Clinical trial results:
Higher vs. Lower Doses of Dexamethasone in Patients with COVID-19 and Severe Hypoxia: the COVID STEROID 2 trial

Summary

EudraCT number	2020-003363-25
Trial protocol	DK
Global end of trial date	16 November 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	v. 1.9, date 27.01.2021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04509973
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Department of Intensive Care, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
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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	01 February 2022

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of higher (12 mg) vs lower doses (6 mg) of intravenous dexamethasone on the number of days alive without life-support in adult patients with COVID-19 and severe hypoxia.

Protection of trial subjects:

The RECOVERY trial (doi: 10.1056/NEJMoa2021436) reported a reduction in 28-day mortality with low-dose dexamethasone (6 mg) for hospitalised patients with suspected or confirmed COVID-19. Yet, higher doses were used in the other trials of corticosteroids in COVID-19 (median dose 12 mg).
We surveyed 278 doctors at COVID STEROID 2 trial sites on their clinical preferences for corticosteroid use in patients with COVID-19. The dose preference varied with 56% of 240 responders preferring a dose of 6 mg of dexamethasone or equivalent, and 36% of 240 responders preferring doses higher than 6 mg of dexamethasone or equivalent (doi: 10.1111/aas.13941). Most would enrol patients in a future trial comparing a higher vs lower dose of dexamethasone, primarily into one comparing 12 mg vs 6 mg of dexamethasone (55% of 237 responders) (doi: 10.1111/aas.13941).
Taken together, it was unclear which dose of dexamethasone was most beneficial to COVID-19, and clinical equipoise existed among clinicians and researchers.
The trial was conducted to the highest of methodological standards with ongoing assessment of the known serious adverse reactions to corticosteroid, including a planned interim analysis. Any serious adverse reactions for single participants and the group of participants receiving higher vs. lower dose of dexamethasone was assessed and handled.

Background therapy:

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

Evidence for comparator:

The control group received the exact same protocol as in the RECOVERY trial (i.e., 6 mg of dexamethasone daily for 10 days) in addition to usual clinical care.

Actual start date of recruitment	27 August 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 79
Country: Number of subjects enrolled	Denmark: 485
Country: Number of subjects enrolled	India: 369
Country: Number of subjects enrolled	Switzerland: 49
Worldwide total number of subjects	982
EEA total number of subjects	564

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)	491
From 65 to 84 years	471
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

We recruited patients from 27 August 2020 to 20 May 2021.

Pre-assignment

Screening details:

We screened adult patients (18 years or above) with confirmed SARS-CoV-2 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 1414, excluded 414, randomised 1000, and included 982 patients in the analyses.

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	12 mg of dexamethasone

Arm description:

12 mg of dexamethasone (14.4 mg dexamethasone phosphate) suspended in sodium chloride 0.9% and administered as a masked bolus injection (5 mL) intravenously once daily for up to 10 days from randomisation.

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	H02AB02
Other name	Dexavit
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

12 mg per day as bolus injection once daily for up to 10 days after randomisation. Used at all sites but one Swedish site that used betamethasone instead.

Investigational medicinal product name	Betamethasone
Investigational medicinal product code	H02AB02
Other name	Betapred
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

12 mg of betamethasone as bolus injection once daily for up to 10 days after randomisation. Only used at one Swedish site, where dexamethasone was not available.

Arm title	6 mg of dexamethasone

Arm description:

6 mg of dexamethasone (7.2 mg dexamethasone phosphate) suspended in sodium chloride 0.9% and administered as a masked bolus injection (5 mL) intravenously once daily for up to 10 days from randomisation.

Arm type	Active comparator

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	H02AB02
Other name	Dexavit
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

6 mg per day as bolus injection once daily for up to 10 days after randomisation. Used at all sites but one Swedish site that used betamethasone instead.

