Clinical trial results:
Hydrocortisone for Prevention of Septic Shock
Placebo-controlled, randomised, double-blind study to investigate the efficacy and safety of low dose hydrocortisone to prevent the development of septic shock in patients with severe sepsis

Summary

EudraCT number	2007-004401-10
Trial protocol	DE
Global end of trial date	29 January 2015

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	HYPRESS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00670254
WHO universal trial number (UTN)	-
Other trial identifiers	clinical trials: NCT 00670254

Notes:

Sponsors

Sponsor organisation name	Charité
Sponsor organisation address	Augustenburger Platz 1, Berlin, Germany, 13353
Public contact	Didier Keh, Charité Universitaetsmedizin Berlin, 0049 30450651048, didier.keh@charite.de
Scientific contact	Didier Keh, Charité Universitaetsmedizin Berlin, 0049 30450651048, didier.keh@charite.de

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	29 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2014
Global end of trial reached?	Yes
Global end of trial date	29 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Prevention of the development of septic shock in patients with severe sepsis

Protection of trial subjects:

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 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	Germany: 380
Worldwide total number of subjects	380
EEA total number of subjects	380

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)	0
From 65 to 84 years	380
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patientswere screened in intermediate care units or intensive
care units (ICUs) of university andcommunity hospitals for eligibility,
and written informed consent was obtained from patients, patient-authorized representatives, or legal representatives.
The main exclusion criterion was septic shock.

Pre-assignment

Screening details:

From January 13, 2009, to August 27, 2013, 9953 patients with
severe sepsis or septic shock were screened at 34 study sites
for eligibility. A total of 380 patients were randomized to receive hydrocortisone (n = 190)or placebo (n = 190).

Pre-assignment period milestones

Number of subjects started	380
Number of subjects completed	353

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 27

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Hydrocortisone

Arm description:

Each vial with the study medication contains a lyophylisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophylisate.

Arm type	Experimental
Investigational medicinal product name	HYDROCORTISONE HYDROGEN SUCCINATE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For bolus application, the lyophylisate of one vial is diluted with 2 ml of distilled water. One ml of this dilution (= 50 mg hydrocortisone or placebo) is diluted to 10 ml with normal saline and administered intravenously. The bolus is immediately followed by
Continuous infusion of the study drug:
Days 1-5: Dilute 2 x 2 ml of study drug (2 vials = 200 mg hydrocortisone) in a 50 ml syringe with normal saline. Infusion rate: 200 mg/24 hours.
Days 6-7: Dilute 1 x 2 ml of study drug (1 vial = 100 mg hydrocortisone) in a 50 ml syringe with normal saline. Infusion rate: 100 mg/24 hours.
Days 8-9: Dilute 1 x 1 ml of study drug (1/2 vial = 50 mg hydrocortisone) in a 50 ml syringe with normal saline. Infusion rate: 50 mg/24 hours.

Days 10-11: Dilute 1 x 1/2 ml of study drug (1/4 vial = 25 mg hydrocortisone) in a 50 ml syringe with normal saline. Infusion rate: 25 mg/24 hours.

Arm title	Placebo

Arm description:

Each vial with the study medication contains a lyophylisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophylisate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

• Days 1-5: Dilute 2 x 2 ml of study drug (2 vials = 200 mg placebo) in a 50 ml syringe with normal saline. Infusion rate: 200 mg/24 hours.• Days 6-7: Dilute 1 x 2 ml of study drug (1 vial = 100 mg placebo) in a 50 ml syringe with normal saline. Infusion rate: 100 mg/24 hours• Days 8-9: Dilute 1 x 1 ml of study drug (1/2 vial = 50 mgplacebo) in a 50 ml syringe with normal saline. Infusion rate: 50 mg/24 hours.• Days 10-11: Dilute 1 x 1/2 ml of study drug (1/4 vial = 25 mg placebo) in a 50 ml syringe with normal saline. Infusion rate: 25 mg/24 hours.

Number of subjects in period 1[1]	Hydrocortisone	Placebo
Started	177	176
Completed	170	170
Not completed	7	6
Consent withdrawn by subject	6	4
Lost to follow-up	1	2

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: 380 patients were screened for enrollment and 353 patients were definitely enrolled in the ITT population.

Baseline characteristics

Reporting groups	
Reporting group title	Hydrocortisone
Reporting group description:	
Each vial with the study medication contains a lyophylisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophylisate.	
Reporting group title	Placebo
Reporting group description:	
Each vial with the study medication contains a lyophylisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophylisate.	

Reporting group values	Hydrocortisone	Placebo	Total
Number of subjects	177	176	353
Age categorical Units: Subjects			
Adults >= 18	177	176	353
Age continuous Units: years			
arithmetic mean	65.5	64.6	
standard deviation	± 14.2	± 14.6	-
Gender categorical Units: Subjects			
Female	59	65	124
Male	118	111	229
Type of admission, No./total No. Units: Subjects			
Surgery, elective	27	42	69
Surgery, emergency	44	32	76
Nonsurgery, elective	5	4	9
Nonsurgery, emergency	100	98	198
N/A	1	0	1
Organ dysfunction: Central nervous system Units: Subjects			
Central nervous system	41	47	88
N/A	136	129	265
Organ dysfunction Coagulation Units: Subjects			
Coagulation	35	26	61
N/A	142	150	292
Organ dysfunction Pulmonary Units: Subjects			
Pulmonary	117	119	236
N/A	60	57	117
Organ dysfunction, No./total No. Renal Units: Subjects			
Renal	70	73	143

N/A	107	103	210

Sequential Organ Failure Assessment			
SOFA			
Units: Score			
arithmetic mean	6.4	6.2	
standard deviation	± 2.6	± 2.4	-
Acute Physiology and Chronic Health Evaluation II			
APACHE II			
Units: Score			
arithmetic mean	19.5	18.5	
standard deviation	± 6.9	± 6.0	-
Simplified Acute Physiology Score II			
SAPS II score			
Units: Score			
arithmetic mean	56.1	52.2	
standard deviation	± 13.3	± 9.9	-
Simplified Acute Physiology Score 3			
SAPS 3 score			
Units: Score			
arithmetic mean	58.5	58.4	
standard deviation	± 11.9	± 11.0	-
Medication within 72 h before randomization			
Intravenous glucocorticoids, No./total No. (%) Placebo :6/176 (3.4) Hydrocortisone: 3/177 (1.7)			
Units: mg			
median	200	600	
full range (min-max)	200 to 400	392 to 1000	-

End points

End points reporting groups

Reporting group title	Hydrocortisone

Reporting group description:

Each vial with the study medication contains a lyophylisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophylisate.

Reporting group title	Placebo

Reporting group description:

Each vial with the study medication contains a lyophylisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophylisate.

Subject analysis set title	Placebo Safty population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population is defined by all patients randomised with informed consent who received at least once the study medication. In the safety analyses, patients will be evaluated according to the treatment they actually received, irrespective of the randomisation.

Subject analysis set title	Safty population Hydrocortisone
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population is defined by all patients randomised with informed consent who received at least once the study medication. In the safety analyses, patients will be evaluated according to the treatment they actually received, irrespective of the randomisation.

Primary: Primärer Endpunkt – Septic Schock within 14 days (ITT)

End point title	Primärer Endpunkt – Septic Schock within 14 days (ITT)

End point description:

End point type	Primary

End point timeframe:

14 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subject				
number (not applicable)				
ITT Population	36	39		

Statistical analyses

Statistical analysis title	Patients with septic shock within 14days

Statistical analysis description:

The primary end point was assessed by χ^2 test; heterogeneity between centers with more than 10 recruited
patients was assessed by I^2

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.9
upper limit	26.9

Primary: Primärer Endpunkt – Septic Schock within 14 days (PP)

End point title	Primärer Endpunkt – Septic Schock within 14 days (PP)
End point description:	
End point type	Primary
End point timeframe:	
14 Days	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	156		
Units: Subjects				
number (not applicable)				
PP population	29	33		

Statistical analyses

Statistical analysis title	Patients with septic shock within 14days
Statistical analysis description:	
The primary end point was assessed by χ^2 test; heterogeneity between centers with more than 10 recruited	
Comparison groups	Placebo v Hydrocortisone
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Chi-squared
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.9
upper limit	26.9

Secondary: Mortality, No./total No. [95% CI] 28 Days

End point title	Mortality, No./total No. [95% CI] 28 Days

End point description:

End point type	Secondary

End point timeframe:
28 Day

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	170		
Units: Subjects				
number (not applicable)				
28 Days	15	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality, No./total No. [95% CI] 90 Days

End point title	Mortality, No./total No. [95% CI] 90 Days

End point description:

End point type	Secondary

End point timeframe:
90 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	168		
Units: Subjects				
number (not applicable)				
90 d	34	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality, No./total No. [95% CI] 180 Days

End point title	Mortality, No./total No. [95% CI] 180 Days

End point description:

End point type	Secondary

End point timeframe:
180 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	167		
Units: Subjects				
number (not applicable)				
180 d	45	37		

Statistical analyses

No statistical analyses for this end point

Secondary: ICU

End point title	ICU

End point description:

End point type	Secondary

End point timeframe:
180

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	172		
Units: Subject				
number (not applicable)	23	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital

End point title	Hospital

End point description:

End point type	Secondary

End point timeframe:

180 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	171		
Units: Subject				
number (not applicable)	23	22		

Statistical analyses

No statistical analyses for this end point

Secondary: length of stay (LOS)

End point title	length of stay (LOS)

End point description:

End point type	Secondary

End point timeframe:

180 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: Days				
arithmetic mean (full range (min-max))				
ICU	8 (6 to 15)	9 (6 to 17)		
Hospital	26 (16 to 46)	25 (16 to 40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mechanical ventilation

End point title	Mechanical ventilation

End point description: Mechanical ventilation, No./total No.	
End point type	Secondary
End point timeframe: 180 Days	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	172		
Units: Subject				
number (not applicable)	91	103		

Statistical analyses

No statistical analyses for this end point

Secondary: MV-free time

End point title	MV-free time
End point description: M/V =MV-free timeMV-free time, median (IQR),	
End point type	Secondary
End point timeframe: 180 Days	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: Days				
median (inter-quartile range (Q1-Q3))	4 (2 to 7)	5 (2 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: RRT, No./total No. [95%CI]

End point title	RRT, No./total No. [95%CI]
End point description: RRT, renal replacement therapy;	

End point type	Secondary

End point timeframe:

180 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	172		
Units: Subject				
number (not applicable)	21	21		

Statistical analyses

No statistical analyses for this end point

Secondary: RRT, renal replacement therapy- free time

End point title	RRT, renal replacement therapy- free time

End point description:

End point type	Secondary

End point timeframe:

up to 180 days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: Score				
arithmetic mean (inter-quartile range (Q1-Q3))				
RRT-free time	6 (4 to 12)	7 (4 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: SOFA score until day 14

End point title	SOFA score until day 14

End point description:

SOFA (Sequential Organ Failure Assessment) score

End point type	Secondary

End point timeframe:

Mean total SOFA (organ dysfunction) and mean SOFA sub-scores until ICU discharge

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: Score				
arithmetic mean (inter-quartile range (Q1-Q3))				
Sofa Score	6 (4 to 12)	5 (2 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Delirium

End point title	Delirium

End point description:

-Delirium was assessed by the Richmond Agitation-Sedation Scale and the Confusion Assessment Method for the ICU in
286 of 353 patients (81.0%).
-Twenty-six patients were excluded from analysis owing to low Richmond Agitation-Sedation Scale score or incomplete data.
-The results remained significant after exclusion of another 60 patients (28 from the placebo group, 32 from the hydrocortisone group) who were diagnosed by the investigator to have no delirium but had at least 1 incomplete delirium assessment or had only 1 baseline assessment (n = 6 in the hydrocortisone group) (with delirium occurring in 11 of 98 patients [11.2%] in the hydrocortisone group vs 25 of 102 patients [24.5%] in the placebo group; difference, −13.3%; 95% CI, −23.7% to −2.6%; P = .01).

End point type	Secondary

End point timeframe:

180 Days

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: Subjects	11	25		

Statistical analyses

No statistical analyses for this end point

Secondary: sodium concentration

End point title	sodium concentration

End point description: Safety endpoints Blood sodium level and frequency of hypernatremia (> 155 mmol/l) within 14 days	
End point type	Secondary
End point timeframe: 14 Days	

End point values	Placebo Safty population	Safty population Hydrocortisone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	189	186		
Units: mEq/L				
arithmetic mean (standard deviation)				
Maximum sodium concentration	141 (± 6)	141 (± 5)		
Sodium concentration during study medication admin	140 (± 6)	141 (± 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: glucose concentration

End point title	glucose concentration
End point description: Safety endpoints: Blood glucose level and frequency of hyperglycemia (> 150 mg/dl) within 14 days	
End point type	Secondary
End point timeframe: 14 Days	

End point values	Placebo Safty population	Safty population Hydrocortisone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	189	186		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
Maximum glucose concentration	160 (134 to 196)	164 (145 to 204)		
Maximum glucose concentration during study medicat	157 (133 to 198)	170 (147 to 208)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

180 Days

Adverse event reporting additional description:

the safety analysis set included 375 patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Total Adverse Events in Safety Set

Reporting group description:

There were more episodes of hyperglycemia (blood glucose level >150mg/dL [to convert to millimoles per liter, multiply by 0.0555]) in the hydrocortisone group (169 of 186 patients [90.9%]) than in the placebo group(154of 189patients [81.5%]) (difference, 9.4%; 95%CI, 2.4%to 16.4%; P = .009). The total amount of administered insulin was not significantly different between the hydrocortisone and placebo groups (safety set analysis: mean [SD], 264.6 [312.2] vs 212.2 [246.8] IU, respectively; difference, 52.4 IU; 95% CI, −21.8 to 126.7 IU; P = .17). Two patients developed severe hypertension during hydrocortisone administration, which required antihypertensive therapy. Both patients recovered without sequelae. Secondary infections, weaning failure, muscleweakness,hypernatremia,orother adverse events were not significantly different between treatment groups.

Serious adverse events	Total Adverse Events in Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 375 (23.47%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			

subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	4 / 375 (1.07%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Post procedural bile leak			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suture related complication			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheal haemorrhage			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheostomy malfunction			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urostomy complication			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weaning failure			

subjects affected / exposed	4 / 375 (1.07%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Wound dehiscence				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Haemorrhage				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 375 (0.53%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
A cute myocardial infraction				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
A trial fibrillation				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
A trial flutter				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
A trioventricular block complete				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				

subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	5 / 375 (1.33%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Laparotomy			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Resuscitation			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 375 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Convulsion			

subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disturbance in attention				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Orthostatic intolerance				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroduodenal haemorrhage				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	4 / 375 (1.07%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal fistula				

subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal haemorrhage				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	2 / 375 (0.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Aspiration				
subjects affected / exposed	2 / 375 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	2 / 375 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 375 (0.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	5 / 375 (1.33%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Stridor			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	2 / 375 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Candida sepsis			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dural abscess			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Mediastine			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	2 / 375 (0.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal gangrene			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Necrotising fasciitis			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	4 / 375 (1.07%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 375 (1.07%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal abscess			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 375 (0.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 375 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Total Adverse Events in Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	323 / 375 (86.13%)		
Injury, poisoning and procedural complications			
Impaired wound healing			
subjects affected / exposed	8 / 375 (2.13%)		
occurrences (all)	8		
Cardiac disorders			
Arterial hypertension			
subjects affected / exposed	6 / 375 (1.60%)		
occurrences (all)	6		
other			
subjects affected / exposed	32 / 375 (8.53%)		
occurrences (all)	32		
Nervous system disorders			
Stroke, TIA or convulsion	Additional description: TIA: transient ischemic attack		
subjects affected / exposed	7 / 375 (1.87%)		
occurrences (all)	7		
Delirium			
subjects affected / exposed	9 / 375 (2.40%)		
occurrences (all)	9		
other			
subjects affected / exposed	1 / 375 (0.27%)		
occurrences (all)	1		
Gastrointestinal disorders			

Gastrointestinal bleeding subjects affected / exposed occurrences (all) Ulcer subjects affected / exposed occurrences (all)	 5 / 375 (1.33%) 5 1 / 375 (0.27%) 1		
Respiratory, thoracic and mediastinal disorders Weaning failure subjects affected / exposed occurrences (all) Respiratory failure subjects affected / exposed occurrences (all) other subjects affected / exposed occurrences (all)	 32 / 375 (8.53%) 32 10 / 375 (2.67%) 10 15 / 375 (4.00%) 15		
Musculoskeletal and connective tissue disorders MRC Scale for Muscle Strength scor available subjects affected / exposed occurrences (all) Muscle weakness subjects affected / exposed occurrences (all)	 301 / 375 (80.27%) 301 82 / 375 (21.87%) 82		
Infections and infestations Secondary infections subjects affected / exposed occurrences (all)	 40 / 375 (10.67%) 40		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2008	investigational medication
30 September 2008	Amendment for the trial protocol
02 April 2009	PI- Change
07 April 2009	PI-Change and subsequent registration of a Trial Centre
27 July 2009	PI-Change
20 November 2009	PI-Change
27 October 2010	PI-Change
29 March 2011	PI-Change
30 August 2011	study term extention
18 January 2012	PI-Change
03 March 2012	Subsequent registration of a Trial Centre
19 March 2013	cancellation of a Trial Centre
14 April 2014	term extension

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/27695824