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
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	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) BUN (mg/dL)	0.3 (± 0.3) 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	1 / 10 (10.00%)		
occurrences (all)	2		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 10 (90.00%)		
occurrences (all)	15		
Hypofibrinogenaemia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
Thrombocytopenia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Catheter site pruritus			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Injection site haemorrhage			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Ascites			

subjects affected / exposed occurrences (all) Gastrointestinal haemorrhage subjects affected / exposed occurrences (all) Mouth haemorrhage subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 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) Peritonitis bacterial subjects affected / exposed occurrences (all) Staphylococcal bacteraemia subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 2 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 2 / 10 (20.00%) 3		
Metabolism and nutrition disorders			

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2012	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. 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. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported