



Clinical trial results: ADRENAL- ADjunctive coRticosteroid trEatment iN criticALLy iLL patients with septic shock.

Summary

EudraCT number	2012-003158-10
Trial protocol	GB DK IE
Global end of trial date	03 October 2017

Results information

Result version number	v1 (current)
This version publication date	04 March 2021
First version publication date	04 March 2021

Trial information

Trial identification

Sponsor protocol code	GI-CCT372273
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01448109
WHO universal trial number (UTN)	-
Other trial identifiers	ANZCTR: ACTRN12611001042932

Notes:

Sponsors

Sponsor organisation name	The George Institute
Sponsor organisation address	Level 5/1 King St, Newtown, Sydney, Australia, 2042
Public contact	Dr. Anders Perner, Intensiv Terapiklinik 4131, 0045 354583333, anders.perner@regionh.dk
Scientific contact	Dr. Anders Perner, Intensiv Terapiklinik 4131, 0045 354583333, anders.perner@regionh.dk

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	31 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2017
Global end of trial reached?	Yes
Global end of trial date	03 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the impact of intravenous hydrocortisone versus placebo on all cause mortality at 90 days in critically ill patients with septic shock. The hypothesis is that hydrocortisone, compared to placebo, reduces 90-day all-cause mortality in patients admitted to an ICU with septic shock.

Protection of trial subjects:

Double blinded trial and individual data were not shown to summary report.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 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: 355
Country: Number of subjects enrolled	Denmark: 142
Country: Number of subjects enrolled	Australia: 2719
Country: Number of subjects enrolled	New Zealand: 420
Country: Number of subjects enrolled	Saudi Arabia: 164
Worldwide total number of subjects	3800
EEA total number of subjects	142

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)	1920

From 65 to 84 years	1751
85 years and over	129

Subject disposition

Recruitment

Recruitment details:

Recruitment from June 2012 to April 2017, location in hospital ICU

Pre-assignment

Screening details:

21818 patients were screened. In details, 16317 were ineligible (8054 did not meet inclusion criteria and 8263 met exclusion criteria);

1701 were eligible but excluded, (446 patients or SDM declined or unable to consent, 659 decline to randomize eligible patients, 95

patients were enrolled in another trial, 501 had other reasons/missing)

Period 1

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

Blinding implementation details:

The above roles were blinded to study treatment allocation. The hydrocortisone sodium succinate sterile powder (equivalent to 100mg of hydrocortisone) has been sourced from the manufacturer of the registered product & supplied in glass vial. The powder is a white or nearly white odourless, hygroscopic amorphous solid which is soluble in water. The placebo is a matching vial holding 0.2 mL sterile water for injection. Hydrocortisone and placebo vials will be covered in blinding label + kit number

Arms

Are arms mutually exclusive?	Yes
Arm title	Hydrocortisone

Arm description:

IV hydrocortisone 200 mg/day for 7 days or until death or discharge from ICU

Arm type	Active comparator
Investigational medicinal product name	Solu-CORTEF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

200mg/day for 7 days. Intravenous administration.

Arm title	Placebo
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Arm description:

placebo, for 7 days or until death or discharge from ICU

Arm type	Placebo
Investigational medicinal product name	PR1
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 Ampule in solution connected to an IV drip. Continuous infusion once per day for 7 days.

Number of subjects in period 1	Hydrocortisone	Placebo
Started	1898	1902
Oct 2014	630 ^[1]	629 ^[2]
Jun 2016	1249 ^[3]	1251 ^[4]
Completed	1832	1826
Not completed	66	76
Consent withdrawn by subject	45	42
Lost to follow-up	12	-
Partial withdrew consent	9	18
Lost to follow-up	-	16

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones referred to are each of the Data Safety Monitoring Board committee meetings. At each meeting more patients had been recruited and therefore the milestones had increased.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones referred to are each of the Data Safety Monitoring Board committee meetings. At each meeting more patients had been recruited and therefore the milestones had increased.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones referred to are each of the Data Safety Monitoring Board committee meetings. At each meeting more patients had been recruited and therefore the milestones had increased.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones referred to are each of the Data Safety Monitoring Board committee meetings. At each meeting more patients had been recruited and therefore the milestones had increased.

Baseline characteristics

Reporting groups

Reporting group title	Hydrocortisone
Reporting group description: IV hydrocortisone 200 mg/day for 7 days or until death or discharge from ICU	
Reporting group title	Placebo
Reporting group description: placebo, for 7 days or until death or discharge from ICU	

Reporting group values	Hydrocortisone	Placebo	Total
Number of subjects	1898	1902	3800
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	948	924	1872
From 65-84 years	847	869	1716
85 years and over	58	67	125
Not recorded	45	42	87
Age continuous			
Units: years			
arithmetic mean	62.3	62.7	-
standard deviation	± 14.9	± 15.2	-
Gender categorical			
Units: Subjects			
Female	734	720	1454
Male	1119	1140	2259
Not recorded	45	42	87
Admission Type			
ICU admission diagnosis category			
Units: Subjects			
Medical	1273	1266	2539
Surgical	576	591	1167
Not recorded	49	45	94
Mechanical ventilation			
Baseline therapies			
Units: Subjects			
Yes	1845	1855	3700
No	4	2	6
Not recorded	49	45	94
Inotropes/vasopressors			
Baseline therapies			

Units: Subjects			
Yes	1843	1854	3697
No	10	6	16
Not recorded	45	42	87
Norepinephrine			
Baseline therapies			
Units: Subjects			
Yes	1823	1821	3644
No	30	39	69
Not recorded	45	42	87
Vasopressin			
Baseline therapies			
Units: Subjects			
Yes	280	321	601
No	1573	1539	3112
Not recorded	45	42	87
Epinephrine			
Baseline therapies			
Units: Subjects			
Yes	134	113	247
No	1719	1747	3466
Not recorded	45	42	87
Other baseline therapy			
Baseline therapies			
Units: Subjects			
Yes	157	173	330
No	1696	1687	3383
Not recorded	45	42	87
Antimicrobias use			
Baseline therapies			
Units: Subjects			
Yes	1817	1821	3638
No	31	36	67
Not recorded	50	45	95
Renal replacement therapy			
Baseline therapies			
Units: Subjects			
Yes	228	242	470
No	1621	1615	3236
Not recorded	49	45	94
Primary site of infection			
Baseline primary site of infection at admission diagnosis			
Units: Subjects			
Pulmonary	623	677	1300
Abdominal	477	467	944
Blood	316	325	641
Skin/soft tissue	137	116	253
Urinary	146	133	279
Others	145	136	281
Not recorded	54	48	102
Catecholamine dose			

Baseline catecholamine dose >15mcg/min			
Units: Subjects			
Yes	981	1013	1994
<15mcg/min	853	819	1672
Not recorded	64	70	134
Weight			
Units: kilogram(s)			
arithmetic mean	85.8	85.6	-
standard deviation	± 26.6	± 26.2	-
APACHE			
APACHE II Score			
Units: APACHE Units			
arithmetic mean	24	23	-
inter-quartile range (Q1-Q3)	19 to 29	18 to 29	-
Heart Rate			
Units: beats/min			
arithmetic mean	96	95	-
standard deviation	± 21.6	± 20.9	-
MAP			
Units: mmhg			
arithmetic mean	72.5	72.2	-
standard deviation	± 8.2	± 8.3	-
CVP			
Units: mmHg			
arithmetic mean	12.0	12.1	-
standard deviation	± 5.2	± 5.3	-
Lowest MAP			
Lowest MAP in prior 24hrs			
Units: mmHg			
arithmetic mean	57.3	57.1	-
standard deviation	± 8.5	± 9.1	-
Lactate			
Highest lactate (mg/dL) in prior 24hrs			
Units: mg/dL			
arithmetic mean	34.2	34.5	-
standard deviation	± 29.1	± 28.2	-
Bilirubin			
Highest bilirubin (mg/dL) in prior 24hrs			
Units: mg/dL			
arithmetic mean	1.7	1.7	-
standard deviation	± 2.4	± 2.4	-
Creatinine			
Highest creatinine (mg/dL) in prior 24 hours			
Units: mg/dL			
arithmetic mean	2.2	2.1	-
standard deviation	± 2.0	± 1.7	-
Lowest PaO2/FiO2			
Lowest PaO2/FiO2 in prior 24hrs			
Units: PaO2/FiO2 ratio			
arithmetic mean	164.6	166.4	-
standard deviation	± 91.3	± 91.9	-
Highest white cell count (10 ⁹ /L)			

Highest white cell count (10 ⁹ /L) in prior 24hrs			
Units: 10 ⁹ /L			
arithmetic mean	17.4	17.8	
standard deviation	± 11.4	± 14.7	-
ICU admission to randomization (hrs)			
ICU admission to randomization (hrs)			
Units: hour			
arithmetic mean	26.1	28.9	
standard deviation	± 70.7	± 72.8	-
Shock to randomization (hrs)			
Shock event onset to randomization (hrs)			
Units: hour			
arithmetic mean	20.9	21.2	
standard deviation	± 91.9	± 83.4	-

End points

End points reporting groups

Reporting group title	Hydrocortisone
Reporting group description:	IV hydrocortisone 200 mg/day for 7 days or until death or discharge from ICU
Reporting group title	Placebo
Reporting group description:	placebo, for 7 days or until death or discharge from ICU

Primary: 90-day mortality

End point title	90-day mortality
End point description:	
End point type	Primary
End point timeframe:	Mortality at 90 days after randomisation

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1832 ^[1]	1826 ^[2]		
Units: number				
Yes	511	526		

Notes:

[1] - missing subjects either withdrawn consent or lost to follow-up

[2] - missing subjects either withdrawn consent or lost to follow-up

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
Statistical analysis description:	Statistical analysis description The primary outcome is presented as the odds ratio (OR) of death and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3658
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.1
Variability estimate	Standard error of the mean

Secondary: 28-day Mortality

End point title	28-day Mortality
End point description:	
End point type	Secondary
End point timeframe:	
Mortality at 28 days after randomisation	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1841	1840		
Units: number				
Yes	410	448		

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
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Statistical analysis description:

The secondary outcome is presented as the odds ratio (OR) of death and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3681
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.03
Variability estimate	Standard error of the mean

Secondary: Reoccurrence of shock

End point title	Reoccurrence of shock
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End point description:

End point type	Secondary
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End point timeframe:

Reoccurrence of shock after randomisation

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: number				
Yes	365	343		

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
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Statistical analysis description:

Statistical analysis description The secondary outcome is presented as the odds ratio (OR) and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.22
Variability estimate	Standard error of the mean

Secondary: Reoccurrence of mechanical ventilation

End point title	Reoccurrence of mechanical ventilation
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End point description:

End point type	Secondary
End point timeframe:	
Reoccurrence of mechanical ventilation after randomisation	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1842	1850		
Units: number				
Yes	180	154		

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
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Statistical analysis description:

The secondary outcome is presented as the odds ratio (OR) and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3692
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.45
Variability estimate	Standard error of the mean

Secondary: Use of RRT

End point title	Use of RRT
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End point description:

End point type	Secondary
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End point timeframe:

Any use of renal replacement therapy after randomisation

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: number				
Yes	567	609		

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
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Statistical analysis description:

The secondary outcome is presented as the odds ratio (OR) and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.03
Variability estimate	Standard error of the mean

Secondary: New bacteremia of fungemia

End point title	New bacteremia of fungemia
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End point description:

End point type	Secondary
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End point timeframe:

New bacteremia of fungemia after randomisation

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: number				
Yes	262	262		

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
Statistical analysis description:	
The secondary outcome is presented as the odds ratio (OR) and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.	
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.16
Variability estimate	Standard error of the mean

Secondary: Blood transfusion

End point title	Blood transfusion
End point description:	
End point type	Secondary
End point timeframe:	
Any blood transfusion after randomisation	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1848	1855		
Units: number				
Yes	683	773		

Statistical analyses

Statistical analysis title	Logistic regression model with random effect
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Statistical analysis description:

Statistical analysis description The secondary outcome is presented as the odds ratio (OR) and the corresponding 95% confidence intervals (CI), analyzed using a logistic regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3703
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.94
Variability estimate	Standard error of the mean

Secondary: Days alive and free of ICU

End point title	Days alive and free of ICU
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End point description:

End point type	Secondary
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End point timeframe:

Days alive and free of ICU after randomisation

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: day				
arithmetic mean (standard deviation)	58.2 (± 34.8)	56.0 (± 35.4)		

Statistical analyses

Statistical analysis title	Generalized linear regression model with random ef
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Statistical analysis description:

The secondary outcome is presented as the mean difference and the corresponding 95% confidence intervals (CI), analyzed using a linear regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Placebo v Hydrocortisone
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Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Generalised linear model
Parameter estimate	Mean difference (final values)
Point estimate	2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	4.49
Variability estimate	Standard error of the mean

Secondary: Days alive and free of hospital

End point title	Days alive and free of hospital
End point description:	
End point type	Secondary
End point timeframe:	
Days alive and free of hospital after randomisation	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: day				
arithmetic mean (standard deviation)	40.0 (± 32.0)	38.6 (± 32.4)		

Statistical analyses

Statistical analysis title	Generalized linear regression model with random ef
Statistical analysis description:	
Generalized linear regression model with random effect. The secondary outcome is presented as the mean difference and the corresponding 95% confidence intervals (CI), analyzed using a linear regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.	
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Generalised linear model
Parameter estimate	Median difference (final values)
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	3.49
Variability estimate	Standard error of the mean

Secondary: Days alive and free of mechanical ventilation

End point title	Days alive and free of mechanical ventilation
End point description:	
End point type	Secondary
End point timeframe:	
Days alive and free of mechanical ventilation after randomisation	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: day				
arithmetic mean (standard deviation)	61.2 (\pm 35.6)	59.1 (\pm 36.1)		

Statistical analyses

Statistical analysis title	Generalized linear regression model with random ef
Statistical analysis description:	
The secondary outcome is presented as the mean difference and the corresponding 95% confidence intervals (CI), analyzed using a linear regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.	
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Generalised linear model
Parameter estimate	Mean difference (final values)
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	4.46
Variability estimate	Standard error of the mean

Secondary: Days alive and free of RRT

End point title	Days alive and free of RRT
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End point description:

End point type	Secondary
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End point timeframe:

Days alive and free of renal replacement therapy after randomisation

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1853	1860		
Units: day				
arithmetic mean (standard deviation)	42.6 (\pm 39.1)	40.4 (\pm 38.5)		

Statistical analyses

Statistical analysis title	Generalized linear regression model with random ef
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Statistical analysis description:

Generalized linear regression model with random effect. The secondary outcome is presented as the mean difference and the corresponding 95% confidence intervals (CI), analyzed using a linear regression adjusted for stratification variables with medical vs. surgical diagnosis as a fixed effect and site as a random effect.

Comparison groups	Placebo v Hydrocortisone
Number of subjects included in analysis	3713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Generalised linear model
Parameter estimate	Mean difference (final values)
Point estimate	2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	6.75
Variability estimate	Standard error of the mean

Secondary: Time to reversal of shock

End point title	Time to reversal of shock
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End point description:

End point type	Secondary
End point timeframe:	
Time to first shock reversal in days	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1843	1854		
Units: day				
number (not applicable)				
Yes	1634	1574		

Statistical analyses

Statistical analysis title	Cox regression model with random effect
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Statistical analysis description:

Time to event analysis was done using a Cox proportional hazard model including the randomized treatment arm, admission type and a random-center effect. Time-to-resolution were analyzed both by treating death as a competing risk and described using cumulative incidence function

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	3697
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Frailty regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	1.41
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the randomisation date to end of the 90th day from randomisation.

Adverse event reporting additional description:

Adverse Event form that is completed by the site and submitted to the Sponsor at the time of recognition of an adverse event.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	TGA Definition
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Dictionary version	1
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Reporting groups

Reporting group title	Hydrocortisone
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Reporting group description:

Hydrocortisone arm. Deaths were not recorded as a Serious Adverse Event as they were the primary outcome of the study.

Reporting group title	Placebo
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Reporting group description:

Placebo arm. Deaths were not recorded as a Serious Adverse Event as they were the primary outcome of the study.

Serious adverse events	Hydrocortisone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 1853 (0.22%)	2 / 1860 (0.11%)	
number of deaths (all causes)	511	526	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Abdominal-wound dehiscence			
subjects affected / exposed	0 / 1853 (0.00%)	1 / 1860 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myopathy			
subjects affected / exposed	1 / 1853 (0.05%)	0 / 1860 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory Shock			

subjects affected / exposed	1 / 1853 (0.05%)	0 / 1860 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bleeding			
subjects affected / exposed	0 / 1853 (0.00%)	1 / 1860 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ischemic bowel			
subjects affected / exposed	1 / 1853 (0.05%)	0 / 1860 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Hydrocortisone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 1853 (0.92%)	4 / 1860 (0.22%)	
Blood and lymphatic system disorders			
Hypernatraemia			
subjects affected / exposed	3 / 1853 (0.16%)	0 / 1860 (0.00%)	
occurrences (all)	3	0	
Hyperchloraemia			
subjects affected / exposed	1 / 1853 (0.05%)	0 / 1860 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	3 / 1853 (0.16%)	0 / 1860 (0.00%)	
occurrences (all)	0	0	
Bleeding			
subjects affected / exposed	2 / 1853 (0.11%)	0 / 1860 (0.00%)	
occurrences (all)	0	0	
Leukocytosis			
subjects affected / exposed	2 / 1853 (0.11%)	0 / 1860 (0.00%)	
occurrences (all)	0	0	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	1 / 1853 (0.05%) 0	0 / 1860 (0.00%) 0	
General disorders and administration site conditions			
Encephalopathy			
subjects affected / exposed	3 / 1853 (0.16%)	0 / 1860 (0.00%)	
occurrences (all)	0	0	
Miscellaneous			
subjects affected / exposed	0 / 1853 (0.00%)	1 / 1860 (0.05%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 1853 (0.32%)	3 / 1860 (0.16%)	
occurrences (all)	6	3	
Infections and infestations			
Septic arthritis			
subjects affected / exposed	1 / 1853 (0.05%)	0 / 1860 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/29347874>