Clinical trial results:
USE OF GLUCOCORTICOIDS IN PATIENTS WITH SARS-COV-2 CORONAVIRUS INFECTION. Pragmatic trial inserted in real practice during a pandemic.

Summary

EudraCT number	2020-005026-28
Trial protocol	ES
Global end of trial date	09 November 2021

Results information

Result version number	v1 (current)
This version publication date	08 January 2023
First version publication date	08 January 2023

Trial information

Trial identification

Sponsor protocol code	GLUCOCOVID-bolus

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04780581
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación IECSCYL-IBSAL.
Sponsor organisation address	Hospital Universitario de Salamanca Edificio Virgen de la Vega, 10.ª planta Pº San Vicente, 55-182, Salamanca, Spain, 37007
Public contact	Clinical Trial Area, IBSAL, 34 9232911005779, esperanza.lopez@scren.es
Scientific contact	Clinical Trial Area, IBSAL, 34 9232911005779, esperanza.lopez@scren.es

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	19 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2021
Global end of trial reached?	Yes
Global end of trial date	09 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of high-dose methylprednisolone bolus administration against the intermediate-dose dexamethasone pattern (RECOVERY trial) in COVID-19 patients with non-critical respiratory failure.

Protection of trial subjects:

Adequate information of each patient and efficient monitoring of treatment safety through pharmacovigilance.

Background therapy:

Standard of therapy for severe SARS-CoV-2 infection.

Evidence for comparator: -

Actual start date of recruitment	15 December 2020
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	Spain: 125
Worldwide total number of subjects	125
EEA total number of subjects	125

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)	74
From 65 to 84 years	46
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Eligible patients were those aged 18 years or older, hospitalized with confirmed SARS-CoV-2 infection, with evidence of pulmonary involvement in radiology, and who required supplementary oxygen

Pre-assignment

Screening details:

Patient were excluded if the patient's situation is so serious that the doctor in charge thinks he could die within 24 hours, patients require one of the following 4 ventilatory supports at the time of randomisation.

Period 1

Period 1 title	Completed (28 d)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	250 mg methylprednisolone

Arm description:

High dose GC

Arm type	Experimental
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	H02AB04
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Intravenous use

Dosage and administration details:

Daily intravenous pulse with methylprednisolone 250 mg (equivalence to 46.9 mg of dexamethasone) for 3 days. There was no placebo from days 4 to 10 for patients in the methylprednisolone group.

Arm title	6 mg dexamethasone

Arm description:

RECOVERY trial

Arm type	Active comparator
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	H02AB02
Other name	
Pharmaceutical forms	Suspension for oral suspension, Tablet
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

daily dose of 6 mg of dexamethasone (equivalence to 32 mg of methylprednisolone) for up to 10 days. For the dexamethasone group, the first 3 days of treatment were intravenous (7.2 mg of dexamethasone phosphate).

Number of subjects in period 1	250 mg methylprednisolone	6 mg dexamethasone
Started	63	62
Completed	63	62

Period 2

Period 2 title	Completed (90 d)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Centralized, web based (https://www.sharecrf.com/)

Arms

Are arms mutually exclusive?	Yes
Arm title	250 mg methylprednisolone

Arm description:

High dose GC

Arm type	Experimental
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	H02AB04
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Intravenous use

Dosage and administration details:

Daily intravenous pulse with methylprednisolone 250 mg (equivalence to 46.9 mg of dexamethasone) for 3 days. There was no placebo from days 4 to 10 for patients in the methylprednisolone group.

Arm title	6 mg dexamethasone

Arm description:

RECOVERY trial

Arm type	Active comparator
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	H02AB02
Other name	
Pharmaceutical forms	Suspension for oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

daily dose of 6 mg of dexamethasone (equivalence to 32 mg of methylprednisolone) for up to 10 days. For the dexamethasone group, the first 3 days of treatment were intravenous (7.2 mg of dexamethasone phosphate).

Number of subjects in period 2	250 mg methylprednisolone	6 mg dexamethasone
Started	63	62
Completed	63	60
Not completed	0	2
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	250 mg methylprednisolone
Reporting group description:	
High dose GC	
Reporting group title	6 mg dexamethasone
Reporting group description:	
RECOVERY trial	

Reporting group values	250 mg methylprednisolone	6 mg dexamethasone	Total
Number of subjects	63	62	125
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)	37	37	74
From 65-84 years	23	23	46
85 years and over	3	2	5
Age continuous			
Units: years			
arithmetic mean	59.81	58.73	
standard deviation	± 16.90	± 16.01	-
Gender categorical			
Units: Subjects			
Female	20	21	41
Male	43	41	84

Subject analysis sets	
Subject analysis set title	Intention to treat patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat patients	

Reporting group values	Intention to treat patients		
Number of subjects	125		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	74		
From 65-84 years	46		
85 years and over	5		
Age continuous			
Units: years			
arithmetic mean	59.27		
standard deviation	± 16.41		
Gender categorical			
Units: Subjects			
Female	41		
Male	84		

End points

End points reporting groups

Reporting group title	250 mg methylprednisolone
Reporting group description: High dose GC	
Reporting group title	6 mg dexamethasone
Reporting group description: RECOVERY trial	
Reporting group title	250 mg methylprednisolone
Reporting group description: High dose GC	
Reporting group title	6 mg dexamethasone
Reporting group description: RECOVERY trial	
Subject analysis set title	Intention to treat patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention to treat patients	

Primary: Mortality within 28 d

End point title	Mortality within 28 d
End point description:	
End point type	Primary
End point timeframe: 28 days	

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	3	3		

Statistical analyses

Statistical analysis title	Primary outcome of 28-day mortality

Statistical analysis description:

For the primary outcome of 28-day mortality, we used the log-rank statistic to test the null hypothesis of equal survival curves. Time-to-event secondary outcomes and the composite outcome were compared between the two groups with the Kaplan–Meier approach.

Comparison groups	250 mg methylprednisolone v 6 mg dexamethasone

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Logrank
Parameter estimate	Log risk ratio

Notes:
[1] - log-rank statistic

Secondary: Admission to intensive care unit within 28 d

End point title	Admission to intensive care unit within 28 d

End point description:

End point type	Secondary

End point timeframe:
28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: subjects	10	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Tracheal intubation within 28d

End point title	Tracheal intubation within 28d

End point description:

End point type	Secondary

End point timeframe:
28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Non-invasive respiratory support within 28d

End point title	Non-invasive respiratory support within 28d

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: High-flow oxygen support within 28d

End point title	High-flow oxygen support within 28d

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	6	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Additional immunosuppressive drugs within 28d

End point title	Additional immunosuppressive drugs within 28d

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	14	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay

End point title	Length of stay

End point description:

End point type	Secondary

End point timeframe:

28 Days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: day				
arithmetic mean (standard deviation)	13 (± 15)	13 (± 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality within 90 d

End point title	Mortality within 90 d

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	60		
Units: subjects	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical evaluation of patient status according to the WHO 10-category scale

End point title	Clinical evaluation of patient status according to the WHO 10-category scale

End point description:

Clinical evaluation of patient status according to the WHO 10-category scale. Minimum value: 1 and maximum value:
10, higher scores mean a worse outcome.

1. Asymptomatic
2. Symptomatic, independent
3. Symptomatic, assistance needed
4. Hospitalized, no oxygen therapy
5. Hospitalized, mask or nasal prongs
6. Hospitalized, NIV o high flow
7. Intubation PaFi >150
8. Intubation PaFI <150 or vasopressors
9. Intubation PaFi <150 plus vasopressors or ECMO or dialysis
10. Dead

End point type	Secondary

End point timeframe:
90 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	60		
Units: subjects				
CAT 1	42	38		
CAT 2	13	14		
CAT 3	0	3		
CAT 4	2	0		
CAT 5	1	0		
CAT 6	0	0		
CAT 7	0	1		
CAT 8	0	0		
CAT 9	0	0		
CAT 10	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary infections within 28d

End point title	Secondary infections within 28d

End point description:

End point type	Secondary

End point timeframe:
28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Hyperglycaemia within 28d

End point title	Hyperglycaemia within 28d

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	17	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Psychotic states within 28d

End point title	Psychotic states within 28d

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	250 mg methylprednisolone	6 mg dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 90 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Treated
Reporting group description: patients on Methyprednisolone 250 mg intravenous per day x 3 days	
Reporting group title	Active group
Reporting group description: control group, patients on RECOVERY scheme of treatment with dexamethasone 6 mg per day x 10 days	

Serious adverse events	Treated	Active group	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 63 (34.92%)	21 / 62 (33.87%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events	6	4	
Vascular disorders			
Thromboembolism			
subjects affected / exposed	1 / 63 (1.59%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	1 / 63 (1.59%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			

subjects affected / exposed	7 / 63 (11.11%)	7 / 62 (11.29%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
COVID worsening			
subjects affected / exposed	9 / 63 (14.29%)	9 / 62 (14.52%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 4	0 / 3	
Pneumonia (no COVID)			
subjects affected / exposed	6 / 63 (9.52%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treated	Active group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 63 (39.68%)	15 / 62 (24.19%)	
Cardiac disorders			
Arial fibrillation			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Heart failure			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			

Systemic blood hypertension			
subjects affected / exposed	2 / 63 (3.17%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Thrombotic disorders			
subjects affected / exposed	1 / 63 (1.59%)	2 / 62 (3.23%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Respiratory function worsening			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	
occurrences (all)	0	1	
Tracheo-bronchitis			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	
occurrences (all)	1	1	
Psychiatric disorders			
Depressive anxiety disorder, confusion or depression			
subjects affected / exposed	3 / 63 (4.76%)	1 / 62 (1.61%)	
occurrences (all)	3	1	
Endocrine disorders			
Hyperglycaemia			
subjects affected / exposed	15 / 63 (23.81%)	6 / 62 (9.68%)	
occurrences (all)	15	6	

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
15 August 2021	The impact of vaccination programmes during early 2021 in Spain dramatically changed the characteristics of hospitalized patients with COVID-19. As older persons were prioritized for vaccination, an impressive decline occurred in the number of hospital admissions for patients aged over 70 years, resulting in a spectacular decrease in mortality rates. Taking this into consideration, our initial estimation for sample size calculation was outdated. In addition to the high percentage of people vaccinated in Spain32, in the summer of 2021 was the end of the fifth wave of COVID-19, with a very small number of patients hospitalized, so the clinical trial committee decided to conditionally stop the trial in August 2021.	-

Notes:

Limitations and caveats

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

The investigators considered that continuing the trial would be unlikely to change the results, so the trial was definitively stopped.

Notes: