Clinical trial results:
Loop Diuretics Dosage in Patients with Acute Heart Failure and Renal Failure: Conventional versus Carbohydrate Antigen 125 guided Strategy

Summary

EudraCT number	2014-001433-83
Trial protocol	ES
Global end of trial date	13 December 2016

Results information

Result version number	v1 (current)
This version publication date	12 June 2022
First version publication date	12 June 2022

Trial information

Trial identification

Sponsor protocol code	IMPROVE-AHF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02643147
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto de Investigación Sanitaria INCLIVA
Sponsor organisation address	Avd. Menéndez Pelayo 4, acc, Valencia, Spain, 46010
Public contact	Marta Peiro, Instituto de Investigación Sanitaria INCLIVA, 0034 961973536, gestioncientifica@incliva.es
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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	12 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2016
Global end of trial reached?	Yes
Global end of trial date	13 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether a dosing strategy of loop diuretics guided by plasma levels of CA125 is superior to a strategy of standard dosage of loop diuretics regarding improving renal function and/or prevent renal deterioration at 24 and 72 hours after admission.

Protection of trial subjects:

The protocol, informed consent form, participant information sheet and any applicable documents were submitted and approved by an appropriate Ethics Committee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2015
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	Spain: 160
Worldwide total number of subjects	160
EEA total number of subjects	160

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	122
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

Patients admitted for AHF and renal failure (cardiorenal syndrome type I) admitted to participating services (Cardiology, Nephrology, Internal Medicine and Intensive Care Unit).

Pre-assignment

Screening details:

Patients who met all inclusion/exclusion criteria were randomized during the first 48 hours after admission to one of the two strategies. All patients were recruited after signing the informed consent form.

Pre-assignment period milestones

Number of subjects started	160
Number of subjects completed	160

Period 1

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

Blinding implementation details:

Once treatment was allocated, the investigator team ensured that patients were blinded to the treatment received.

Arms

Are arms mutually exclusive?	Yes
Arm title	Conventional strategy

Arm description:

The dosage of loop diuretics was according to the presence of symptoms and signs of systemic congestion and according to current recommendations. To keep the scheduled starting dose for at least the first 24 hours of admission was advised. Maintaining or later revision was made based on clinical and/or laboratory criteria, recommending the assessment of renal function and plasma electrolytes (sodium and potassium) during the first 24 hours.

Arm type	Active comparator
Investigational medicinal product name	Furosemide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dosage of loop diuretics was done according to the presence of symptoms and signs of systemic congestion and according to current recommendations.

Arm title	CA125-guided strategy

Arm description:

Patients with CA125 ≤35 U/ml: In this subgroup of patients an initial dose of intravenous furosemide ≤80 mg/day was recommend, regardless of previous dose of loop diuretics they were receiving. To keep the starting dose for the first 24 hours was advised. The removal of thiazides or chlorthalidone was also recommended.

Patients with CA125 >35 U/ml: In these patients an initial dose of intravenous furosemide >120 mg/day or 2.5 times the oral dose of furosemide that the patient was taking was recommended. In

cases with striking elevation of CA125 (>100 U/ml) and/or concomitant unequivocal clinical signs of systemic congestion, doses >160 mg/day was recommended.

Arm type	Experimental
Investigational medicinal product name	Furosemide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients with CA125 ≤35 U/ml: Initial dose of intravenous furosemide ≤80 mg/day.
Patients with CA125 >35 U/ml: Initial dose of intravenous furosemide >120 mg/day or 2.5 times the oral dose of furosemide that the patient was taking.

Number of subjects in period 1	Conventional strategy	CA125-guided strategy
Started	81	79
Completed	81	79

Baseline characteristics

Reporting groups	
Reporting group title	Conventional strategy

Reporting group description:

The dosage of loop diuretics was according to the presence of symptoms and signs of systemic congestion and according to current recommendations. To keep the scheduled starting dose for at least the first 24 hours of admission was advised. Maintaining or later revision was made based on clinical and/or laboratory criteria, recommending the assessment of renal function and plasma electrolytes (sodium and potassium) during the first 24 hours.

Reporting group title	CA125-guided strategy

Reporting group description:

Patients with CA125 ≤35 U/ml: In this subgroup of patients an initial dose of intravenous furosemide ≤80 mg/day was recommend, regardless of previous dose of loop diuretics they were receiving. To keep the starting dose for the first 24 hours was advised. The removal of thiazides or chlorthalidone was also recommended.

Patients with CA125 >35 U/ml: In these patients an initial dose of intravenous furosemide >120 mg/day or 2.5 times the oral dose of furosemide that the patient was taking was recommended. In cases with striking elevation of CA125 (>100 U/ml) and/or concomitant unequivocal clinical signs of systemic congestion, doses >160 mg/day was recommended.

Reporting group values	Conventional strategy	CA125-guided strategy	Total
Number of subjects	81	79	160
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)	4	4	8
From 65-84 years	57	65	122
85 years and over	20	10	30
Gender categorical Units: Subjects			
Female	26	27	53
Male	55	52	107

End points

End points reporting groups

Reporting group title	Conventional strategy
Reporting group description:	
The dosage of loop diuretics was according to the presence of symptoms and signs of systemic congestion and according to current recommendations. To keep the scheduled starting dose for at least the first 24 hours of admission was advised. Maintaining or later revision was made based on clinical and/or laboratory criteria, recommending the assessment of renal function and plasma electrolytes (sodium and potassium) during the first 24 hours.	
Reporting group title	CA125-guided strategy
Reporting group description:	
Patients with CA125 ≤35 U/ml: In this subgroup of patients an initial dose of intravenous furosemide ≤80 mg/day was recommend, regardless of previous dose of loop diuretics they were receiving. To keep the starting dose for the first 24 hours was advised. The removal of thiazides or chlorthalidone was also recommended. Patients with CA125 >35 U/ml: In these patients an initial dose of intravenous furosemide >120 mg/day or 2.5 times the oral dose of furosemide that the patient was taking was recommended. In cases with striking elevation of CA125 (>100 U/ml) and/or concomitant unequivocal clinical signs of systemic congestion, doses >160 mg/day was recommended.	

Primary: Change in renal function (GFR)

End point title	Change in renal function (GFR)
End point description:	
Glomerular filtration rate (GFR) estimated by Modification of Diet in Renal Disease (MDRD)	
End point type	Primary
End point timeframe:	
24 hours, 72 hours and 30 days	

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: mL/min/1.73m2	81	79		

Statistical analyses

Statistical analysis title	Linear mixed model regression analysis
Comparison groups	CA125-guided strategy v Conventional strategy
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 5
Method	Mixed models analysis
Parameter estimate	Least square means
Point estimate	5

Confidence interval	
level	95 %
sides	2-sided
lower limit	5
upper limit	95
Variability estimate	Standard error of the mean

Secondary: Improvement in signs and symptoms of heart failure (NYHA)

End point title	Improvement in signs and symptoms of heart failure (NYHA)
End point description:	
Evaluation of dyspnea (changes in the functional class of the New York Heart Association -NYHA)	
End point type	Secondary
End point timeframe:	
24 hours, 72 hours and 30 days	

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Number	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in signs and symptoms of heart failure (VAS)

End point title	Improvement in signs and symptoms of heart failure (VAS)
End point description:	
Evaluation of signs of systemic congestion, and patient global assessment (by visual analogue scale -VAS-)	
End point type	Secondary
End point timeframe:	
72 hours and 30 days	

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Number	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in plasma levels of natriuretic peptide (NT-proBNP)

End point title	Changes in plasma levels of natriuretic peptide (NT-proBNP)

End point description:

End point type	Secondary

End point timeframe:

24 hours, 72 hours and 30 days

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: pg/ml	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in plasma levels of high sensitive troponin

End point title	Changes in plasma levels of high sensitive troponin

End point description:

End point type	Secondary

End point timeframe:

72 hours

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: ng/ml	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Time required to change intravenous diuretics to oral administration

End point title	Time required to change intravenous diuretics to oral administration

End point description:

End point type	Secondary

End point timeframe:

Through study completion (30-day follow-up)

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Hours	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Composite of all-cause mortality plus acute heart failure related rehospitalization

End point title	Composite of all-cause mortality plus acute heart failure related rehospitalization

End point description:

Number of events in each group during 30-day follow-up

End point type	Secondary

End point timeframe:

30 days

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: days				
number (not applicable)	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in renal function (creatinin)

End point title	Change in renal function (creatinin)
End point description: Serum levels of creatinine	
End point type	Secondary
End point timeframe: 24 h, 72 h and 30 days	

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: mg/dL	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in renal function (urea)

End point title	Change in renal function (urea)
End point description: Serum levels of urea	
End point type	Secondary
End point timeframe: 24 h, 72 h and 30 days	

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: mg/dL	81	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in renal function (cystatin C)

End point title	Change in renal function (cystatin C)
End point description: Serum levels of Cystatin C	
End point type	Secondary
End point timeframe: 24 h, 72 h and 30 days	

End point values	Conventional strategy	CA125-guided strategy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: mg/l	81	79		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the patient's participation in the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups	
Reporting group title	Experimental: CA125 guided strategy
Reporting group description:	
In this group loop diuretic (Furosemide) dosage was guided by Carbohydrate Antigen 125 (CA125) plasma levels	
Reporting group title	Conventional strategy
Reporting group description:	
Standard treatment strategy Therapy was based on established european guidelines	

Serious adverse events	Experimental: CA125 guided strategy	Conventional strategy	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 79 (18.99%)	21 / 81 (25.93%)	
number of deaths (all causes)	3	7	
number of deaths resulting from adverse events	1	2	
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Heart Faliure			
subjects affected / exposed	8 / 79 (10.13%)	11 / 81 (13.58%)	
occurrences causally related to treatment / all	0 / 8	0 / 12	
deaths causally related to treatment / all	0 / 2	0 / 3	
Acute myocardial infarction			
subjects affected / exposed	1 / 79 (1.27%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			

subjects affected / exposed	0 / 79 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastrointestinal disorders			
Biliary Colic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 79 (1.27%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 79 (2.53%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock			

subjects affected / exposed	0 / 79 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Experimental: CA125 guided strategy	Conventional strategy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 79 (5.06%)	1 / 81 (1.23%)	
Cardiac disorders			
Acute heart failure			
subjects affected / exposed	4 / 79 (5.06%)	1 / 81 (1.23%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2015	Protocol modification version 2.1 25 september 2014
24 September 2015	Protocol modification version 2.2 17 agost 2015

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported