Clinical trial results:
Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia: The COVID STEROID randomised, placebo-controlled trial

Summary

EudraCT number	2020-001395-15
Trial protocol	DK
Global end of trial date	12 June 2021

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	v. 2.1, date 12.05.2020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04348305
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Intensive Care, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Prof. Anders Perner, Department of Intensive Care, Copenhagen University Hospital - Rigshospitalet, Denmark, +45 35458333, contact@cric.nu
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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	14 October 2021
Is this the analysis of the primary	No

completion data?	
Global end of trial reached?	Yes
Global end of trial date	12 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess benefits and harms of low dose IV hydrocortisone versus placebo on patient-important outcome measures in adult patients with COVID-19 and severe hypoxia.

Protection of trial subjects:

Patients with COVID-19 and severe hypoxia are at high risk of death. When this trial was initiated, there was no proven treatment for COVID-19; the care was only supportive, including respiratory and circulatory support. For other patient groups with similar critical illnesses, lower dose corticosteroids were used because they mitigate critical illness and potentially also mortality without serious adverse reactions. Therefore, there was reason to believe that similar positive effects could be obtained in patients with COVID-19 and severe hypoxia without serious adverse reactions.
The trial was conducted to the highest of methodological standards with ongoing assessment of the known serious adverse reactions to corticosteroid and three planned interim analyses. The control group received placebo and best clinical care without corticosteroids as was recommended for these patients in Denmark at that time.
The trial was ended prematurely due to the results from a WHO-initiated prospective meta-analysis of ongoing or recently completed trials demonstrating benefit from systemic corticosteroids on 28-day mortality in critically ill patients with COVID-19, which in turn led to an update in the guideline from the WHO strongly recommending the use of systemic corticosteroids for patients with severe or critical COVID-19.

Background therapy:

All other treatments than the trial drug were at the discretion of the treating clinicians.

Evidence for comparator:

Placebo

Actual start date of recruitment	15 April 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	19
From 65 to 84 years	8
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

We recruited patients from 15 April 2020 to 16 June 2020.

Pre-assignment

Screening details:

We screened adult patients (18 years or above) with confirmed SARS-CoV-2 infection and severe hypoxia (i.e., use of invasive mechanical ventilation, NIV, or continuous
use of CPAP for hypoxia, or oxygen supplementation with an oxygen flow of at least 10 L/min). We screened 67, excluded 37, and randomised 30 patients.

Period 1

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

Blinding implementation details:

The Management Committee, investigators, trial site staff registering outcome data, trial statistician, clinical staff, relatives, and patients were all blinded to the allocation. Trial medication was prepared daily using shelf-medication by unblinded staff (medical students and/or research nurses and doctors). The unblinded staff were not involved in the care of patients, outcome data entry, or statistical analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Hydrocortisone

Arm description:

Intravenous hydrocortisone 200 mg per day for 7 days

Arm type	Experimental
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	H02AB09
Other name	Solu-Cortef
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/day given as continuous infusion over 24 hours or bolus injection (50 mg per bolus) every 6 hours.

Arm title	Placebo

Arm description:

Isotonic saline for 7 days

Arm type	Placebo
Investigational medicinal product name	Sodium Chloride
Investigational medicinal product code	B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Continuous infusion over 24 hours or as bolus injections every 6 hours for 7 days.

Number of subjects in period 1	Hydrocortisone	Placebo
Started	16	14
Completed	14	13
Not completed	2	1
Physician decision	1	-
Withdrew from active therapy	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Hydrocortisone
Reporting group description:	
Intravenous hydrocortisone 200 mg per day for 7 days	
Reporting group title	Placebo
Reporting group description:	
Isotonic saline for 7 days	

Reporting group values	Hydrocortisone	Placebo	Total
Number of subjects	16	14	30
Age categorical Units: Subjects			
Adults (18-64 years)	11	8	19
From 65-84 years	4	4	8
85 years and over	1	2	3
Not recorded	0	0	0
Age continuous			
Age in years at the time of randomisation			
Units: years			
median	59	62	
inter-quartile range (Q1-Q3)	52 to 74	55 to 71	-
Gender categorical Units: Subjects			
Female	2	4	6
Male	14	10	24

End points

End points reporting groups

Reporting group title	Hydrocortisone
Reporting group description:	
Intravenous hydrocortisone 200 mg per day for 7 days	
Reporting group title	Placebo
Reporting group description:	
Isotonic saline for 7 days	

Primary: Days alive without life support at day 28

End point title	Days alive without life support at day 28
End point description:	
Days alive without the use of life support (i.e., invasive mechanical ventilation, circulatory support, or renal replacement therapy, including days in between intermittent renal replacementtherapy)	
End point type	Primary
End point timeframe:	
From randomisation to day 28.	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Days				
median (inter-quartile range (Q1-Q3))	7 (2 to 24)	10 (3 to 26)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Linear regression adjusted for invasive mechanical ventilation and age below 70 years. We were unable to adjust for site due to the reduced sample size.	
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 0.79
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5

upper limit	7.3

Notes:

[1] - We had to conduct another statistical analysis than the pre-planned due to the reduced sample size.

