



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 |
| Scientific contact | Marta Peiro, Instituto de Investigación Sanitaria INCLIVA, 0034 961973536, gestioncientifica@incliva.es |

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 \leq 35 U/ml: Initial dose of intravenous furosemide \leq 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 \leq 35 U/ml: In this subgroup of patients an initial dose of intravenous furosemide \leq 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/1.73m ² | 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 Failure | | | |
| 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