBNP between baseline visit and final visit

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	68		
Units: picogram(s)/milliliter				
arithmetic mean (standard deviation)				
NT-proBNP change	-33.63 (± 844.86)	-49.33 (± 1032.57)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8592
Method	Wilcoxon (Mann-Whitney)

Secondary: Signs and symptoms derived from heart failure: Urinary symptoms

End point title	Signs and symptoms derived from heart failure: Urinary symptoms
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End point description:

End point type	Secondary
End point timeframe:	
Changes in the urge to urinate between baseline visit and last available questionnaire	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
Improvement	15	12		
Maintenance	47	43		
Deterioration	11	20		
Not available	4	3		

Statistical analyses

Statistical analysis title	Chi-square test
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.22
Method	Chi-squared

Secondary: Changes in clinical parameters: Systolic Blood Pressure

End point title	Changes in clinical parameters: Systolic Blood Pressure
End point description:	

End point type	Secondary
End point timeframe:	
Changes in systolic blood pressure between baseline visit and final visit	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	71		
Units: millimeter(s) of mercury				
arithmetic mean (standard deviation)				
Systolic blood pressure change	-0.22 (± 20.86)	3.20 (± 22.82)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes in clinical parameters: Diastolic Blood Pressure

End point title	Changes in clinical parameters: Diastolic Blood Pressure
End point description:	
End point type	Secondary
End point timeframe:	
Changes in diastolic blood pressure between baseline visit and final visit	

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	71		
Units: millimeter(s) of mercury				
arithmetic mean (standard deviation)				
Diastolic blood pressure change	1.91 (± 13.93)	1.80 (± 14.10)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes in clinical parameters: Cardiac Frequency

End point title	Changes in clinical parameters: Cardiac Frequency
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End point description:

End point type	Secondary
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End point timeframe:

Changes in cardiac frequency between baseline visit and final visit

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	71		
Units: beats per minute				
arithmetic mean (standard deviation)				
Cardiac frequency change	0.97 (± 10.45)	0.83 (± 16.38)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torasemide-PR Group v Furosemide Group
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes in clinical parameters: Renal function

End point title	Changes in clinical parameters: Renal function
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End point description:

End point type	Secondary
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End point timeframe:

Changes in serum creatinine between baseline visit and final visit

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	69		
Units: milligram(s)/deciliter				
arithmetic mean (standard deviation)				
Serum creatinine change	-0.04 (± 0.15)	-0.05 (± 0.24)		

Statistical analyses

Statistical analysis title	Test U de Mann-Whitney
Comparison groups	Torsemide-PR Group v Furosemide Group
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of cardiovascular events: Hospital admissions

End point title	Incidence of cardiovascular events: Hospital admissions
End point description:	
End point type	Secondary
End point timeframe:	
Patients admitted to hospital for cardiovascular causes linked to the pathology under study	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
With hospital admissions	4	2		
Without hospital admissions	73	76		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of cardiovascular events: Emergency care

End point title	Incidence of cardiovascular events: Emergency care
End point description:	

End point type	Secondary
End point timeframe:	
Patients with care in the emergency room for cardiovascular causes linked to the pathology under study	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
With emergency care visits	4	4		
Without emergency care visits	73	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of cardiovascular events: Home care

End point title	Incidence of cardiovascular events: Home care
End point description:	
End point type	Secondary
End point timeframe:	
Patients with home care for cardiovascular causes linked to the pathology under study	

End point values	Torsemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: subjects				
With home care	0	1		
Without home care	77	77		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Therapeutic compliance

End point title	Therapeutic compliance
End point description:	
As specified in the study protocol, records of the study medication used and the doses administered had to be kept. The medication record was completed by the investigator throughout the entire study. To assess compliance with treatment, the study monitor compared the amount of medication dispensed	

with that the patient returned.

End point type	Other pre-specified
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End point timeframe:

Treatment compliance (%) was calculated for each patient at the first month, at the third month, at the sixth month and at the eighth month.

End point values	Torasemide-PR Group	Furosemide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: unit(s)				
arithmetic mean (standard error)				
Compliance (%) at 1st month	94.37 (± 35.30)	93.97 (± 41.45)		
Compliance (%) at 3rd month	102.65 (± 26.86)	105.18 (± 36.38)		
Compliance (%) at 6th month	108.00 (± 41.18)	124.22 (± 72.92)		
Compliance (%) at 8th month	105.94 (± 52.81)	117.58 (± 72.17)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded after each visit from baseline to 8 months of treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	Torasemide-PR Group
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Reporting group description: -

Reporting group title	Furosemide Group
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Reporting group description: -

Serious adverse events	Torasemide-PR Group	Furosemide Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 77 (11.69%)	9 / 78 (11.54%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Toxicity to various agents	Additional description: Treatment toxicity		
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Syncope			

subjects affected / exposed	3 / 77 (3.90%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 77 (2.60%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery	Additional description: Surgery for obesity		
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Pancreatitis acute			
subjects affected / exposed	0 / 77 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: Lobar pneumonia		
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			

subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Torasemide-PR Group	Furosemide Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 77 (58.44%)	44 / 78 (56.41%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 77 (2.60%)	3 / 78 (3.85%)	
occurrences (all)	2	3	
Epistaxis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Traumatic haematoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 77 (2.60%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Chest pain			
subjects affected / exposed	0 / 77 (0.00%)	2 / 78 (2.56%)	
occurrences (all)	0	2	
Oedema			

subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Chest discomfort subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Reproductive system and breast disorders Atrophic vulvovaginitis subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	2 / 78 (2.56%) 2	
Bronchitis subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 3	3 / 78 (3.85%) 8	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 3	0 / 78 (0.00%) 0	
Lung neoplasm subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Rhinitis subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 2	3 / 78 (3.85%) 3	
Cognitive disorder			

subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Confusional state subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Anxiety subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Somnolence subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Mood altered subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Investigations Urine abnormality subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Injury, poisoning and procedural complications Vitreous detachment subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Wound subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Fall subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Bone fissure subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Cardiac disorders Dizziness subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	3 / 78 (3.85%) 3	
Atrial fibrillation			

subjects affected / exposed	0 / 77 (0.00%)	2 / 78 (2.56%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	1 / 77 (1.30%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Angina pectoris			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Cardiac failure			
subjects affected / exposed	1 / 77 (1.30%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Transient ischaemic attack			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	

Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Ear pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 77 (0.00%)	2 / 78 (2.56%)	
occurrences (all)	0	2	
Gastroenteritis viral			
subjects affected / exposed	2 / 77 (2.60%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	3 / 77 (3.90%)	0 / 78 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Dental caries			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	

Liver disorder subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Dermatitis subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	2 / 78 (2.56%) 2	
Pruritus subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Nodule subjects affected / exposed occurrences (all)	Additional description: Subcutaneous nodule		
	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Cellulitis subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Intertrigo subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 2	1 / 78 (1.28%) 1	
Drug eruption subjects affected / exposed occurrences (all)	Additional description: Eruption		
	1 / 77 (1.30%) 2	0 / 78 (0.00%) 0	
Seborrhoeic keratosis subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Skin ulcer subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Renal and urinary disorders			
Fluid retention subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Micturition urgency subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Pollakiuria			

subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Endocrine disorders Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	3 / 78 (3.85%) 6	
Arthralgia subjects affected / exposed occurrences (all)	2 / 77 (2.60%) 3	1 / 78 (1.28%) 1	
Osteoarthritis subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	2 / 78 (2.56%) 2	
Back injury subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Arthritis subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Spinal osteoarthritis subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Rib fracture subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Pain in extremity	Additional description: Pain in limb		

subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Joint dislocation			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness	Additional description: Stiff neck		
subjects affected / exposed	1 / 77 (1.30%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 77 (1.30%)	2 / 78 (2.56%)	
occurrences (all)	2	3	
Pharyngitis			
subjects affected / exposed	1 / 77 (1.30%)	2 / 78 (2.56%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	2 / 77 (2.60%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 77 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	

Post herpetic neuralgia subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	Additional description: Lung infection
Haematoma infection subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Tracheobronchitis subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Viral infection subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Metabolism and nutrition disorders			
Gout subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 2	2 / 78 (2.56%) 2	
Hyperuricaemia subjects affected / exposed occurrences (all)	3 / 77 (3.90%) 3	0 / 78 (0.00%) 0	
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	1 / 78 (1.28%) 1	
Gouty arthritis subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	1 / 78 (1.28%) 1	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 77 (1.30%) 1	0 / 78 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2006	The title of the clinical trial was modified by adding the reference to the evaluation of serum levels of carboxy-terminal peptide of procollagen type I (PICP) and specifying the type of heart failure (HF) studied in the trial. The amendment also served to specify in the wording of the main objective the type of HF studied in the trial and to specify in the inclusion criterion number 2 that the patients to be included had to have grade II, III and IV heart failure. In order to establish the study population more adequately, inclusion criteria number 3 and exclusion criteria 7 and 21 were modified. The definition of non-response to treatment was improved and added as a clinical manifestation New York Heart Association (NYHA) functional grade related to congestive HF. Additionally, the fact that patients had to maintain pharmacological treatment for heart failure was clarified at the screening visit (Vs). Finally, Annex XV was added to the protocol to clarify the clinical relevance of the changes in PICP as a biomarker of myocardial deposition of collagen fibers and the value of its levels as a marker of the clinical evolution of heart failure, and the wording of point 2 of Annex VIII regarding the definition of heart failure was improved. Other corrections to the study protocol were also made.
03 October 2006	Since the request for approval of the Hospital General de Mallorca center in the sole discretion of the IEC of Reference (Hospital Clínic I Provincial de Barcelona) of September 7, 2006, was denied, this amendment 2 was proposed to expand the participating centers in order to reconsider the participation of Hospital General de Mallorca center in the clinical trial and once again request its evaluation by the Illes Balears IEC.
15 November 2006	Due to the updating of the electronic CRF system used in the trial, the text of the protocol corresponding to the Case Report Form section was modified.
15 February 2007	<p>The exclusion criterion that established that patients receiving treatment with antiarrhythmic group 1a, 1b or 2 could not be included in the trial. However, some of the drugs included in this list (especially β-blockers) are of routine use in patients with heart failure. For this reason, it was proposed to carry out this amendment, with the aim of adapting the exclusion criteria to the reality of the pharmacological treatment of patients with this pathology and, consequently, increasing the number of eligible patients. It is also important to note that no pharmacological interactions have been described between group 1a, 1b or 2 antiarrhythmics and the drugs under study (torasemide and furosemide) and that these drugs have not been shown to interfere in the process of myocardial fibrosis.</p> <p>Through this amendment, the person who appears in the protocol as medical writer was changed and the members of the Scientific Committee that have supported the project since its inception were included in the study protocol. The principal investigator of one of the participating centers was also modified.</p>

20 June 2007	<p>The reason for this amendment was to change the validity of the echocardiogram as a diagnostic test for hypertrophy, applicable to the screening visit (Vs), from 3 months to 6 months. It was considered that this modification does not affect the diagnosis of hypertrophy because this pathology is a process with a slow evolution period, so no significant differences will be detected between the two tests.</p> <p>Exclusion criterion number 5 of the protocol was clarified due to confusion. This criterion establishes that patients with severe cardiac arrhythmia could not be included in the trial, so that patients with atrial fibrillation, common in most patients with heart failure, which does not show severity, could be included.</p> <p>Clarification is proposed in order to unify the interpretation of the criterion among all collaborators, adapting the exclusion criteria to the reality of the pharmacological treatment of patients with this pathology. The degree of severity of a cardiac arrhythmia (in this case, atrial fibrillation) is defined as poorly controlled atrial fibrillation, since it can make difficult the data acquisition and interpretation of the echocardiogram.</p>
03 July 2007	<p>The reason for this amendment was the expansion of the number of centers participating in the trial in order to speed up the inclusion of patients, which was being lower than expected.</p>
03 September 2007	<p>The reason for this amendment was the expansion of the number of centers participating in the trial in order to speed up the inclusion of patients, which was being lower than expected.</p>
15 November 2007	<p>The reason for this amendment was the expansion of the number of centers participating in the trial in order to speed up the inclusion of patients, which was being lower than expected. On the other hand, the Principal Investigator of the Hospital Gregorio Marañón was changed, since according to him, the typology of patients in the study is not the one usually treated in Internal Medicine. It was decided to change the department (Internal Medicine) to the Cardiology department to be in charge of the selection/inclusion of patients. The new Principal Investigator became Dr. Francisco Fernández Avilés.</p> <p>Through this amendment, the modification of exclusion criterion number 10 was proposed. The aforementioned criterion established the following:</p> <p>Patients with chronic renal failure defined by the following analytical parameters:</p> <ul style="list-style-type: none"> - serum creatinine greater than 2.5 mg / dl, - glomerular filtration <30%. <p>During the course of the study, it was found that the diagnosis of renal failure in potential patients to be included in the study was established mainly by routine clinical practice, by the clinical assessment of the investigators and by a creatinine value greater than 2.5 mg, not being a determining factor in this case the glomerular filtration value. In other words, glomerular filtration was not a determining factor by itself when it presented values close to 30. In these cases, in the opinion of the investigators, it was the creatinine value that determined inclusion in the study. Due to the aforementioned and at the request of the investigators, a change in the exclusion criteria was proposed in order to adapt the protocol to routine clinical practice in such a way that only the serum creatinine value was used to determine chronic renal insufficiency, since creatininemia determines the clinical decision in routine practice.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported