



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
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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
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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
- If serum albumin 26-29g/l, give 200mls 20% HAS
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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
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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
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Physiological variable – median (IQR) Units: mg/dl median inter-quartile range (Q1-Q3)	0 0 to 0	0 0 to 0	-
Bilirubin (mg/dl) Units: mg/dl median inter-quartile range (Q1-Q3)	5.70 2.75 to 10.47	5.56 2.63 to 9.68	-
INR			
International Normalised Ratio			
Units: mg/dl median inter-quartile range (Q1-Q3)	1.6 1.4 to 1.9	1.6 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 inter-quartile range (Q1-Q3)	19.6 15.4 to 22.9	19.5 15.4 to 23.4	-
Creatinine (mg/dl) Units: mg/dl median inter-quartile range (Q1-Q3)	0.75 0.58 to 0.97	0.78 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.
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Statistical analyses

Statistical analysis title	Primary outcome
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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‡:
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Albumin
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Reporting group description:

20% Human Albumin Solution (HAS)

Reporting group title	Standard Care
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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