Investigational medicinal product name	Betamethasone
Investigational medicinal product code	H02AB02
Other name	Betapred
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

6 mg of betamethasone as bolus injection once daily for up to 10 days after randomisation. Only used at one Swedish site, where dexamethasone was not available.

Number of subjects in period 1	12 mg of dexamethasone	6 mg of dexamethasone
Started	497	485
Completed	461	446
Not completed	36	39
Protocol deviation	36	39

Baseline characteristics

Reporting groups	
Reporting group title	12 mg of dexamethasone
Reporting group description:	
12 mg of dexamethasone (14.4 mg dexamethasone phosphate) suspended in sodium chloride 0.9% and administered as a masked bolus injection (5 mL) intravenously once daily for up to 10 days from randomisation.	
Reporting group title	6 mg of dexamethasone
Reporting group description:	
6 mg of dexamethasone (7.2 mg dexamethasone phosphate) suspended in sodium chloride 0.9% and administered as a masked bolus injection (5 mL) intravenously once daily for up to 10 days from randomisation.	

Reporting group values	12 mg of dexamethasone	6 mg of dexamethasone	Total
Number of subjects	497	485	982
Age categorical Units: Subjects			
Adults (18-64 years)	248	243	491
From 65-84 years	239	232	471
85 years and over	10	10	20
Not reported	0	0	0
Age continuous			
Age at the time of randomisation.			
Units: years			
median	65	64	
inter-quartile range (Q1-Q3)	56 to 74	54 to 72	-
Gender categorical Units: Subjects			
Female	151	154	305
Male	346	331	677

End points

End points reporting groups

Reporting group title	12 mg of dexamethasone
Reporting group description:	
12 mg of dexamethasone (14.4 mg dexamethasone phosphate) suspended in sodium chloride 0.9% and administered as a masked bolus injection (5 mL) intravenously once daily for up to 10 days from randomisation.	
Reporting group title	6 mg of dexamethasone
Reporting group description:	
6 mg of dexamethasone (7.2 mg dexamethasone phosphate) suspended in sodium chloride 0.9% and administered as a masked bolus injection (5 mL) intravenously once daily for up to 10 days from randomisation.	

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 replacement therapy).	
End point type	Primary
End point timeframe:	
From randomisation to day 28.	

End point values	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	480		
Units: Days				
median (inter-quartile range (Q1-Q3))	22.0 (6.0 to 28.0)	20.5 (4.0 to 28.0)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
P-value calculated using the Kryger Jensen and Lange test adjusted for stratification variables (site, age younger than 70 years, and use of invasive mechanical ventilation). The mean difference and confidence interval were calculated using an adjusted linear regression and bootstrapping with 50,000 resamples.	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	971
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Kryger Jensen and Lange test

Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.6

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	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	489	478		
Units: Days				
median (inter-quartile range (Q1-Q3))	84.0 (9.3 to 90.0)	80.0 (6.0 to 90.0)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

P-value calculated using the Kryger Jensen and Lange test adjusted for stratification variables (site, age younger than 70 years, and use of invasive mechanical ventilation).
The mean difference and confidence interval were calculated using an adjusted linear regression and bootstrapping with 50,000 resamples.

Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	967
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	Kryger Jensen and Lange test
Parameter estimate	Mean difference (final values)
Point estimate	4.4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1.6

upper limit	10.4

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	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490	478		
Units: Days				
median (inter-quartile range (Q1-Q3))	61.5 (0.0 to 78.0)	48.0 (0.0 to 76.0)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
P-value calculated using the Kryger Jensen and Lange test adjusted for stratification variables (site, age younger than 70 years, and use of invasive mechanical ventilation). The mean difference and confidence interval were calculated using an adjusted linear regression and bootstrapping with 50,000 resamples.	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	968
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Kryger Jensen and Lange test
Parameter estimate	Mean difference (final values)
Point estimate	4.1
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-1.3
upper limit	9.5

Secondary: Mortality at day 28

End point title	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	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	480		
Units: Number	133	155		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Logistic regression adjusted for the stratification variables and g-computation.	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	971
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.1
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.68
upper limit	1.08

Secondary: Mortality at day 90

End point title	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	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490	478		
Units: Number	157	180		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Logistic regression adjusted for the stratification variables and g-computation.	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	968
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.09
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.87
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.7
upper limit	1.07

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

End point title	Number of patients with one or more serious adverse reactions
End point description:	
The number of patients with 1 or more serious adverse reactions (i.e., new episodes of septic shock, invasive fungal infection, clinically important gastrointestinal bleeding, or anaphylactic reaction to dexamethasone).	
End point type	Secondary
End point timeframe:	
From randomisation to day 28	

End point values	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	485		
Units: Number	56	65		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Logistic regression adjusted for the stratification variables and g-computation.	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	982
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.27
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.83
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.54
upper limit	1.29

Secondary: Mortality at day 180

End point title	Mortality at day 180
End point description:	
All-cause mortality	
End point type	Secondary
End point timeframe:	
From randomisation to day 180.	

End point values	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	486	477		
Units: Number	164	184		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Logistic regression adjusted for the stratification variables and g-computation.	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	963
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.13
Method	Regression, Logistic

Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	0.72
upper limit	1.09

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 day 180.	

End point values	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	485		
Units: mm				
median (inter-quartile range (Q1-Q3))	65 (0 to 90)	55 (0 to 85)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
P-value calculated using the Kryger Jensen and Lange test adjusted for stratification variables (site, age younger than 70 years, and use of invasive mechanical ventilation). The mean difference and confidence interval were calculated using an adjusted linear regression and bootstrapping with 50,000 resamples. Non-survivors were assigned the worst possible value (i.e., 0 mm). Data from non-responders were multiply imputed (n = 58).	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	982
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Kryger Jensen and Lange test
Parameter estimate	Mean difference (final values)
Point estimate	4
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-3

upper limit	10

Secondary: EQ-5D-5L index value

End point title	EQ-5D-5L index value
End point description:	
Health-related quality of life assessed by the EQ-5D-5L index values.	
End point type	Secondary
End point timeframe:	
At day 180.	

End point values	12 mg of dexamethasone	6 mg of dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	497	485		
Units: Index value				
median (inter-quartile range (Q1-Q3))	0.80 (0.0 to 0.97)	0.68 (0.0 to 0.95)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
P-value calculated using the Kryger Jensen and Lange test adjusted for stratification variables (site, age younger than 70 years, and use of invasive mechanical ventilation). The mean difference and confidence interval were calculated using an adjusted linear regression and bootstrapping with 50,000 resamples. Non-survivors were assigned scores of zero corresponding to a health state equivalent to death for EQ-5D-5L index values. Data from non-responders were multiply imputed (n = 60).	
Comparison groups	12 mg of dexamethasone v 6 mg of dexamethasone
Number of subjects included in analysis	982
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Kryger Jensen and Lange test
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	Other: 99 %
sides	2-sided
lower limit	-4
upper limit	4

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomisation to day 28.

Adverse event reporting additional description:

For SARs and SAEs, refer to Table 2 and Supplement 2, eTable 10.
Link:
https://jamanetwork.com/journals/jama/fullarticle/2785529?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jama.2021.18295

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? Yes

Date	Amendment
09 January 2021	We generally recommended against the use of other immunosuppresive agents during the intervention period. However, after 9 January 2021, we allowed the use of interleukin 6 (IL-6) inhibitors after the publications of the results from the IL-6 inhibitor domain of the REMAP-CAP trial (doi: 10.1056/NEJMoa2100433).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Changes in the treatment of COVID-19 during the course of the trial. Intervention period varied from 6-10 days according to the number of days of steroid treatment before randomisation (max 4 days allowed). Both may have influenced the trial results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34673895