



Clinical trial results:

Effects of plasma exchange on the serum albumin functional capacity, circulatory dysfunction, renal and cerebral function in cirrhotic subjects with acute-on-chronic liver failure

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-021360-15 |
| Trial protocol | ES |
| Global end of trial date | 17 September 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 11 August 2019 |
| First version publication date | 11 August 2019 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | IG0905 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01201720 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Instituto Grifols, S.A. |
| Sponsor organisation address | Can Guasch 2, Parets del Valles, Barcelona, Spain, 08150 |
| Public contact | Mireia Torres, MSc, Instituto Grifols S.A., mireia.torres@grifols.com |
| Scientific contact | Mireia Torres, MSc, Instituto Grifols S.A., mireia.torres@grifols.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 | 24 May 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the effects of plasma exchange (PE) with albumin 5% as a replacement fluid on the albumin functional capacity and circulatory dysfunction in cirrhotic subjects with acute-on-chronic liver failure (ACLF).

Protection of trial subjects:

Standards for Good Clinical Practice were adhered to for all procedures in this clinical study. The investigators ensured that the clinical study was conducted in full conformance with appropriate local laws and regulations and the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 17 March 2011 |
| 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: 10 |
| Worldwide total number of subjects | 10 |
| EEA total number of subjects | 10 |

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) | 9 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Ten subjects with liver cirrhosis established by biopsy or clinical, laboratory, and ultrasound data and ACLF determined as an acute deterioration in liver function occurring in 2 to 4 weeks with jaundice and hepatic encephalopathy (HE) and/or renal insufficiency were enrolled from March 2011 to July 2013 in this single-center study.

Pre-assignment

Screening details:

Subjects with liver cirrhosis and ACLF admitted to the study center, who gave their written informed consent to participate, were included in the study. In the case of HE, written informed consent was given by a first-degree relative of the subject. Subjects underwent various clinical tests to check their suitability to participate in the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open-label study; no blinding techniques were applicable.

Arms

| Arm title | Enrolled Population |
|-----------|---------------------|
|-----------|---------------------|

Arm description:

All Subjects were included in the Enrolled population. The Enrolled population was defined as all subjects who met the inclusion criteria and performed at least one PE with albumin 5%. The Enrolled population was used for safety analysis.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Albutein (Human Albumin Grifols 5% solution for infusion) |
| Investigational medicinal product code | B05AA01 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The volume of each replacement was approximately that of the plasma volume of the subjects as calculated from body weight, height, and hematocrit (approximately 35 to 45 mL/kg, corresponding to a volume of 2500 to 3000 mL).

Plasma exchange (PE) was performed every 2 days over 11 days, for a total of 6 PEs. Additionally, fresh frozen plasma (FFP) was administered at the end of each plasma exchange session (~30% of total plasma exchanged).

| Number of subjects in period 1 | Enrolled Population |
|--------------------------------|---------------------|
| Started | 10 |
| Completed | 8 |
| Not completed | 2 |
| Hepatic transplant | 1 |
| Renal failure | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

A total of 10 subjects were included in the Enrolled population and treated with the study drug. The Enrolled population was defined as all subjects who met the inclusion criteria and performed at least one PE with albumin 5%.

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 10 | 10 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 9 | 9 | |
| From 65-84 years | 1 | 1 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.0 | | |
| standard deviation | ± 9.32 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 6 | 6 | |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | Enrolled Population |
| Reporting group description: All Subjects were included in the Enrolled population. The Enrolled population was defined as all subjects who met the inclusion criteria and performed at least one PE with albumin 5%. The Enrolled population was used for safety analysis. | |

Primary: Albumin Functional Capacity

| | |
|--|--|
| End point title | Albumin Functional Capacity ^[1] |
| End point description: Changes in albumin functional capacity within Day 1 (first PE) and last PE (whichever day this occurred) measured using 3 techniques: albumin binding capacity (ABiC), Electronic Paramagnetic Resonance (EPR), and albumin redox state. | |
| End point type | Primary |
| End point timeframe: Day 1 (first assessment) to Day 10 or 11 (last assessment) | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this study was not controlled, no statistical analysis can be drawn as a comparator. Only one study arm exists.

| End point values | Enrolled Population | | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: albumin functional capacity | | | | |
| least squares mean (standard error) | | | | |
| ABiC Concentration (mg/dL) Pre-PE | -3.7 (± 1.9) | | | |
| HMA Concentration (mg/mL) Pre-PE | -5.1 (± 1.5) | | | |
| HMA Concentration (mg/mL) PE +1hr | -5.4 (± 0.9) | | | |
| HMA Fraction (%) Pre-PE | -12.6 (± 3.7) | | | |
| HMA Fraction (%) PE +1hr | -10.4 (± 1.9) | | | |
| HMA Fraction (%) Post-PE | -8.5 (± 2.2) | | | |
| HNA-1 Concentration (mg/mL) Post-PE | 2.4 (± 1.4) | | | |
| HNA-1 Fraction (%) Pre-PE | 14.5 (± 3.5) | | | |
| HNA-1 Fraction (%) PE +1hr | 10.8 (± 2.2) | | | |
| HNA-1 Fraction (%) Post-PE | 6.9 (± 2.1) | | | |
| HSA Reduced Concentration (mg/mL) Pre-PE | -6.3 (± 1.7) | | | |
| HSA Reduced Concentration (mg/mL) PE +1hr | -6.5 (± 1.0) | | | |
| HSA Reduced Fraction (%) Pre-PE | -16.0 (± 4.3) | | | |
| HSA Reduced Fraction (%) PE +1hr | -12.3 (± 2.4) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Circulatory Dysfunction

End point title Circulatory Dysfunction^[2]

End point description:

Changes in circulatory dysfunction throughout the study.

End point type Primary

End point timeframe:

Day 1 (first assessment) to Day 11 (last assessment)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As this study was not controlled, no statistical analysis can be drawn as a comparator. Only one study arm exists.

| End point values | Enrolled Population | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: circulatory dysfunction | | | | |
| least squares mean (standard error) | | | | |
| Plasma renin activity (ng/mL*h) | 1.4 (± 1.5) | | | |
| Noradrenaline plasma concentration (pg/mL) | -313 (± 632.2) | | | |
| Diastolic blood pressure (mmHg) | -6.7 (± 1.8) | | | |
| Mean arterial pressure (mmHg) | -8.4 (± 3.0) | | | |
| Heart rate (bpm) | -17.4 (± 5.3) | | | |
| Cardiac index (L*-min ⁻¹ *m ⁻²) | -1.3 (± 0.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Dysfunction

End point title Renal Dysfunction

End point description:

Change in Renal dysfunction throughout the study.

End point type Secondary

End point timeframe:

Pre-PE, Day 1 (first assessment) to Month 1 (last assessment)

| End point values | Enrolled Population | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: mg/dL | | | | |
| least squares mean (standard error) | | | | |
| Creatinine (mg/dL) | 0.3 (± 0.3) | | | |
| BUN (mg/dL) | 16.1 (± 13.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebral Dysfunction

| | |
|------------------------|--|
| End point title | Cerebral Dysfunction |
| End point description: | Change in cerebral dysfunction measured by the grade of encephalopathy throughout the study. |
| End point type | Secondary |
| End point timeframe: | Pre-PE, Day 1 (first assessment) to Month 1 (last assessment) |

| End point values | Enrolled Population | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: hepatic encephalopathy grade | | | | |
| least squares mean (standard error) | 69.1 (± 22.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Liver Function

| | |
|------------------------|---|
| End point title | Liver Function |
| End point description: | Change in liver function throughout the study. |
| End point type | Secondary |
| End point timeframe: | Pre-PE, Day 1 (first assessment) to Month 1 (last assessment) for all parameters except Score prognostics (Day 1 to Day 10) |

| End point values | Enrolled Population | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: liver function | | | | |
| least squares mean (standard error) | | | | |
| ALT (IU/L) | -31.8 (± 15.8) | | | |
| GGT (IU/L) | -78.9 (± 30.8) | | | |
| ALP (IU/L) | -108 (± 35.8) | | | |
| Total bilirubin (mg/dL) | 7.5 (± 2.9) | | | |
| Conjugated bilirubin (mg/dL) | 14.1 (± 5.0) | | | |
| AST (IU/L) | -8.0 (± 39.4) | | | |
| Score prognostics (MELD) | 5.3 (± 1.1) | | | |
| Score prognostics (SOFA) | -0.3 (± 0.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Inflammation

| | |
|------------------------|---|
| End point title | Systemic Inflammation |
| End point description: | Change in systemic inflammation throughout the study. |
| End point type | Secondary |
| End point timeframe: | Pre-PE, Baseline (first assessment) to Day 11 (last assessment) for aldosterone. Pre-PE, Day 1 (first assessment) to Day 10 (last assessment) for vW:Ag and vW:RCo |

| End point values | Enrolled Population | | | |
|-------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: Concentration | | | | |
| least squares mean (standard error) | | | | |
| Aldosterone (mg/dL) | 16.3 (± 6.5) | | | |
| vW:Ag (UL/dL) | 38.1 (± 8.9) | | | |
| vW:RCo (UL/dL) | 152.8 (± 74.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of signature of the ICF to Day 11.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Enrolled population |
|-----------------------|---------------------|

Reporting group description:

The Enrolled population was defined as all subjects who met the inclusion criteria and performed at least one PE with albumin 5%. The Enrolled population was used for safety analysis.

| Serious adverse events | Enrolled population | | |
|--|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 10 (80.00%) | | |
| number of deaths (all causes) | 4 | | |
| number of deaths resulting from adverse events | 4 | | |
| Injury, poisoning and procedural complications | | | |
| Wound evisceration | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Organ failure | Additional description: (multi-organ failure) | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Gastrointestinal disorders | | | |
| Melaena | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia cytomegaloviral | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Enrolled population | | |
|---|---------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 10 (100.00%) | | |
| Injury, poisoning and procedural complications | | | |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |

| | | | |
|---|--|--|--|
| Atrial fibrillation subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 2 | | |
| Nervous system disorders Hepatic encephalopathy subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Hypofibrinogenaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 9 / 10 (90.00%) 15 3 / 10 (30.00%) 5 3 / 10 (30.00%) 5 | | |
| General disorders and administration site conditions Catheter site pruritus subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Injection site haemorrhage subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 2 / 10 (20.00%) 4 1 / 10 (10.00%) 1 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Ascites | 1 / 10 (10.00%) 1 | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Gastrointestinal haemorrhage subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Mouth haemorrhage subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | | |
| Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Psychiatric disorders Delirium subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Infections and infestations Device related sepsis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 2 | | |
| Peritonitis bacterial subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Staphylococcal bacteraemia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 3 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 10 (50.00%) | | |
| occurrences (all) | 6 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 2 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 16 February 2012 | <p>The aim of the amendment was to modify the number of subjects to be included in the study. The initial number of subjects planned was 10 in total, without taking into account the number of PE received.</p> <p>At the beginning of the study, there were some subject early discontinuations which corresponded to several causes, including severity of underlying subject pathologies, inclusion/exclusion criteria violations, possibility of study withdrawal due to liver transplantation, etc.</p> <p>Therefore, it was considered appropriate to specify that it was necessary to obtain 10 subjects who had completed the 6 PE planned in the protocol.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported