Clinical trial results:
Prospective randomised controlled open-label explorative multi-centre pilot trial of Volulyte®-supplemented versus Albumin-supplemented fluid resuscitation for major burns

Summary

EudraCT number	2011-005734-18
Trial protocol	GB
Global end of trial date	13 September 2013

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	VOLU-011-C P4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01689506
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi Deutschland GmbH
Sponsor organisation address	Else-Kroener-Str. 1, Bad Homburg, Germany, 61352
Public contact	Division Medical & Clinical Affairs Generics & Standard Solutions, Volume Therapy, Fresenius Kabi Deutschland GmbH, scientific-contact@fresenius-kabi.com
Scientific contact	Division Medical & Clinical Affairs Generics & Standard Solutions, Volume Therapy, Fresenius Kabi Deutschland GmbH, scientific-contact@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	19 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2013
Global end of trial reached?	Yes
Global end of trial date	13 September 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This explorative pilot trial compared 2 burn fluid resuscitation regimes (supplementation with 6% hydroxyethyl starch (HES) 130/0.4 in a balanced isotonic electrolyte solution, Volulyte 6%, versus supplementation with human serum albumin (HSA) 50g/L on outcome with particular regard to fluid balance at 24 hours after burn injury (primary variable).

Protection of trial subjects:

Written Informed Consent/Assent was received from all patients/relatives/ independent physicians prior to enrolment into the trial, as dictated by the Declaration of Helsinki. In the setting of major burns, a positive vote was required (in accordance with the local ethical guidelines) to permit enrolment of unconscious patients in an emergency situation, where assent was sought from the legal representative prior to enrolment. Surviving patients were informed of the trial as soon as possible after enrolment. A legal representative could be a personal or a nominated legal representative. A personal legal representative could be a relative (next-of-kin) or friend who gave assent representing the patient's presumed will. A nominated legal representative could be a doctor responsible for patient's treatment or nominated by the healthcare provider. Both could not be connected with the trial. The investigator was responsible for giving each patient/legal representative full and adequate verbal and written information about the objectives and procedures of the trial and the potential benefits, discomforts, and risks involved prior to inclusion in the trial.

An independent data monitoring committee (IDMC) with a purpose of a data safety monitoring board (DSMB) was implemented in this phase IV trial to ensure that there would be no unavoidable risk for harm for patients in any of the 2 treatment groups. As part of the trial, 2 physicians (both anaesthesiologists) with relevant training reviewed the data from the trial on a routine basis for safety assessments. The DSMB was restricted to individuals free of significant conflicts of interest. The DSMB met a total of 3 times during the conduct of the trial. At the final meeting the DSMB concluded that there were no safety concerns.

Background therapy: -

Evidence for comparator:

Although recent publications led to a reduction in the use of human albumin in burns resuscitation in the United Kingdom (UK), albumin was still used in some UK burns centres at the start of the trial. Therefore, a prevalent resuscitation therapy based on crystalloids (Parkland formula using Ringer's Lactate) and 5% human albumin was used a comparator.

Actual start date of recruitment	02 December 2012
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: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 3 centres, 2 have recruited patients. The intention was to enrol 60 patients (30 per arm). 1st patient was enrolled on 02 Dec 2012. On 14 Jun 2013, the present trial was terminated early because of low recruitment, with 11 patients recruited and 9 patients randomised and treated. The last patient completed the trial on 13 Sep 2013.

Pre-assignment

Screening details:

11 patients were screened within 7 months. Two of these patients failed screening because their % total body surface area (TBSA) of affected skin was outside the protocol mandated 15% ≤ % TBSA ≤ 60%.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Volulyte

Arm description:

6 % hydroxyethyl starch 130/0.4 in an isotonic electrolyte solution (solution for infusion)

Arm type	Experimental
Investigational medicinal product name	Volulyte 6% Solution for Infusion
Investigational medicinal product code	
Other name	6% hydroxyethyl starch 130/0.4 in an isotonic electrolyte solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Randomisation was within 8 hours after burn injury. Within the first 24 hours after burn injury, both treatment arms received up to 2 mL/kg/% total body surface area (TBSA) Hartmann's Lactated Ringer's solution (LR) as per modified Parkland regime (including the initial treatment phase from rescue to arrival at the hospital).
Patients in the Volulyte 6%-supplemented arm received 250 mL Volulyte 6% boluses (after randomisation) as required to achieve haemodynamic goals, in addition to Hartmann's (LR) infusion, during the 0 to 24 hours after burn injury. The total volume of Volulyte 6% infusion was not to exceed 50 mL/kg/24 hours. For patients who failed to respond to the above and/or in whom the maximum daily dosage of Volulyte 6% had been reached but still more fluid was required, the investigator was recommended to proceed with Hartmann's (LR) or give vasoactive drugs.

Arm title	Human Serum Albumin

Arm description:

Human Serum Albumin (HSA 50g/L, solution for infusion)

Arm type	Active comparator
Investigational medicinal product name	Albunorm 5%, 50 g/L, solution for infusion
Investigational medicinal product code	
Other name	human serum albumin 50 g/L
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Randomisation was within 8 hours after burn injury. Within the first 24 hours after burn injury, both

treatment arms received up to 2 mL/kg/% total body surface area Hartmann's (LR) as per modified Parkland regime (including the initial treatment phase from rescue to arrival at the hospital).
Patients in the albumin-supplemented arm received 250 mL Hartmann's (LR) boluses after randomisation as required to achieve haemodynamic goals, in addition to Hartmann's (LR) infusion, during the 0 to 8 hours after burn injury. A patient was also allowed to receive 5% albumin boluses as rescue colloid at the investigator's discretion.
During the 8 to 24 hours after burn injury, 250 mL 5% albumin (HSA 50 g/L) boluses were administered as required to achieve haemodynamic goals in addition to Hartmann`s (LR) infusion. There was no daily dose limit. For patients who failed to respond to the pure crystalloid or crystalloid/albumin regime, the investigator was allowed to give vasoactive drugs.

Number of subjects in period 1	Volulyte	Human Serum Albumin
Started	5	4
Completed	1	2
Not completed	4	2
Adverse event, serious fatal	2	-
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Volulyte
Reporting group description:	
6 % hydroxyethyl starch 130/0.4 in an isotonic electrolyte solution (solution for infusion)	
Reporting group title	Human Serum Albumin
Reporting group description:	
Human Serum Albumin (HSA 50g/L, solution for infusion)	

Reporting group values	Volulyte	Human Serum Albumin	Total
Number of subjects	5	4	9
Age categorical Units: Subjects			
Adults (18-64 years)	5	4	9
Age continuous Units: years			
arithmetic mean	30.4	35.3	
standard deviation	± 11.01	± 13.28	-
Gender categorical Units: Subjects			
Female	3	2	5
Male	2	2	4

Subject analysis sets	
Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat population (mITT) consisted of all patients in the ITT population (patients who were randomised) for whom the primary variable (fluid balance at 24 hours after burn injury) was evaluable and that were analysed according to actual treatment. Following the database lock 2 violations regarding the treatment allocation were detected. One male patient was randomised to the HSA arm but treated with Volulyte while another male patient was randomised to the Volulyte arm but treated with HSA. Therefore, the total number of patients for analysis of ITT and mITT population was not affected.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of all randomised patients who received at least 1 dose of randomised study medication.	

Reporting group values	mITT Population	Safety Population	
Number of subjects	9	7	
Age categorical Units: Subjects			
Adults (18-64 years)	9	7	
Age continuous Units: years			
arithmetic mean	32.6	29.6	
standard deviation	± 11.54	± 9.11	

Gender categorical Units: Subjects			
Female	5	4	
Male	4	3	

End points

End points reporting groups

Reporting group title	Volulyte
Reporting group description:	
6 % hydroxyethyl starch 130/0.4 in an isotonic electrolyte solution (solution for infusion)	
Reporting group title	Human Serum Albumin
Reporting group description:	
Human Serum Albumin (HSA 50g/L, solution for infusion)	
Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat population (mITT) consisted of all patients in the ITT population (patients who were randomised) for whom the primary variable (fluid balance at 24 hours after burn injury) was evaluable and that were analysed according to actual treatment. Following the database lock 2 violations regarding the treatment allocation were detected. One male patient was randomised to the HSA arm but treated with Volulyte while another male patient was randomised to the Volulyte arm but treated with HSA. Therefore, the total number of patients for analysis of ITT and mITT population was not affected.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of all randomised patients who received at least 1 dose of randomised study medication.	

Primary: Cumulative Fluid Balance at 24 Hours after Burn Injury

End point title	Cumulative Fluid Balance at 24 Hours after Burn Injury[1]
End point description:	
The primary efficacy endpoint of this trial was the cumulative fluid balance (input-output) at 24 hours after burn injury.	
End point type	Primary
End point timeframe:	
24 Hours after Burn Injury	
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: This trial was planned as a pilot study with explorative statistics only, and sample size thus was not based on any statistical considerations. The trial was terminated early because of slow recruitment; therefore, only descriptive statistics were planned in the statistical analysis plan. No formal statistical analyses (statistical tests) were planned for this trial.	

End point values	Volulyte	Human Serum Albumin	mITT Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	4	9	
Units: millilitre(s)				
median (full range (min-max))	8499 (4012 to 24161)	7027 (2518 to 9812)	8499 (2518 to 24161)	

Statistical analyses

No statistical analyses for this end point

Secondary: 28-Day Mortality

End point title	28-Day Mortality

End point description:

Mortality was continuously evaluated until day 28

End point type	Secondary

End point timeframe:

28 calendar days after burn injury

End point values	Volulyte	Human Serum Albumin	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	2	7	
Units: Number of Patients	2	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: 90-Day Mortality

End point title	90-Day Mortality

End point description:

Mortality was continuously evaluated until day 90

End point type	Secondary

End point timeframe:

90 calendar days after burn injury

End point values	Volulyte	Human Serum Albumin	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	2	7	
Units: Number of Patients	2	0	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the trial at any time from admission to burns unit on T0 (≤ 8 hours after burn injury) until last subject last visit on T10 (day 90)

Adverse event reporting additional description:

For this trial only treatment-emergent adverse events (TEAEs), i.e. adverse events (AEs) including serious AEs that began or worsened after the start of study medication, were reported and summarised in tables. Thus the number of serious and non-serious AEs below reflects the number of serious and non-serious TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Volulyte

Reporting group description:

6 % hydroxyethyl starch 130/0.4 in an isotonic electrolyte solution (solution for infusion)

Reporting group title	Human Serum Albumin

Reporting group description:

Human Serum Albumin (HSA 50g/L, solution for infusion)

Reporting group title	Safety Population

Reporting group description:

The safety population consisted of all randomised patients who received at least 1 dose of randomised study medication. The safety population was to be used for all safety analyses.

Serious adverse events	Volulyte	Human Serum Albumin	Safety Population
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Volulyte	Human Serum Albumin	Safety Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	1 / 2 (50.00%)	6 / 7 (85.71%)
Investigations			
Acinetobacter test positive			
subjects affected / exposed	1 / 5 (20.00%)	1 / 2 (50.00%)	2 / 7 (28.57%)
occurrences (all)	1	1	2
Alanine aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Bacterial test positive			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Blood alkaline phosphatase abnormal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Platelet count decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
White blood cell count increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Hypertension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Hypothermia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 5 (60.00%)	0 / 2 (0.00%)	3 / 7 (42.86%)
occurrences (all)	3	0	3
Coagulopathy			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Leukopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	2

Thrombocytopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Impaired gastric emptying			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Pulmonary oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Wound infection bacterial			

subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Wound infection pseudomonas			
subjects affected / exposed	0 / 5 (0.00%)	1 / 2 (50.00%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Wound infection staphylococcal			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	3	0	3
Hypoalbuminaemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Hypophosphataemia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	3	0	3
Electrolyte imbalance			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2012	Amendment No. 1 was implemented to establish a Data Safety Monitoring Board (DSMB) in the trial to ensure that there would be no unavoidable risk for harm for patients in any of the 2 treatment groups. Further changes referred to the gender (assessment of the gender was added to the demographic criteria) and the calculation of fluid balance (two additional time points were added for the assessment of fluid balance in the protocol).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial was planned as a pilot trial with explorative statistics only. The trial was terminated early because of slow recruitment. The primary and secondary variables could only be analysed in a descriptive manner.

Notes: