Clinical trial results:
Pragmatic, prospective, randomised, controlled, double-blind, multicentre, multinational study on the safety and efficacy of a 6% Hydroxyethyl starch (HES) solution versus an electrolyte solution in trauma patients (TETHYS)

Summary

EudraCT number	2016-002176-27
Trial protocol	DE BE CZ NL ES FR
Global end of trial date	25 June 2022

Results information

Result version number	v1 (current)
This version publication date	25 August 2023
First version publication date	25 August 2023

Trial information

Trial identification

Sponsor protocol code	HC-G-H-1505

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03338218
WHO universal trial number (UTN)	-
Other trial identifiers	Fresenius Kabi: HE06-021-CP4

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi Deutschland GmbH
Sponsor organisation address	Else-Kröner-Straße 1, Bad Homburg v.d.H, Germany, 61352
Public contact	Medical Scientific Affairs Pharma and Nutrition, Fresenius Kabi Deutschland GmbH, Trial-Disclosure@Fresenius-Kabi.com
Scientific contact	Medical Scientific Affairs Pharma and Nutrition, Fresenius Kabi Deutschland GmbH, Trial-Disclosure@Fresenius-Kabi.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	16 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety of a 6% HES in a balanced electrolyte solution for infusion compared to a balanced electrolyte solution for infusion in trauma patients

Protection of trial subjects:

Subject protection was ensured by medical and ethical standards in accordance with Declaration of Helsinki, Good Clinical Practice and applicable national and local laws and regulation. The signed informed consent was obtained prior to inclusion in the study. The patients were informed in writing about their right to withdraw from the study at any time. Furthermore, a data safety monitoring board was established to protect the patients participating in the study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2019
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	Spain: 1
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	South Africa: 252
Worldwide total number of subjects	262
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)	235

From 65 to 84 years	24
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potential candidates for study participation were screened at admission to hospital. Before enrolling into screening informed consent had to be provided in writing. A patient was randomized only after eligibility was proven by checking the inclusion and exclusion criteria

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Volulyte

Arm description:

Started = Number of patients randomised for this arm

Arm type	Experimental
Investigational medicinal product name	Volulyte 6% solution for infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing of IP was individualised to the patient’s volume needs and at the discretion of the treating physician. It could have been guided, e.g., by a volume algorithm based on mean arterial pressure or dynamic circulatory variables, or by other haemodynamic parameters. The maximum daily dose of 30 ml/kg should not have been exceeded. If patients were still hypotensive during IP administration, they could also have received vasoactive/inotropic drugs, if regarded necessary due to the clinical condition. Since HES preparations may rarely cause allergic reactions, the first 10-20 ml of the solution should have been infused slowly. In case of an allergic reaction, the infusion had to be stopped immediately, and appropriate treatment given.

IP: Investigational product

Arm title	Ionolyte

Arm description:

Started = Number of patients randomised for this arm

Arm type	Active comparator
Investigational medicinal product name	Ionolyte solution for infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosing of IP was individualised to the patient’s volume needs and at the discretion of the treating physician. It could have been guided, e.g., by a volume algorithm based on mean arterial pressure or dynamic circulatory variables, or by other haemodynamic parameters. The maximum daily dose of 30 ml/kg should not have been exceeded. If patients were still hypotensive during IP administration, they could also have received vasoactive/inotropic drugs, if regarded necessary due to the clinical condition.

Number of subjects in period 1[1]	Volulyte	Ionolyte
Started	120	118
Completed	100	97
Not completed	20	21
Adverse event, serious fatal	3	5
Consent withdrawn by subject	-	1
Other	-	2
Randomised but not treated with IP	4	5
Lost to follow-up	13	8

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period is the number of randomised patients, whereas under 'population of trial subjects' all patients enrolled (including screen failures) are mentioned.

Baseline characteristics

Reporting groups	
Reporting group title	Volulyte
Reporting group description:	
Started = Number of patients randomised for this arm	
Reporting group title	Ionolyte
Reporting group description:	
Started = Number of patients randomised for this arm	

Reporting group values	Volulyte	Ionolyte	Total
Number of subjects	120	118	238
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	37.8	37.4	
standard deviation	± 17.0	± 16.7	-
Gender categorical			
Units: Subjects			
Female	20	19	39
Male	100	99	199

Subject analysis sets	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who had at least one application of IP, independent of the administered amount	
Subject analysis set title	Full analysis set for the primary endpoint (FASpEP)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients from the SAF, who reached the post-traumatic period and were monitored at least once with respect to components of primary composite endpoint of 90-day mortality and 90-day renal failure, i.e., with respect to mortality or renal function (serum creatinine concentration or initiation of renal replacement therapy).	
Subject analysis set title	Full analysis set for efficacy analyses (FASEff)
Subject analysis set type	Full analysis

Subject analysis set description:

All patients from the SAF providing any efficacy data after IP start

Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients from the FASpEP, who did not have any major protocol deviations with regard to the primary endpoint

Reporting group values	Safety analysis set (SAF)	Full analysis set for the primary endpoint (FASpEP)	Full analysis set for efficacy analyses (FASEff)
Number of subjects	229	229	229
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	37.8	37.8	37.8
standard deviation	± 16.9	± 16.9	± 16.9
Gender categorical Units: Subjects			
Female	39	39	39
Male	190	190	190

Reporting group values	Per protocol set (PPS)		
Number of subjects	216		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	36.7		
standard deviation	± 16.2		

Gender categorical Units: Subjects			
Female	36		
Male	180		

End points

End points reporting groups

Reporting group title	Volulyte
Reporting group description:	
Started = Number of patients randomised for this arm	
Reporting group title	Ionolyte
Reporting group description:	
Started = Number of patients randomised for this arm	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who had at least one application of IP, independent of the administered amount	
Subject analysis set title	Full analysis set for the primary endpoint (FASpEP)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients from the SAF, who reached the post-traumatic period and were monitored at least once with respect to components of primary composite endpoint of 90-day mortality and 90-day renal failure, i.e., with respect to mortality or renal function (serum creatinine concentration or initiation of renal replacement therapy).	
Subject analysis set title	Full analysis set for efficacy analyses (FASEff)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients from the SAF providing any efficacy data after IP start	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients from the FASpEP, who did not have any major protocol deviations with regard to the primary endpoint	

Primary: Composite of 90-day mortality and 90-day renal failure

End point title	Composite of 90-day mortality and 90-day renal failure
End point description:	
The primary endpoint of this study was a composite of 90-day mortality and 90-day renal failure reflected by a biomarker increase and defined by AKIN stage ≥2, or RIFLE injury or failure stage, or need for RRT (including haemodialysis, peritoneal dialysis, haemofiltration, and renal transplantation) at any time during the first 3 months after surgery AKIN: Acute Kidney Injury Network RIFLE: Risk, Injury, Failure, Loss of kidney, and End-stage renal kidney disease (classification system for acute kidney injury) RRT: Renal replacement therapy	
End point type	Primary
End point timeframe:	
From IP treatment start (T1) to Day 90 (±14 days) after randomisation (T4)	

End point values	Volulyte	Ionolyte		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[1]	99[2]		
Units: cases	5	4		

Notes:

[1] - PPS, N missing=3

[2] - PPS, N missing=4

Statistical analyses

Statistical analysis title	Analysis of the Primary Endpoint

Statistical analysis description:

Primary hypothesis was that treatment with Volulyte is non-inferior to treatment with Ionolyte regarding the primary composite endpoint of 90-day mortality and 90-day renal failure considering a non-inferiority margin (NIM) defined as a risk difference of Δ = 15% (adjusted for dichotomised age and gender). The NIM on the odds ratio scale corresponds to the odds ratio between the risk of the control group plus non-inferiority margin on the risk difference scale & the risk of the control group.

Comparison groups	Volulyte v Ionolyte
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	4.18

Notes:

[3] - In the PPS, the odds ratio was 1.08 (95% CI= 0.28; 4.18) and the non-inferiority margin on the odds ratio scale was 4.87. Since the upper limit of the 95% CI (4.18) was lower than the non-inferiority margin on the odds ratio scale (4.87), non-inferiority of Volulyte versus Ionolyte was significantly demonstrated in the PPS.

Secondary: Cystatin C-based minimal estimated glomerular filtration rate during post-traumatic days 1 to 3

End point title	Cystatin C-based minimal estimated glomerular filtration rate during post-traumatic days 1 to 3

End point description:

The lowest cystatin C-based eGFR during post-traumatic days (PTD) 1 to 3 was calculated from the highest cystatin C level during PTDs 1 to 3.

End point type	Secondary

End point timeframe:

Post-traumatic days 1 to 3

End point values	Volulyte	Ionolyte		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105[4]	101[5]		
Units: ml/min/1.73 m2				
arithmetic mean (standard deviation)	-4.21 (± 17.664)	-2.17 (± 19.650)		

Notes:

[4] - SAF, N missing = 11

[5] - SAF, N missing = 12

Statistical analyses

Statistical analysis title	Analysis of Key Secondary Endpoint
Comparison groups	Volulyte v Ionolyte
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.3882
Method	ANCOVA
Parameter estimate	LS Mean
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.562
upper limit	2.561

Notes:

[6] - Model-adjusted change from baseline between the treatment groups. The ANCOVA model with treatment (Volulyte, Ionolyte) and baseline as covariate. Least squares (LS) mean value is the difference in LS means beween groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for adverse events (AEs) started at baseline (T0) and ended at Day 90 after randomisation (T4)

Adverse event reporting additional description:

Only treatment-emergent adverse events included

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Volulyte
Reporting group description: -	
Reporting group title	Ionolyte
Reporting group description: -	

Serious adverse events	Volulyte	Ionolyte	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 116 (10.34%)	14 / 113 (12.39%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Hospitalisation	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium tremens	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state	Additional description: Treatment-emergent		

subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gun shot wound	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin laceration	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Ischaemic cerebral infarction	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Seizure	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subarachnoid haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peptic ulcer haemorrhage	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis	Additional description: Treatment-emergent		
subjects affected / exposed	0 / 116 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural cellulitis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Treatment-emergent		

subjects affected / exposed	1 / 116 (0.86%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Wound sepsis	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: Treatment-emergent		
subjects affected / exposed	1 / 116 (0.86%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Volulyte	Ionolyte	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 116 (72.41%)	84 / 113 (74.34%)	
Investigations			
Blood creatine decreased	Additional description: Treatment-emergent		
subjects affected / exposed	6 / 116 (5.17%)	5 / 113 (4.42%)	
occurrences (all)	7	6	
C-reactive protein increased	Additional description: Treatment-emergent		
subjects affected / exposed	61 / 116 (52.59%)	54 / 113 (47.79%)	
occurrences (all)	79	67	
Cardiac disorders			
Tachycardia	Additional description: Treatment-emergent		
subjects affected / exposed	5 / 116 (4.31%)	6 / 113 (5.31%)	
occurrences (all)	5	6	
Blood and lymphatic system disorders			
Anaemia	Additional description: Treatment-emergent		
subjects affected / exposed	17 / 116 (14.66%)	17 / 113 (15.04%)	
occurrences (all)	21	21	
Thrombocytopenia	Additional description: Treatment-emergent		
subjects affected / exposed	4 / 116 (3.45%)	10 / 113 (8.85%)	
occurrences (all)	5	10	

General disorders and administration site conditions			
Pyrexia	Additional description: Treatment-emergent		
subjects affected / exposed	6 / 116 (5.17%)	5 / 113 (4.42%)	
occurrences (all)	7	5	
Respiratory, thoracic and mediastinal disorders			
Respiratory acidosis	Additional description: Treatment-emergent		
subjects affected / exposed	12 / 116 (10.34%)	13 / 113 (11.50%)	
occurrences (all)	13	16	
Respiratory alkalosis	Additional description: Treatment-emergent		
subjects affected / exposed	59 / 116 (50.86%)	46 / 113 (40.71%)	
occurrences (all)	106	81	
Metabolism and nutrition disorders			
Hypocalcaemia	Additional description: Treatment-emergent		
subjects affected / exposed	17 / 116 (14.66%)	15 / 113 (13.27%)	
occurrences (all)	20	16	
Hypokalaemia	Additional description: Treatment-emergent		
subjects affected / exposed	15 / 116 (12.93%)	7 / 113 (6.19%)	
occurrences (all)	17	8	
Hyponatraemia	Additional description: Treatment-emergent		
subjects affected / exposed	16 / 116 (13.79%)	16 / 113 (14.16%)	
occurrences (all)	21	18	
Metabolic acidosis	Additional description: Treatment-emergent		
subjects affected / exposed	40 / 116 (34.48%)	32 / 113 (28.32%)	
occurrences (all)	53	42	
Metabolic alkalosis	Additional description: Treatment-emergent		
subjects affected / exposed	21 / 116 (18.10%)	14 / 113 (12.39%)	
occurrences (all)	24	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2016	The main reasons for this amendment* were the following: - Adjustment of "duration per patient" - Clarification that (serious) adverse events/reactions are recorded and processed on T4 - Addition of discontinuation criteria related to the study site and to the patient - Explanation of actions in case of a breach against the data protection - Further definition of sample size estimation T4: Day 90 (±14 days) after randomisation (i.e., Day 90 Visit) * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to Germany, as representative information.
10 July 2017	The main reasons for this amendment* were the following: - Clarification of performance of pregnancy test - Correction of table on secondary variables compared to tabular overview and study schedule - Further details on statistical methods * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to Germany, as representative information.
27 February 2018	The main reasons for this amendment* were the following: - To reflect the referral procedure in relation to risk-benefit-assessment - Addition of subgroup analysis regarding 'Hemodynamics' - Clarification of T0 (baseline parameters can be assessed until IP treatment start) and harmonisation of T1 thereof - Clarification regarding the definition of the exclusion criterion 'Renal impairment' in related sections T0 (Baseline): Hospital/emergency room until start of IP administration T1: First 24 hours after IP treatment start * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to Germany, as representative information.
01 August 2019	The main reason for this amendment* was to reflect sponsor transfer from B. Braun to Fresenius Kabi. * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to Germany, as representative information.

07 November 2019	The main reasons for this amendment* was to adapt MAP-guided volume algorithm and inclusion criteria MAP: Mean arterial pressure * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to Germany, as representative information.
13 August 2021	The main reasons for this amendment* was to add explanatory text to address standard of care at the hospitals in South Africa * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to South Africa, as representative information.
27 January 2022	The main reasons for this amendment* was to allow treatment of a minimum of 109 patients per treatment group independent from the perioperative study HC-G-H-1504 (PHOENICS). Different sections were modified * Depending on the ethics committees' and national authorities' feedback and on timepoint of initial submission the number of amendments, the amendment dates, as well as the changes to the protocol may differ between the participating countries. The content and the date of this amendment refers to South Africa, as representative information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35655234