



Clinical trial results: Albumin To prevenT Infection in chronic liveR failurE (ATTIRE) Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-002300-24 |
| Trial protocol | GB |
| Global end of trial date | 11 December 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 09 May 2021 |
| First version publication date | 09 May 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | 6.0 |
|-----------------------|-----|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN14174793 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University College London (UCL) |
| Sponsor organisation address | Gower Street, London, United Kingdom, WC1E 6BT |
| Public contact | CCTU Enquiry Desk, University College London (UCL), CCTU-enquiries@ucl.ac.uk |
| Scientific contact | CCTU Enquiry Desk, University College London (UCL), CCTU-enquiries@ucl.ac.uk |

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 | 11 December 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 October 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 December 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a phase III randomised controlled trial to verify whether targeting a serum albumin level of >30g/l in patients hospitalised with acutely decompensated cirrhosis using repeated 20% HAS infusions will reduce incidence of infection, renal dysfunction and mortality for the treatment period (maximum 14 days or until discharge/assessed as medically fit for discharge prior to 14 days) compared to standard medical care. In AD patients, the frequent course of events is that infection precipitates organ dysfunction and this combination is the commonest cause of hospital mortality. Equally data are emerging to indicate that even in survivors, long term mortality is also substantially reduced i.e. this represents a "tipping point" in the clinical course of cirrhosis. Preventing infection and subsequent organ dysfunction would be expected to therefore improve short and long term mortality.

Protection of trial subjects:

The trial was conducted in compliance with the approved protocol, UCL CCTU Standard Operating Procedures (SOPs), the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites complied with the approved protocol, UCL CCTU SOPs, the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable) and other national and local applicable regulations. While HAS is routinely given to patients with liver disease and its safety is well established, provision for stopping in the rare event of severe reactions (such as shock) was made in the trial protocol. In case of hypersensitivity or allergic reactions, in some cases severe anaphylaxis, it was noted in the protocol that epinephrine would be available immediately to treat any acute hypersensitivity reaction. Albumin was prescribed to participants on the 20% HAS arm, as per the suggested protocol, which could be amended by the prescribing clinician with the clinical reasons for this recorded in the trial documentation. If the prescribing clinician or the ward staff administering the 20% HAS had safety concerns with the continuation of treatment, infusions could be halted until/if it was deemed safe to resume treatment. Where 20% HAS was halted due to safety concerns this was not considered to be a protocol deviation. Three reasons was provided in the trial protocol for albumen being given in the standard of care arm: Large Volume Paracentesis (LVP), Spontaneous Bacterial Peritonitis (SBP), Hepatorenal Syndrome (HRS).

Background therapy:

In the original protocol re-randomization was permitted >30 days after completing trial treatment, accounting for albumin's 21 day half-life. However, as ATTIRE was not blinded, knowledge of original treatment could influence the decision to participate again and only survivors could do so, introducing potential bias. Therefore, primary randomisations are presented here, and analyses that included re-randomizations are reported in the Supplementary Appendix.

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 30 April 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 777 |
| Worldwide total number of subjects | 777 |
| EEA total number of subjects | 0 |

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) | 667 |
| From 65 to 84 years | 108 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

The eligibility of the patient were reviewed on the observations and bloods taken for screening. Blood tests required for screening and randomisation were part of standard of care when an AD patient is admitted to hospital (FBC, LFTs, U&Es, CRP and INR).

Pre-assignment

Screening details:

This trial used a two stage consent process. Written informed consent to be randomised into the RCT were obtained, after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures were performed or any samples are taken for the trial.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Albumin |

Arm description:

20% Human Albumin Solution (HAS)

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | 20% Human Albumin Solution (HAS) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

20% HAS prescribed daily according to the patient's serum albumin concentration that day (or closest previous measurement). A suggested dosing protocol was:

- If serum albumin 30-34g/l, give 100mls 20% HAS
- If serum albumin 26-29g/l, give 200mls 20% HAS
- If serum albumin 20-25g/l, give 300mls 20% HAS
- If serum albumin <20g/l, give 400mls 20% HAS

This is based on clinical experience and also the reported regimen used in the ALBIOS study (that examines the repeated use of albumin infusions in patients with sepsis on intensive care). HAS may be prescribed using another regimen as long as the aim is to raise albumin level to >30g/l, but this must be fully recorded in the Case Reports Forms (CRF) and medical notes. Equally differing regimens may be used to cover paracentesis procedures or treat HRS and SBP as per local trial site and national guidelines but HAS must be prescribed and given if serum albumin <35g/l, unless there are any safety concerns.

| | |
|------------------|---------------|
| Arm title | Standard Care |
|------------------|---------------|

Arm description:

Hospitalized decompensated cirrhosis patients with serum albumin <30g/L at enrollment received standard care.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Albumin | Standard Care |
|--------------------------------|---------|---------------|
| Started | 380 | 397 |
| Completed | 380 | 397 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Endpoints |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Albumin |

Arm description:

20% Human Albumin Solution (HAS)

| | |
|--|----------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | 20% Human Albumin Solution (HAS) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

20% HAS prescribed daily according to the patient's serum albumin concentration that day (or closest previous measurement). A suggested dosing protocol was:

- If serum albumin 30-34g/l, give 100mls 20% HAS
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- If serum albumin 20-25g/l, give 300mls 20% HAS
- If serum albumin <20g/l, give 400mls 20% HAS

This is based on clinical experience and also the reported regimen used in the ALBIOS study (that examines the repeated use of albumin infusions in patients with sepsis on intensive care). HAS may be prescribed using another regimen as long as the aim is to raise albumin level to >30g/l, but this must be fully recorded in the Case Reports Forms (CRF) and medical notes. Equally differing regimens may be used to cover paracentesis procedures or treat HRS and SBP as per local trial site and national guidelines but HAS must be prescribed and given if serum albumin <35g/l, unless there are any safety concerns.

| | |
|------------------|---------------|
| Arm title | Standard Care |
|------------------|---------------|

Arm description:

Hospitalized decompensated cirrhosis patients with serum albumin <30g/L at enrollment will receive standard care.

| | |
|---|---------------|
| Arm type | Standard Care |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Albumin | Standard Care |
|---------------------------------------|---------|---------------|
| Started | 380 | 397 |
| Completed | 380 | 397 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Albumin |
| Reporting group description: 20% Human Albumin Solution (HAS) | |
| Reporting group title | Standard Care |
| Reporting group description: Hospitalized decompensated cirrhosis patients with serum albumin <30g/L at enrollment received standard care. | |

| Reporting group values | Albumin | Standard Care | Total |
|------------------------------------|---------|---------------|-------|
| Number of subjects | 380 | 397 | 777 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|--------|--------|-----|
| Age continuous | | | |
| Age Mean (s.d.) 1 Missing observation with no data for age | | | |
| Units: years | | | |
| arithmetic mean | 53.8 | 53.8 | |
| standard deviation | ± 10.6 | ± 10.7 | - |
| Gender categorical | | | |
| Sex | | | |
| Units: Subjects | | | |
| Female | 123 | 104 | 227 |
| Male | 257 | 293 | 550 |
| Admitted to ward – no. | | | |
| Units: Subjects | | | |
| Yes | 370 | 384 | 754 |
| No | 10 | 13 | 23 |
| Admitted to Intensive Care Unit – no. | | | |
| Units: Subjects | | | |
| Yes | 8 | 10 | 18 |
| No | 372 | 387 | 759 |
| Alcohol | | | |
| Aetiology of cirrhosis - no. | | | |
| Units: Subjects | | | |
| Yes | 347 | 350 | 697 |
| No | 33 | 47 | 80 |
| Hepatitis C | | | |
| Aetiology of cirrhosis† - no. | | | |
| Units: Subjects | | | |
| Yes | 24 | 35 | 59 |
| No | 356 | 362 | 718 |
| NAFLD | | | |
| Aetiology of cirrhosis - no. | | | |
| Units: Subjects | | | |
| Yes | 26 | 29 | 55 |

| | | | |
|--|-----|-----|-----|
| No | 354 | 368 | 722 |
| Encephalopathy | | | |
| Reason for decompensation admission† - no. | | | |
| Units: Subjects | | | |
| Yes | 80 | 69 | 149 |
| No | 300 | 328 | 628 |
| Suspected variceal Bleed | | | |
| Reason for decompensation admission† - no. | | | |
| Units: Subjects | | | |
| Yes | 52 | 63 | 115 |
| No | 328 | 334 | 662 |
| New onset or worsening ascites | | | |
| Reason for decompensation admission† - no. | | | |
| Units: Subjects | | | |
| Yes | 236 | 281 | 517 |
| No | 144 | 116 | 260 |
| Diagnosed with infection‡ | | | |
| Infection - no. | | | |
| Units: Subjects | | | |
| Yes | 98 | 113 | 211 |
| No | 282 | 284 | 566 |
| Prescribed antibiotics | | | |
| Infection - no. | | | |
| Units: Subjects | | | |
| Yes | 195 | 199 | 394 |
| No | 185 | 198 | 383 |
| Serum albumin level – no. | | | |
| Units: Subjects | | | |
| <20 g/L | 61 | 60 | 121 |
| 20-25 g/L | 207 | 224 | 431 |
| 26-29 g/L | 112 | 113 | 225 |
| Cerebral: >Grade III Hepatic Encephalopathy | | | |
| Baseline Organ Dysfunction | | | |
| Units: Subjects | | | |
| Yes | 10 | 8 | 18 |
| No | 370 | 389 | 759 |
| Circulatory: Mean Arterial Pressure <60 mmHg | | | |
| Baseline Organ Dysfunction | | | |
| Units: Subjects | | | |
| Yes | 10 | 6 | 16 |
| No | 370 | 391 | 761 |
| Respiratory: SpO2 / FiO2 | | | |
| Units: Subjects | | | |
| 0 (>357) | 345 | 367 | 712 |
| 1 (>214 ≤357) | 29 | 23 | 52 |
| 2 (≤214 or Mechanical Ventilation) | 5 | 5 | 10 |
| Not recorded | 1 | 2 | 3 |
| Renal: Creatinine >1.5mg/dl | | | |
| Units: Subjects | | | |
| Yes | 36 | 46 | 82 |

| | | | |
|----|-----|-----|-----|
| No | 344 | 351 | 695 |
|----|-----|-----|-----|

| | | | |
|---|---------------|--------------|---|
| Physiological variable – median (IQR) | | | |
| Units: mg/dl | | | |
| median | 0 | 0 | |
| inter-quartile range (Q1-Q3) | 0 to 0 | 0 to 0 | - |
| Bilirubin (mg/dl) | | | |
| Units: mg/dl | | | |
| median | 5.70 | 5.56 | |
| inter-quartile range (Q1-Q3) | 2.75 to 10.47 | 2.63 to 9.68 | - |
| INR | | | |
| International Normalised Ratio | | | |
| Units: mg/dl | | | |
| median | 1.6 | 1.6 | |
| inter-quartile range (Q1-Q3) | 1.4 to 1.9 | 1.4 to 1.9 | - |
| MELD Score | | | |
| Model for end stage liver disease https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/ range <9 to >40, higher values indicate higher 3-month mortality. | | | |
| Units: MELD score | | | |
| median | 19.6 | 19.5 | |
| inter-quartile range (Q1-Q3) | 15.4 to 22.9 | 15.4 to 23.4 | - |
| Creatinine (mg/dl) | | | |
| Units: mg/dl | | | |
| median | 0.75 | 0.78 | |
| inter-quartile range (Q1-Q3) | 0.58 to 0.97 | 0.64 to 1.06 | - |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | Albumin |
| Reporting group description: 20% Human Albumin Solution (HAS) | |
| Reporting group title | Standard Care |
| Reporting group description: Hospitalized decompensated cirrhosis patients with serum albumin <30g/L at enrollment received standard care. | |
| Reporting group title | Albumin |
| Reporting group description: 20% Human Albumin Solution (HAS) | |
| Reporting group title | Standard Care |
| Reporting group description: Hospitalized decompensated cirrhosis patients with serum albumin <30g/L at enrollment will receive standard care. | |

Primary: Primary outcome

| | |
|---|-----------------|
| End point title | Primary outcome |
| End point description: A composite endpoint comprising incidence of infection, renal dysfunction and mortality occurring between treatment day 3 and day 15 (end of treatment period), or date of discharge/being assessed as medically fit for discharge if prior to day 15. The definition of the three components of the endpoint are: 1. New Infection: indicated by clinician diagnosis and clinical evidence provided on completed infection CRFs. 2. Renal Dysfunction: indicated by a serum creatinine increase of $\geq 50\%$ as compared to serum creatinine at randomisation OR the patient initiated on renal replacement support (either haemodialysis or haemofiltration) OR a rise in serum creatinine of $\geq 26.5 \mu\text{mol/L}$ within 48hours. If patients are on renal replacement support at baseline, they will not be able to reach this outcome. 3. Death | |
| End point type | Primary |
| End point timeframe: A composite endpoint comprising incidence of infection, renal dysfunction and mortality occurring between treatment day 3 and day 15 (end of treatment period), or date of discharge/being assessed as medically fit for discharge if prior to day 15. | |

| End point values | Albumin | Standard Care | | |
|--------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 380 | 397 | | |
| Units: number (%) | | | | |
| Primary outcome – no. | 113 | 120 | | |
| Composite endpoint components | 0 | 0 | | |
| Incidence of new Infection | 79 | 71 | | |
| Incidence of renal dysfunction | 40 | 57 | | |
| Incidence of death | 30 | 33 | | |
| Mortality at 28 days | 53 | 62 | | |
| Mortality at 3 months | 92 | 93 | | |

| | | | | |
|---------------------------------------|-----|-----|--|--|
| Mortality at 6 months | 132 | 119 | | |
| Total Albumin infused per patient (g) | 200 | 20 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Revised.Supplementary Appendix.24.11.20.pdf/Revised. |
|-----------------------------------|--|

Statistical analyses

| | |
|-----------------------------------|-----------------|
| Statistical analysis title | Primary outcome |
|-----------------------------------|-----------------|

Statistical analysis description:

For the primary outcome, we fitted a mixed-effects logistic regression model, with binary treatment indicator and stratification variables included as fixed effects, and random intercepts for sites. We also performed a time to event analysis, with patients censored at the earliest of: hospital discharge, day deemed fit for discharge, or study day 15.

| | |
|---|----------------------------|
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.87 ^[2] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.33 |

Notes:

[1] - ATTIRE was a superiority trial, the primary purpose of which was to demonstrate that repeated 20% HAS infusions, according to the ATTIRE protocol, reduces the incidence of new infection, renal dysfunction, and death on days 3 to 15 of the trial, compared to standard care.

[2] - All applicable statistical tests were 2-sided and will be performed using a 5% significance level, unless otherwise specified. All confidence intervals presented were 95% and two-sided.

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Composite endpoint components‡: |
|-----------------------------------|---------------------------------|

Statistical analysis description:

Incidence of new Infection

| | |
|---|-------------------------|
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.75 |

| | |
|---|-------------------------------|
| Statistical analysis title | Composite endpoint components |
| Statistical analysis description: | |
| Incidence of renal dysfunction | |
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 1.11 |

| | |
|---|-------------------------------|
| Statistical analysis title | Composite endpoint components |
| Statistical analysis description: | |
| Incidence of death | |
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.59 |

| | |
|---|-------------------------|
| Statistical analysis title | Mortality at 28 days |
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 1.3 |

| | |
|---|-------------------------|
| Statistical analysis title | Mortality at 3 months |
| Comparison groups | Standard Care v Albumin |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.48 |

| | |
|---|-------------------------|
| Statistical analysis title | Mortality at 6 months |
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.73 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Total Albumin infused per patient (g) |
| Comparison groups | Albumin v Standard Care |
| Number of subjects included in analysis | 777 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 142.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 127 |
| upper limit | 158.2 |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Investigators would notify UCL CCTU of any SAEs occurring from the time of enrolment until the last protocol treatment administration. SARs and SUSARs notified to UCL CCTU until trial closure.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Albumin |
|-----------------------|---------|

Reporting group description:

20% Human Albumin Solution (HAS)

| | |
|-----------------------|---------------|
| Reporting group title | Standard Care |
|-----------------------|---------------|

Reporting group description:

Hospitalized decompensated cirrhosis patients with serum albumin <30g/L at enrollment will receive standard care.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Adverse events were not collected by the investigators (only Serious Adverse Events).

| Serious adverse events | Albumin | Standard Care | |
|--|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 87 / 380 (22.89%) | 66 / 397 (16.62%) | |
| number of deaths (all causes) | 42 | 48 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 4 / 380 (1.05%) | 1 / 397 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 1 / 380 (0.26%) | 1 / 397 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 23 / 380 (6.05%) | 31 / 397 (7.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|---|------------------|--|
| Gastrointestinal disorders Esophageal varices hemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 5 / 380 (1.32%) | 6 / 397 (1.51%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Gastric hemorrhage subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 5 / 380 (1.32%) | 4 / 397 (1.01%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Any mention of GI bleeding | Additional description: Serious Adverse Events mentioning pulmonary edema or GI bleeding*** *** SAEs were individually labelled with a primary event but could have a mention of other contributing events | | |
| subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 11 / 380 (2.89%) | 13 / 397 (3.27%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders Adult respiratory distress syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 0 / 380 (0.00%) | 2 / 397 (0.50%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Hypoxia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 1 / 380 (0.26%) | 1 / 397 (0.25%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 1 / 380 (0.26%) | 1 / 397 (0.25%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Pulmonary edema subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | | | |
| | 15 / 380 (3.95%) | 4 / 397 (1.01%) | |
| | 0 / 0 | 0 / 0 | |
| | 0 / 0 | 0 / 0 | |
| Any mention of pulmonary edema or fluid overload | Additional description: Serious Adverse Events mentioning pulmonary edema or GI bleeding*** *** SAEs were individually labelled with a primary event but could have a mention of other contributing events | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 23 / 380 (6.05%) | 8 / 397 (2.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 380 (0.53%) | 0 / 397 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infections and infestations - Other: SBP | | | |
| subjects affected / exposed | 0 / 380 (0.00%) | 5 / 397 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 15 / 380 (3.95%) | 8 / 397 (2.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 4 / 380 (1.05%) | 3 / 397 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Albumin | Standard Care | |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 380 (0.00%) | 0 / 397 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 12 February 2015 | Protocol update to v2.0 - first version of the protocol that was approved for use. |
| 17 July 2015 | Protocol update to v3.0 - allowed for co-enrolment in CI approved CTIMP; Clarification of Standard guidelines for administration of HAS ; Clarification of dosing requirements; Change to reporting of SAEs for Stage 1 (only reporting up to end of treatment). |
| 26 August 2015 | Protocol update to v4.0 - Change was made in response to the non-acceptance from the MHRA; Change of SAR and SUSAR reporting until trial closure instead of 30 days post last protocol treatment. |
| 14 June 2016 | Protocol update to v5.0 - Clarified the outcomes for the RCT; Allow blood, urine and stool samples to be collected from patients who provide additional consent. |
| 15 January 2018 | Protocol update to v6.0 - Change in definition of primary outcome; Incidence of extra-Hepatic organ dysfunctions added as secondary outcome; Removal and clarification of a some of the secondary and exploratory outcomes; Highlighting throughout that IMP administration can be halted if there are safety concerns by members of trial or ward staff; Change in format of glossary and introduction section. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported