Clinical trial results:
PROSPECTIVE, RANDOMIZED, CONTROLLED, DOUBLE-BLIND, MULTI-CENTRIC, INTERNATIONAL, STUDY ON THE EFFICACY AND SAFETY OF AN EARLY TARGET CONTROLLED PLASMA VOLUME REPLACEMENT THERAPY WITH A BALANCED GELATIN SOLUTION VS A BALANCED ELECTROLYTE SOLUTION IN PATIENTS WITH SEVERE SEPSIS / SEPTIC SHOCK

Summary

EudraCT number	2015-000057-20
Trial protocol	HU CZ AT DE ES
Global end of trial date	08 December 2021

Results information

Result version number	v1 (current)
This version publication date	28 August 2025
First version publication date	28 August 2025

Trial information

Trial identification

Sponsor protocol code	HC-G-H-1209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02715466
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	B. Braun Melsungen AG, Division Hospital Care
Sponsor organisation address	Carl-Braun-Straße 1, Melsungen, Germany, 34212
Public contact	Medical Scientific Affairs Hospital Care / Clinical Development, B. Braun Melsungen AG, studies@bbraun.com
Scientific contact	Medical Scientific Affairs Hospital Care / Clinical Development, B. Braun Melsungen AG, studies@bbraun.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	03 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2021
Global end of trial reached?	Yes
Global end of trial date	08 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Investigate the efficacy of early goal directed fluid management of a combination of a gelatin and crystalloid regime in comparison to a pure crystalloid regime in achieving haemodynamic stability (HDS) in patients with severe sepsis / septic shock.

Protection of trial subjects:

An informed consent, written in accordance with the origins of the Declaration of Helsinki and the applicable laws of the countries has been obtained from all patients or their legal representatives, authorized persons or relatives, depending on local regulations. In the applicable emergency setting the procedure of deferred consent was used, provided that all legal requirements have been met. Where required according to local regulations a confirmation of an independent physician not involved in the study conduct was obtained, before any study related activity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 120
Worldwide total number of subjects	167
EEA total number of subjects	167

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)	63
From 65 to 84 years	100
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

First patient in: 11APR2016
Last patient out: 21JUN2021
Male and female patients aged ≥ 18 years, with body weight ≤ 140 kg, diagnosed with severe sepsis / septic shock at ICU admission able to be randomized to study treatment within 90 minutes after ICU admission OR during ICU stay and being able to be enrolled within 90 min after diagnosis

Pre-assignment

Screening details:

174 patients were screened according to inclusion and exclusion criteria. Seven of these patients were not eligible. The remaining 167 patients were randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Patients were randomized into either treatment group (Gelatin or Crystalloid groups) in a 1:1 ratio, stratified by site and RBC pre-treatment 24 h prior to randomization. All randomization lists were generated by a statistician who was not involved in the study data analysis. The first randomization list was generated prior to study initiation.
Treatment assignments comprised of consecutive blocks with the order of assignments chosen at random.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test group

Arm description:

Alternating infusion of blinded gelatin solution (Gelaspan) and open-label electrolyte solution Sterofundin ISO in a 1:1 ratio.

Arm type	Experimental
Investigational medicinal product name	Gelaspan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

The maximum daily dose of blinded IMP was 30 mL/kg/day. In addition, open-label Sterofundin ISO was applied in a ratio of 1:1.
Treatment with IMP was guided by a dedicated volume algorithm assesing fluid responsiveness by Mean Arterial Pressure (MAP) or Stroke Volume Index (SVI) after Passive Leg Raising (PLR) manoevre or fluid challenge. In case a patient was not fluid responsive anymore, administration of study fluids was stopped and achievement of HDS was determined.

Investigational medicinal product name	Sterofundin ISO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

The maximum daily dose of blinded IMP was 30 mL/kg/day. In addition, open-label Sterofundin ISO was applied in a ratio of 1:1.

Treatment with IMP was guided by a dedicated volume algorithm assesing fluid responsiveness by MAP or SVI after PLR manoevre or fluid challenge. In case a patient was not fluid responsive anymore, administration of study fluids was stopped and achievement of HDS was determined.

Arm title	Control Group

Arm description:

Alternating infusion of blinded electrolyte solution (Sterofundin ISO) and open-label Sterofundin ISO in a 1:1 ratio.

Arm type	Active comparator
Investigational medicinal product name	Sterofundin ISO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

The maximum daily dose of blinded IMP was 30 mL/kg/day. In addition, open-label Sterofundin ISO was applied in a ratio of 1:1.
Treatment with IMP was guided by a dedicated volume algorithm assesing fluid responsiveness by MAP or SVI after PLR manoevre or fluid challenge. In case a patient was not fluid responsive anymore, administration of study fluids was stopped and achievement of HDS was determined.

Number of subjects in period 1	Test group	Control Group
Started	83	84
Completed	70	61
Not completed	13	23
Consent withdrawn by subject	1	-
transfer to ICU of external hospital	-	1
Adverse event, non-fatal	12	18
emergency surgery due to initial disease	-	1
Protocol deviation	-	1
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Test group
Reporting group description:	
Alternating infusion of blinded gelatin solution (Gelaspan) and open-label electrolyte solution Sterofundin ISO in a 1:1 ratio.	
Reporting group title	Control Group
Reporting group description:	
Alternating infusion of blinded electrolyte solution (Sterofundin ISO) and open-label Sterofundin ISO in a 1:1 ratio.	

Reporting group values	Test group	Control Group	Total
Number of subjects	83	84	167
Age categorical Units: Subjects			
Adults (18-64 years)	29	34	63
From 65-84 years	53	47	100
85 years and over	1	3	4
Age continuous Units: years			
arithmetic mean	65.3	65.9	
standard deviation	± 14.20	± 14.14	-
Gender categorical Units: Subjects			
Female	21	20	41
Male	62	64	126
Type of patient Units: Subjects			
Trauma	8	5	13
Medical	23	22	45
Surgical	52	57	109
Diagnosis Units: Subjects			
Severe sepsis	20	18	38
Septic shock	63	66	129
RBC therapy 24h prior to randomization			
Red blood cell therapy within 24 hours prior randomization yes/no			
Units: Subjects			
yes	14	14	28
no	69	70	139
Total amount of fluids 24h prior randomization Units: millilitre(s)			
arithmetic mean	2309.6	2439.5	
standard deviation	± 1504.62	± 1802.82	-
SOFA total score			
Sequential Organ Failure Assessment total score			
Units: unknown			
arithmetic mean	8.3	8.1	

standard deviation	± 2.73	± 3.39	-

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All enrolled patients who were randomized to a treatment group in the study. Following the ITT principle, all patients were analyzed according to the treatment group to which they were randomized.

Reporting group values	ITT		
Number of subjects	167		
Age categorical Units: Subjects			
Adults (18-64 years)	63		
From 65-84 years	100		
85 years and over	4		
Age continuous Units: years			
arithmetic mean	65.6		
standard deviation	± 14.13		
Gender categorical Units: Subjects			
Female	41		
Male	126		
Type of patient Units: Subjects			
Trauma	13		
Medical	45		
Surgical	109		
Diagnosis Units: Subjects			
Severe sepsis	38		
Septic shock	129		
RBC therapy 24h prior to randomization			
Red blood cell therapy within 24 hours prior randomization yes/no			
Units: Subjects			
yes	28		
no	139		
Total amount of fluids 24h prior randomization Units: millilitre(s)			
arithmetic mean	2374.1		
standard deviation	± 1655.26		
SOFA total score			
Sequential Organ Failure Assessment total score			
Units: unknown			
arithmetic mean	8.2		
standard deviation	± 3.07		

End points

End points reporting groups

Reporting group title	Test group
Reporting group description:	
Alternating infusion of blinded gelatin solution (Gelaspan) and open-label electrolyte solution Sterofundin ISO in a 1:1 ratio.	
Reporting group title	Control Group
Reporting group description:	
Alternating infusion of blinded electrolyte solution (Sterofundin ISO) and open-label Sterofundin ISO in a 1:1 ratio.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled patients who were randomized to a treatment group in the study. Following the ITT principle, all patients were analyzed according to the treatment group to which they were randomized.	

Primary: Time to Hemodynamic Stability

End point title	Time to Hemodynamic Stability
End point description:	
The primary efficacy endpoint, defined as time from first administration of IMP to first achievement of confirmed HDS, was analyzed using data from patients who achieved HDS (i.e. for whom the HDS was confirmed at the 2nd and 4th hour after achievement of first HDS documented in the eCRF).	
End point type	Primary
End point timeframe:	
time from first administration of IMP to first achievement of confirmed HDS	

End point values	Test group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: hour				
arithmetic mean (standard deviation)	4.7 (± 5.88)	5.8 (± 6.46)		

Statistical analyses

Statistical analysis title	Difference in time to achieve first HDS /Wilcoxon
Statistical analysis description:	
To assess the difference in time to achieve first HDS using a gelatin solution combined with a balanced electrolyte solution (Gelatin group) versus a balanced electrolyte solution only (Crystalloid group)	
Comparison groups	Test group v Control Group
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.3716
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - H0: HDSGelatin = HDScrystalloid
H1: HDSGelatin ≠ HDScrystalloid

Statistical analysis title	Difference in time to achieve first HDS/v. Elteren

Statistical analysis description:

To assess the difference in time to achieve first HDS using a gelatin solution combined with a balanced electrolyte solution (Gelatin group) versus a balanced electrolyte solution only (Crystalloid group)

Comparison groups	Test group v Control Group
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.1995
Method	Van Elteren Test

Notes:

[2] - H0: HDSGelatin = HDScrystalloid
H1: HDSGelatin ≠ HDScrystalloid

Secondary: Duration of stay at ICU

End point title	Duration of stay at ICU

End point description:

End point type	Secondary

End point timeframe:

Length of stay in ICU (days): date of ICU discharge-date of ICU admission+1

End point values	Test group	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	53		
Units: day				
arithmetic mean (standard deviation)	11.9 (± 9.32)	12.8 (± 10.98)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Study treatment phase until ICU discharge or day 28 (whatever occured first), TEAS	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	Gelatin
Reporting group description: -	
Reporting group title	Crystalloid
Reporting group description: -	

Serious adverse events	Gelatin	Crystalloid	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 83 (36.14%)	34 / 84 (40.48%)	
number of deaths (all causes)	11	18	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 83 (2.41%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Haematoma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Explorative laparotomy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	7 / 83 (8.43%)	12 / 84 (14.29%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 3	0 / 3	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	2 / 83 (2.41%)	4 / 84 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial obstruction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Failure to anastomose			
subjects affected / exposed	3 / 83 (3.61%)	3 / 84 (3.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative delirium			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weaning failure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	0 / 83 (0.00%)	4 / 84 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 83 (0.00%)	3 / 84 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tachyarrhythmia			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 83 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord ischaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Antiphospholipid syndrome			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			

subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 83 (1.20%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatic infarction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 83 (2.41%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	6 / 83 (7.23%)	9 / 84 (10.71%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 4	
Abdominal abscess			
subjects affected / exposed	0 / 83 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 83 (2.41%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Gelatin	Crystalloid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 83 (66.27%)	54 / 84 (64.29%)	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	3 / 83 (3.61%)	4 / 84 (4.76%)	
occurrences (all)	3	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	9 / 83 (10.84%)	10 / 84 (11.90%)	
occurrences (all)	9	12	
Bradycardia			
subjects affected / exposed	4 / 83 (4.82%)	2 / 84 (2.38%)	
occurrences (all)	4	2	
Nervous system disorders			
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 83 (1.20%)	4 / 84 (4.76%)	
occurrences (all)	1	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 83 (18.07%)	15 / 84 (17.86%)	
occurrences (all)	15	16	
Thrombocytosis			
subjects affected / exposed	4 / 83 (4.82%)	10 / 84 (11.90%)	
occurrences (all)	4	10	
Thrombocytopenia			
subjects affected / exposed	6 / 83 (7.23%)	4 / 84 (4.76%)	
occurrences (all)	6	4	
Respiratory, thoracic and mediastinal disorders			

Pleural effusion			
subjects affected / exposed	7 / 83 (8.43%)	6 / 84 (7.14%)	
occurrences (all)	7	6	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	10 / 83 (12.05%)	6 / 84 (7.14%)	
occurrences (all)	12	6	
Psychiatric disorders			
Delirium			
subjects affected / exposed	3 / 83 (3.61%)	5 / 84 (5.95%)	
occurrences (all)	3	5	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 83 (2.41%)	4 / 84 (4.76%)	
occurrences (all)	2	4	
Septic shock			
subjects affected / exposed	4 / 83 (4.82%)	1 / 84 (1.19%)	
occurrences (all)	4	1	
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	9 / 83 (10.84%)	5 / 84 (5.95%)	
occurrences (all)	9	5	
Hypoalbuminaemia			
subjects affected / exposed	3 / 83 (3.61%)	4 / 84 (4.76%)	
occurrences (all)	3	4	
Hypokalaemia			
subjects affected / exposed	2 / 83 (2.41%)	5 / 84 (5.95%)	
occurrences (all)	2	5	
Hyperglycaemia			
subjects affected / exposed	2 / 83 (2.41%)	4 / 84 (4.76%)	
occurrences (all)	2	4	
Hypocalcaemia			
subjects affected / exposed	4 / 83 (4.82%)	1 / 84 (1.19%)	
occurrences (all)	4	1	
Iron deficiency			
subjects affected / exposed	0 / 83 (0.00%)	4 / 84 (4.76%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2015	Implementation of additional site-specific coagulation parameters (fibrinogen, AT, platelets absolute) – mandatory for site Innsbruck, optional for all other sites. Changes of exclusion criteria including: "moribund patients as defined by ASA ≥ class V" was added to further specify "death expected within 48 h"; 'hyperkalemia and hypercalcemia' were modified to exclude 'requiring medical treatment'; "severe cardiac insufficiency (defined as New York Heart Association (NYHA) ≥III)" was changed to "severe congestive cardiac failure"; "chronic renal failure with oliguria or anuria' was replaced with "renal failure with oliguria or anuria"; and definition of "burns" was added to further specify this exclusion criterion. Addition of explanation of patient number assignment to RBC stratum. Addition of secondary variables assessments to planned statistical analysis. Harmonization of one clinical criterion for RRT replacement (i.e., "urine output <0.3 mL/kg/h for > 24 h or absolute anuria for 12 h with current guidelines") Further specification of recording and reporting procedure for AE/SAEs, reporting timeframes and DSMB involvement in safety evaluations Added text from Gelaspan SmPC for drug interactions with respect to potential risks and potential AEs as well as information on precautionary measures. Added definition of drop-out patients and patient selection for analyses.
02 May 2017	Addition of new study sites and prolongation of total study duration due to slow recruitment Changes or re-wordings for clarity of inclusion criteria, including: deletion of upper BMI limit (i.e. changed from "BMI ≥ 18 kg/m2 and ≤ 35 kg/m2 " to BMI ≥ 18 kg/m2 "); rewording of inclusion criterion to specify that patients on antibiotic therapy started prior to randomization are only eligible; further specification of fluid responsiveness definition (changed from "increase of at least 10% in MAP after PLR' to "increase of > 10%"); change of exclusion criterion "administration of artificial colloids within the 24 h prior to randomization" to facilitate patient recruitment; further definition of exclusion criterion "patients receiving heparin / anticoagulation therapy"; clarification on lactate measurements, mechanical ventilation, and concomitant medication documentation. Change of APACHE II score documentation Rewording of the planned subgroup analyses "APACHE II score" and addition of subgroup analyses "Administration of gelatin solution prior randomization" Clarification on the informed consent procedure (specified time after randomization), RBC-pre-treatment 24 h prior randomization stratum and patient number Clarification on drug accountability procedure, destruction of dedicated infusion lines on-site, and definition of maintenance infusion rate Clarification on HDS criteria, ICU discharge criteria Further explanation and specification on the dedicated performance of the volume algorithm in both treatment phases Exclusion of "Administration of sodium bicarbonate" from the list of not permitted concomitant medication
20 July 2018	Addition of hypersensitivity to galactose-α-1,3-galactose (alpha-Gal) to exclusion criteria Update of precautionary measures referenced in the protocol to refer to allergen galactose-α-1,3-galactose Update of potential risks and potential AEs to include cross-references for hypersensitivity to galactose-α-1,3-galactose
10 January 2020	Prolongation of study recruitment period

16 July 2020	Deletion of the secondary variable SAPS II score in all concerned sections as all necessary information could be concluded from APACHE II and SOFA scores documentation. Deletion of upper age limit and lower BMI limit from the respective inclusion criteria to ease patient enrollment. Update of the fluid responsiveness definition in inclusion criteria to allow also a volume challenge (including altered age and weight criteria) instead of PLR for assessment to enroll patients where PLR was generally not feasible. Deletion of exclusion criterion "Patients whose medical condition does preclude the PLR maneuver" as volume challenge would be allowed for assessment. Addition of the exclusion criterion "Patients with confirmed acute SARS-CoV-2 (COVID-19) infection (as available from routine medical records/ patient chart)". Deletion of secondary variables including: 1) urine creatinine and Ccr as renal function could properly be assessed by the remaining renal function variables; 2) non-mandatory secondary variables ROTEM, perfusion index, pCO2 gap, ITBVI, EVLWI, CFI, and SVRI to ease data documentation; 3) Mg2+ and PO43- as these parameters were not routinely measured by participating sites. Clarification added that KDIGO score, arterial oxygen content, and DO2 are calculated. Update of the visit schedule for temperature, fluid output, and concomitant medications (antibiotics, contrast agents, coagulation therapy) to reflect clinical routine procedures at participating sites Re-wording of the conditions to use inotropes and/or vasopressors to further clarify the HDS criteria and update of the definition of burns.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 April 2021	The temporary halt is based on the result of the Data Safety Monitoring Board (DSMB) meeting which took place on 08-APR-2021. The DSMB recommended to stop recruitment due to elevated laboratory parameters, that need further clarification. The sponsor followed this DSMB recommendation.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The planned sample size of 608 patients for the final statistical analysis was not reached due to premature study termination.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34078421