Secondary: Number of patients with one or more serious adverse reactions at day 14

End point title	Number of patients with one or more serious adverse reactions at day 14

End point description:

Number of patients with one or more serious adverse reactions (i.e., new episodes of septic shock, invasive fungal infection, clinically important gastrointestinal bleeding, or anaphylactic reaction).

End point type	Secondary

End point timeframe:

From randomisation to day 14

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Number	1	0		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: All-cause mortality at day 28

End point title	All-cause mortality at day 28

End point description:

All-cause mortality

End point type	Secondary

End point timeframe:

From randomisation to day 28

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Number	6	2		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Unadjusted generalised linear model with log link and binomial error distribution	
Comparison groups	Placebo v Hydrocortisone
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.19
Method	GLM log link/binomial error distrib.
Parameter estimate	Risk ratio (RR)
Point estimate	2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	16.03

Secondary: All-cause mortality at day 90

End point title	All-cause mortality at day 90
End point description: All-cause mortality	
End point type	Secondary
End point timeframe: From randomisation to day 90	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Number	7	3		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	

Unadjusted generalised linear model with log link and binomial error distribution.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	GLM log link/binomial error distrib.
Parameter estimate	Risk ratio (RR)
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	8.16

Secondary: Days alive without life support at day 90

End point title	Days alive without life support at day 90

End point description:

Days alive without the use of life support (i.e., invasive mechanical ventilation, circulatory support, or renal replacement therapy, including days in between intermittent renal replacement therapy)

End point type	Secondary

End point timeframe:

From randomisation to day 90

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Days				
median (inter-quartile range (Q1-Q3))	41 (6 to 86)	72 (52 to 88)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 (y/n).

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.25
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-14.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.4
upper limit	10.9

Secondary: Days alive and out of hospital at day 90

End point title	Days alive and out of hospital at day 90
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to day 90.	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Days				
median (inter-quartile range (Q1-Q3))	31 (8 to 78)	53 (42 to 68)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 (y/n).	
Comparison groups	Placebo v Hydrocortisone
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.57
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.6
upper limit	16.7

Secondary: All-cause mortality at 1 year

End point title	All-cause mortality at 1 year

End point description: All-cause mortality	
End point type	Secondary
End point timeframe: From randomisation to 1 year.	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	14		
Units: Number	8	3		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Unadjusted generalised linear model with log link and binomial error distribution.	
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	GLM log link/binomial error distrib.
Parameter estimate	Risk ratio (RR)
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	9.17

Secondary: EQ-VAS

End point title	EQ-VAS
End point description: Health-related quality of life assessed by EQ-VAS	
End point type	Secondary
End point timeframe: At 1 year	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: mm				
median (inter-quartile range (Q1-Q3))	27.5 (0.0 to 75.0)	60.0 (15.0 to 67.5)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
EQ-VAS ranges from 0-100 mm. Analysed using a linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 years (y/n).	
Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.61
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.5
upper limit	23

Secondary: EQ-5D-5L index value

End point title	EQ-5D-5L index value
End point description:	
EQ-5D-5L index value are anchored at 1 (perfect health) and 0 (health state as bad as being dead) with negative values representing health states worse than death.	
End point type	Secondary
End point timeframe:	
At 1 year.	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	11		
Units: Index value				
median (inter-quartile range (Q1-Q3))	0.3 (0.0 to 0.9)	0.6 (0.2 to 0.8)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Analysed using a linear regression adjusted for invasive mechanical ventilation (y/n) and age below 70 years (y/n).

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.61
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.25

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomisation to day 14.

Adverse event reporting additional description:

Serious adverse reactions were a predefined outcome in the trial. The following SARs occured in the two reporting groups:
Hydrocortisone: septic shock 1/16
Placebo: septic shock 0/14

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: We only recorded serious adverse reactions and serious adverse events in the trial. No non-serious adverse events were recorded, but the patient charts contain daily registrations of clinical data, which can be obtained on request from the medical authorities.

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? Yes

Date	Interruption	Restart date
16 June 2020	Enrolment paused due to external evidence reporting benefit from systemic corticosteroids on 28-day mortality in hospitalised patients with COVID-19	03 September 2020
03 September 2020	Enrolment terminated due to update in the guideline from the WHO strongly recommending systemic corticosteroids for patients with severe or critical COVID-19	-

Notes:

Limitations and caveats

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

Highly uncertain results due to the reduced sample size (3% of the planned sample size).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34138478

http://www.ncbi.nlm.nih.gov/pubmed/35067914