Clinical trial results:
Efficacy and safety of 6 % hydroxyethyl starch 130/0.4 (Voluven) vs. 5% HSA in volume replacement therapy during elective open-heart surgery in paediatric patients

Summary

EudraCT number	2008-006749-18
Trial protocol	AT BE
Global end of trial date	05 August 2010

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	HE06-001-C P4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00860405
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi Deutschland GmbH
Sponsor organisation address	Else-Kröner-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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2010
Global end of trial reached?	Yes
Global end of trial date	05 August 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study compared the clinical efficacy and safety of Voluven and Human Albumin during elective open-heart surgery in paediatric patients.

Protection of trial subjects:

At the screening visit the parent(s) of patients who were considered potential candidates for the study were asked to provide a written informed consent (signed parental written informed consent) and patient assent was obtained (where achievable [patients ≥ 6 years]). The investigator considered 4 patients ≥ 6 years unable to sign the informed assent. The parent(s) and patient (if applicable) were informed in writing about their right to withdraw from the study at any time without specification of reasons. Written patient information was given to each parent and patient (if applicable) before enrolment. Patients could only participate if their eligibility had been proven.
As this study dealt with a specific patient population, i.e. children at the age of 2-12 years, study specific modifications of the common terminology criteria for adverse events (CTCAE) v3.0 for vital signs and laboratory values were used. The criteria for the adverse event (AE) intensity assessment were adjusted as well.
The study could also be terminated prematurely for medical or ethical reasons following consultation with the investigators.
Patients who were withdrawn due to one or more (serious) AEs were to be treated and followed-up according to established medical practice to evaluate the course of the AE, and to ensure reversibility or stabilisation of the event.

Background therapy: -

Evidence for comparator:

In the past, human albumin has beeen widely accepted as the therapeutic "gold standard" in paediatric volume replacement therapy because of the physiological hypoproteinemia in newborns and infants. Therefore, HSA was used as comparator.

Actual start date of recruitment	31 March 2009
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	Austria: 21
Country: Number of subjects enrolled	Belgium: 40
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	59
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited in paediatric care units of 2 hospitals in Austria and Belgium from March 2009 (First Patient In) until July 2010 and were followed up until August 2010 (Last Patient Out).

Pre-assignment

Screening details:

In total 99 patients were screened in paediatric care units of the participating 2 study sites in Austria (39 patients) and Belgium (60 patients).
Male or female paediatric patients, 2 to 12 years of age, suffering from congenital heart-disease and undergoing elective open-heart surgery requiring extracorporeal circulation (ECC) were eligible.

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	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

An independent perfusionist was the only unblinded person at the study site responsible for preparing the heart-lung machine and those bottles of the study medication needed by the investigator for volume replacement.

Arms

Are arms mutually exclusive?	Yes
Arm title	Voluven 6% Arm

Arm description:

6% Hydroxyethylstarch (HES) 130/0.4, i.v.

Arm type	Experimental
Investigational medicinal product name	HES 130/0.4 (6%) in isotonic sodium chloride (0.9%) solution
Investigational medicinal product code	
Other name	Trade name: Voluven
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The investigational drug Voluven (6%) was given as part of the priming of the extracorporeal circulation (ECC) and for plasma volume replacement before and/or after start of ECC up to the maximum dosage of 50 mL/kg body weight/day; once the maximum dose was reached, 5% human serum albumin (HSA 50 g/L) for which there was no daily dose limitation was used as rescue colloid in both groups, if required. During the priming of the ECC the dosage depended on the patient's body weight and the total volume of the ECC.

Arm title	HSA 5% Arm

Arm description:

Human Serum Albumin (HSA) 50g/L, i.v.

Arm type	Active comparator
Investigational medicinal product name	Human serum albumin (HSA 50g/L)
Investigational medicinal product code	
Other name	Trade name: Human Albumin Baxter
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The comparator human serum albumin (HSA) was given as part of the priming of the extracorporeal circulation (ECC) and for plasma volume replacement before and/or after start of ECC up to the

maximum dosage of 50 mL/kg body weight/day; once the maximum dose was reached, 5% human serum albumin (HSA 50 g/L) for which there was no daily dose limitation was used as rescue colloid in both groups, if required. During the priming of the ECC the dosage depended on the patient's body weight and the total volume of the ECC.

Number of subjects in period 1	Voluven 6% Arm	HSA 5% Arm
Started	31	30
Day 28 follow-up performed	31	29
Completed treatment	31	29
Completed	26	26
Not completed	5	4
Randomised in error (not treated)	-	1
Lost to follow-up	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Voluven 6% Arm
Reporting group description:	
6% Hydroxyethylstarch (HES) 130/0.4, i.v.	
Reporting group title	HSA 5% Arm
Reporting group description:	
Human Serum Albumin (HSA) 50g/L, i.v.	

Reporting group values	Voluven 6% Arm	HSA 5% Arm	Total
Number of subjects	31	30	61
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	5.2	4	
standard deviation	± 2.9	± 2	-
Gender, Male/Female Units: participants			
Female	16	13	29
Male	15	17	32
Region of Enrollment Units: Subjects			
Belgium	20	20	40
Austria	11	10	21
Weight Units: kg			
arithmetic mean	18.2	15.4	
standard deviation	± 8.9	± 4.4	-
Height Units: cm			
arithmetic mean	106.6	101.3	
standard deviation	± 16.8	± 12.8	-

End points

End points reporting groups

Reporting group title	Voluven 6% Arm
Reporting group description:	
6% Hydroxyethylstarch (HES) 130/0.4, i.v.	
Reporting group title	HSA 5% Arm
Reporting group description:	
Human Serum Albumin (HSA) 50g/L, i.v.	

Primary: Total volume of colloid solution required intraoperatively

End point title	Total volume of colloid solution required intraoperatively
End point description:	
The primary efficacy variable was the total volume of colloid solution (Voluven/HSA plus rescue colloid, if applicable) in mL/kg body weight required for intraoperative volume replacement therapy including priming of the ECC.	
End point type	Primary
End point timeframe:	
Study drug was used intraoperatively before ECC, for priming of the heart-lung-machine, and after ECC until end of surgery according to the patient's demands.	

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[1]	26[2]		
Units: ml/kg				
arithmetic mean (standard deviation)	36.6 (± 11.76)	36.97 (± 11.86)		

Notes:

[1] - Per-protocol (PP) population

[2] - Per-protocol (PP) population

Statistical analyses

Statistical analysis title	Therapeutic Equivalence
Statistical analysis description:	
The aim of the study was to prove equivalence, i.e. H0: μVoluven/μHSA ≤ 0.55 or μVoluven/μHSA ≥ 1.82 H1: 0.55 < μVoluven/μHSA < 1.82 where μVoluven was the mean infused volume of Voluven and μHSA was the mean infused volume of HSA 5%.	
Comparison groups	HSA 5% Arm v Voluven 6% Arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Method	ANOVA
Parameter estimate	Ratio of LS-means (LS = Least square)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.16

Notes:

[3] - Assuming a CV of 0.363 and a desired power of 90 % with a type I level of 2.5 %, N=11 patients per treatment group were needed. Nevertheless, more patients were required for the assessment of safety, therefore 2 × 30 patients were planned to be included in this study. Primary endpoint specified and analysed for PP and ITT population. Confirmatory analysis based on PP population only, no adjustment for multiplicity.
Considered ratio: µVoluven/µHSA = LS-mean of Voluven/LS-mean of HSA 5%

Secondary: Mean arterial pressure (MAP)

End point title	Mean arterial pressure (MAP)

End point description:

Mean arterial pressure (MAP) from beginning of anaesthesia (baseline) until arrival on intensive care unit (ICU).
Description of time points:
T0 Baseline: Immediately after induction of anaesthesia
T1 Treatment period: Immediately before ECC
T2 Treatment period: Immediately after protamine application
T3 Treatment period: After skin closure
T4 Treatment period: Arrival on the intensive care unit (ICU) (after complete installation)

End point type	Secondary

End point timeframe:

Beginning of anaesthesia (baseline) until arrival on intensive care unit (ICU)

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	26		
Units: mm Hg				
arithmetic mean (standard deviation)				
T0, Baseline	64.1 (± 11.3)	66.5 (± 12.5)		
T1, before ECC (Extracorporeal circulation)	54 (± 7.4)	51.3 (± 8)		
T2, after ECC	56.6 (± 7.6)	58.2 (± 9.7)		
T3, after skin closure	61.2 (± 9.7)	62 (± 9.9)		
T4, arrival on ICU	65.3 (± 14.8)	65.2 (± 8.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid input

End point title	Fluid input

End point description:

Quantity of total fluids administered from beginning of anaesthesia until 2nd postop morning

End point type	Secondary

End point timeframe:

2 days

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	26		
Units: ml/kg				
arithmetic mean (standard deviation)	246.76 (± 119.29)	248.2 (± 105.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid output

End point title	Fluid output

End point description:

Quantity of total fluids excreted or lost from beginning of anaesthesia until 2nd postop morning

End point type	Secondary

End point timeframe:

2 days

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	26		
Units: ml/kg				
arithmetic mean (standard deviation)	195.48 (± 95.67)	181.13 (± 68.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid balance

End point title	Fluid balance

End point description:

Fluid balance was calculated as total fluid input minus total fluid output

End point type	Secondary

End point timeframe:

2 days

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	26		
Units: ml/kg				
arithmetic mean (standard deviation)	51.28 (± 47.46)	67.07 (± 62.57)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Calculated perioperative Red Blood Cell (RBC) loss

End point title	Calculated perioperative Red Blood Cell (RBC) loss

End point description:

Calculated perioperative RBC loss = Predicted blood volume [1] × (hematocrit [baseline] – hematocrit [2nd postop morning]) + transfused RBC volume [2];
[1] Predicted blood volume (mL) = 80 × body weight (kg)
[2] Transfused RBC volume = 0.7 × infused packed RBC

End point type	Other pre-specified

End point timeframe:

2 days

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[4]	29[5]		
Units: ml/kg				
arithmetic mean (standard deviation)	14.45 (± 14.38)	15.35 (± 15.48)		

Notes:

[4] - Safety population

[5] - Safety population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Length of stay on the intensive care unit (ICU)

End point title	Length of stay on the intensive care unit (ICU)

End point description:

Length of stay (number of days) on the intensive care unit (ICU).

End point type	Other pre-specified

End point timeframe:

From admission to ICU until discharge from ICU

End point values	Voluven 6% Arm	HSA 5% Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	29		
Units: Days				
median (inter-quartile range (Q1-Q3))	3.08 (1.96 to 5.79)	3.06 (2.29 to 6.92)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event recording was performed throughout the study (from signing the informed consent until the follow-up visit at 28 days after discharge from operating room).

Adverse event reporting additional description:

Regular assessment by Pharmacovigilance and Safety Assessor. Only treatment emergent adverse events were reported and summarized in tables.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Voluven Arm

Reporting group description:

6% Hydroxyethylstarch 130/0.4, i.v.

Reporting group title	HSA 5% Arm (Comparison group)

Reporting group description:

Human Serum Albumin (HSA) 50g/L, i.v.

Serious adverse events	Voluven Arm	HSA 5% Arm (Comparison group)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 31 (35.48%)	7 / 29 (24.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
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			
Cardiac procedure complication			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
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			
Coagulopathy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
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			
Device breakage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Internal hernia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (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			
Apnoea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 31 (0.00%)	3 / 29 (10.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
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: 0 %

Non-serious adverse events	Voluven Arm	HSA 5% Arm (Comparison group)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 31 (96.77%)	29 / 29 (100.00%)	
Vascular disorders			
Arterial thrombosis limb			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Deep vein thrombosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Haemodynamic instability			
subjects affected / exposed	4 / 31 (12.90%)	4 / 29 (13.79%)	
occurrences (all)	4	4	
Hypotension			
subjects affected / exposed	10 / 31 (32.26%)	4 / 29 (13.79%)	
occurrences (all)	13	4	
General disorders and administration			

site conditions			
Device occlusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Drug withdrawal syndrome			
subjects affected / exposed	0 / 31 (0.00%)	3 / 29 (10.34%)	
occurrences (all)	0	3	
Exposure to contaminated device			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Impaired healing			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Infusion site extravasation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Infusion site urticaria			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Systemic inflammatory response syndrome			
subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Aspiration			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Atelectasis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Bradypnoea			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Haemoptysis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Hypercapnia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Hyperventilation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Increased bronchial secretion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Lung disorder			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	7 / 31 (22.58%)	0 / 29 (0.00%)	
occurrences (all)	7	0	
Pneumothorax			
subjects affected / exposed	2 / 31 (6.45%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Pulmonary congestion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pulmonary oedema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Respiratory acidosis			

subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Respiratory depression			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Stridor			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	6 / 31 (19.35%)	3 / 29 (10.34%)	
occurrences (all)	6	3	
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 31 (19.35%)	4 / 29 (13.79%)	
occurrences (all)	6	4	
Blood urea increased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Blood lactic acid increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Enterovirus test positive			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Venous oxygen saturation decreased			

subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Cardiac procedure complication			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Dilutional coagulopathy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Endotracheal intubation complication			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Procedural vomiting			
subjects affected / exposed	7 / 31 (22.58%)	6 / 29 (20.69%)	
occurrences (all)	8	8	
Traumatic haematoma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Bradycardia			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Cardiac aneurysm			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Nodal rhythm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	5 / 31 (16.13%)	3 / 29 (10.34%)	
occurrences (all)	6	3	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Myoclonus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Phrenic nerve paralysis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 31 (6.45%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Coagulopathy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Leukocytosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Ascites			
subjects affected / exposed	4 / 31 (12.90%)	1 / 29 (3.45%)	
occurrences (all)	4	1	
Constipation			
subjects affected / exposed	7 / 31 (22.58%)	4 / 29 (13.79%)	
occurrences (all)	7	4	
Dyspepsia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	13 / 31 (41.94%)	9 / 29 (31.03%)	
occurrences (all)	13	10	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Pruritus allergic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Purpura			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Urticaria			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Anuria			
subjects affected / exposed	2 / 31 (6.45%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Haematuria			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	2 / 31 (6.45%)	2 / 29 (6.90%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Aspergillosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Enterobiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Device related infection			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
H1n1 Influenza			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Laryngitis			
subjects affected / exposed	1 / 31 (3.23%)	4 / 29 (13.79%)	
occurrences (all)	1	4	
Lobar pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Post procedural pneumonia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Postoperative wound infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Skin candida			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	17 / 31 (54.84%)	13 / 29 (44.83%)	
occurrences (all)	22	14	

Hyperlactacidaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Hypernatraemia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Hypocalcaemia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Hypoglycaemia			
subjects affected / exposed	4 / 31 (12.90%)	2 / 29 (6.90%)	
occurrences (all)	4	2	
Hypokalaemia			
subjects affected / exposed	4 / 31 (12.90%)	6 / 29 (20.69%)	
occurrences (all)	4	6	
Hyponatraemia			
subjects affected / exposed	3 / 31 (9.68%)	3 / 29 (10.34%)	
occurrences (all)	3	3	
Hypophosphataemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Hypoproteinaemia			
subjects affected / exposed	10 / 31 (32.26%)	0 / 29 (0.00%)	
occurrences (all)	10	0	
Hypovolaemia			
subjects affected / exposed	2 / 31 (6.45%)	4 / 29 (13.79%)	
occurrences (all)	2	4	
Metabolic acidosis			
subjects affected / exposed	8 / 31 (25.81%)	8 / 29 (27.59%)	
occurrences (all)	8	9	
Metabolic alkalosis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2009	In the first protocol amendment the study drug label for Belgium was revised as required by the Belgian Competent Authority.
28 May 2009	In the second protocol amendment the recipient of serious adverse event (SAE) reports/emergency contact during out-of office hours at the sponsor was updated. It was clarified that intraoperative study drug administration could already be started before ECC, but remained limited to the intraoperative period. The maximum daily dosage for the study drug was not changed. Therefore this change in the treatment schedule was not considered relevant regarding evaluations of efficacy and safety in this study. Furthermore stratum (≤ 12 kg, > 12 kg) was included in ANOVA and ANCOVA models, the unit of pump flow corrected in the footer of the study schedule and section 12.3.3, the use of a cell saver device was allowed as this device was introduced as routine procedure in paediatric cardiac surgery, the total volumes of ECC were clarified and in Appendix 5b the symbol < for ranges of SaO2 and SpO2 was corrected and changed to >.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported