Supplementary Results

Supplementary Results for the manuscript Entitled:

Effect of high vs low dose of dexamethasone on clinical worsening in patients hospitalized with moderate or severe COVID-19 Pneumonia: an open-label, randomized clinical trial.

This supplement contains supplementary results

Trial registration:

The trial was approved January 14, 2021, by the Spanish Agency of Medicines and Health Products (AEMPS, Nº EudraCT 2020-005702-25)

The trial was approved January 13, 2021, by the Ethics Committee of Galicia, Spain. (CEIm-G, code No. 2020-636).

Registered in clinicaltrials.gov: NCT04726098.
https://clinicaltrials.gov/ct2/show/record/NCT04726098
term=dexamethasone&cond=Covid19&cntry=ES&draw=2&rank=1

Keywords: COVID-19, SARS-CoV-2, acute respiratory distress (ARDS), corticosteroids, dexamethasone, failure respiratory, randomized clinical trial.

Effect of high vs low dose of dexamethasone on clinical worsening in patients hospitalized with moderate or severe COVID-19 Pneumonia: an open-label, randomized clinical trial.

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In ClinicalTrials.gov there is an 8-day delay between the start of recruitment and study registration
These were the dates and the reason for the delay:

1. On December 2, 2020, the trial protocol (Nº EudraCT: 2020-005702-25) was sent to the "Galicia (Spain) Drug Research Ethics Committee" requesting permission to conduct the clinical trial urgently due to the serious situation that was being experienced in Spain with COVID-19.
2. On December 18, 2020, the trial protocol was sent to the "The Spanish Agency of Medicines and Medical Devices" (AEMPS) requesting permission to conduct the clinical trial urgently due to the serious situation that was being experienced in Spain with COVID-19.
3. On January 13, 2021, the "Galicia (Spain) Drug Research Ethics Committee" authorizes to carry out the clinical trial with registration number: : 2020/636.
4. On January 14, 2021, The Spanish Agency of Medicines and Medical Devices" (AEMPS), authorizes to carry out the clinical trial (Nº EudraCT 2020-005702-25).
5. On January 15, 2021, (Friday), starting the third wave (COVID-19) in Spain, we decided to urgently start the recruitment of patients in the trial as well as register them in "clinical trials gov", after having been authorized by the two institutions that oblige in Spain, the "Galicia (Spain) Drug Research Ethics Committee" and the "The Spanish Agency of Medicines and Medical Devices" (AEMPS).
6. On January 15, 2021 (11:15) (Friday) we sent an email to register@clinicaltrials.gov,, requesting login information to register the trial.
7. On January 15, 2021 (12.49), (Friday) register@clinicaltrials.gov sent us an email with the login to access clinicaltrials.gov and to register the trial. This email
8. On January 18, 2021 (Monday) we found the email sent by register@clinicaltrials.gov with the Login to access to the clinicaltrials.gov. The message was flagged as spam. During the week of January 18-24, the data from the clinical trial (Study Description, Study Design, Outcome Measures, Eligibility Criteria, other information...) were incorporated in "clinical trials gov" and it was finally registered.
9. The first patient was enrolled on January 15 in the afternoon. Second patient on January 16. Third patient on January 18. Six patients were randomized before January 23. When the trial was registered in clinicaltrials gov, the trial was registered as in the "recruitment phase" and the registered *study start date* in ClinicalTrials.gov was January 15th.

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1. Background

After RECOVERY trial publication, low dose (6 mg dexamethasone for 10 days) was recommended as the usual care treatment in hospitalized patients with respiratory failure by COVID-19 needing oxygen therapy. At present, it is unclear what dose of dexamethasone: low dose: 6 mg daily for 10 days, versus high dose: 20 mg daily for 5 days and 10 mg daily another 5 days, is most beneficial in patients with COVID-19 and respiratory failure.

In this context, our hypothesis was that high doses of dexamethasone would have greater benefits than low doses of dexamethasone in patients with respiratory failure and COVID-19

2. Objectives

To investigate the efficacy of high dose of dexamethasone (20 mg daily 5 days + 10 mg daily 5 days) versus low dose of dexamethasone (6 mg daily 10 days) in patients with respiratory failure by COVID-19

2.1 The primary outcome

The primary outcome was **clinical worsening within 11 days since randomization**, defined by the occurrence of one of the following events, whichever occurred first:

- Death from any cause (**score 7** on the seven-level ordinal scale).
- Admission to ICU and need of invasive ventilation or ECMO (**score 6** on the seven-level ordinal scale).
- Need of non-invasive ventilation or nasal high-flow oxygen therapy (**score 5** on the seven-level ordinal scale)
- Worsening of the condition clinic of the patient during treatment (two of these: need to increase fraction of inspired oxygen inspired>20%, need for fraction inspired oxygenation>50%, increase in respiratory rate>25).

2.2. Secondary outcomes

- Clinical status of patients using the 7-point Ordinal Scale of the World Health Organization for clinical improvement (WHO-CIS) at day 5, 11, 14, 28, and 60 after randomization.
- Time to recovery (time to clinical improvement: defined as the first day after enrollment, on which a patient attained category 1, 2, 3-point ordinal scale WHO-CIS)
- Number of patients admitted to the ICU admission
- Number of patients who needed mechanical ventilation
- Duration of mechanical ventilation
- Duration of ICU admission.
- Length of Hospital stay
- Mortality during hospitalization, at day 28 and at day 60.
- Adverse drug reactions
- Complications during hospitalization:
    - Nosocomial infection:

Pneumonia,

Catheter-related bloodstream infection,

Bacteremia,

Urinary infection,

Others...

- Insulin use for hyperglycemia
- Gastrointestinal bleeding
- Thrombosis
- Pneumothorax
- Renal replacement therapy

3. Tables and Results

Table S1: Enrolment rate of 200 patients through the 5 months of the trial

Period (weeks)	Number of randomized patients
15 January – 17 January 2021	2
18 January – 24 January 2021	11
25 January- 31 January 2021	45
1 February – 7 February 2021	27
8 February – 14 February 2021	21
15 February – 21 February 2021	17
22 February – 28 February 2021	11
1 March – 7 March 2021	5
8 March – 14 March 2021	4
15 March – 21 March 2021	2
22 March – 28 March 2021	1
29 March – 4 April 2021	3
5 April – 11 April 2021	6
12 April – 18 April 2021	4
19 April – 25 April 2021	5
26 April – 2 May 2021	9
3 May – 9 May 2021	9
10 May – 16 May 2021	11
17 May – 23 May 2021	2
24 may – 26 May 2021	5

Table S2: Distribution of patients´ scores on the 7-point ordinal scale at 5, 11, 14, and 28 days.

Outcomes * *					
Outcome	**All patients N = 200**	**Low dose Dexamethasone N = 102**	**High dose Dexamethasone No = 102**	**Risk Ratio (95% CI)†**	**P value**
Seven-level ordinal scale at 5 days					
Distribution – no. (%) ‡				**0.979 (0.737 – 1.301)**	**0.885**
1:	**10 (5.0)**	**6 (5.9)**	**4 (4.1)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**26 (13.0)**	**10 (9.8)**	**16 (16.3)**		
4:	**139 (69.5)**	**73 (71.6)**	**66 (67.3)**		
5:	**8 (4.0)**	**4 (3.9)**	**4 (4.1)**		
6:	**17(8.5)**	**9 (8.8)**	**8 (8.2)**		
7:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
Seven-level ordinal scale at 11 days					
Distribution – no. (%)				**0.964 (0.818 – 1.137)**	**0.666**
1:	**114 (57)**	**58 (56.9)**	**56 (57.1)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**21 (10.5)**	**9 (8.8)**	**12 (12.2)**		
4:	**44 (22.0)**	**22 (21.6)**	**22 (22.4)**		
5:	**2 (1.0)**	**1 (1.0)**	**1 (1.0)**		
6:	**14 (7.0)**	**9 (8.8)**	**5 (5.1)**		
7:	**5 (2.5)**	**3 (2.9)**	**2 (2.0)**		
Seven-level ordinal scale at 14 days					
Distribution – no. (%)				**1.014 (0.854 – 1.206)**	**0.870**
1:	**141 (70.5)**	**73 (71.6)**	**68 (69.4)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**15 (7.5)**	**6 (5.9)**	**9 (9.2)**		
4:	**28 (14.0)**	**14 (13.7)**	**14 (14.3)**		
5:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
6:	**10 (5.0)**	**6 (5.9)**	**4 (4.1)**		
7:	**6 (3.0)**	**3 (2.9)**	**3 (3.1)**		
Seven-level ordinal scale at 28 days					
Distribution – no. (%)				**1.021 (0.845 – 1.233)**	**0.831**
1:	**175 (87.5)**	**90 (88.2)**	**85 (86.7)**		
2:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
3:	**6 (3.0)**	**2 (2.0)**	**4 (4.1)**		
4:	**6 (3.0)**	**3 (2.9)**	**3 (3.1)**		
5:	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**		
6:	**1 (0.5)**	**1 (1.0)**	**0 (0.0)**		
7:	**12 (6.0)**	**6 (5.9)**	**6 (6.1)**		

***** * Abbreviations: CI: confidence interval; %: percentage; IQR: interquartile range.

‡ Scores on the ordinal scale are follows: 1, not hospitalized; 2, not hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care (independent); 3, hospitalized, not requiring supplemental oxygen, but in need of ongoing medical care (COVID-19 related or otherwise); 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring non-invasive ventilation or high flow nasal cannula; 6, hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 7, death.

† Rate ratios have been adjusted for age with respect to the outcomes studied.

Table S 3: Subgroup Analyses of Clinical Worsening through Day 11.

Subgroup	No. of Patients	Risk Ratio (95% CI)
Overall	**200**	**0.427 (0.216 – 0.842)**
Sex		
Male	123	0.477 (0.204 – 1.113)
Female	76	0.335 (0.106 – 1.061)
Age		
< 65 years	91	0.594 (0.178 – 1.976)
≥ 65 years	**109**	**0.349 (0.149 – 0.816) ***
Obesity		
Yes	**106**	**0.367 (0.145 – 0.931) ***
No	94	0.504 (0.185 – 1.374)
PaO2:FiO2 ratio		
≤294	**100**	**0.399 (0.166 – 0.959) ***
>294	100	0.407 (0.132 – 1.257)
SpO2:FiO2 ratio		
≤339	**108**	**0.410 (0.177 – 0.948) ***
>339	92	0.285 (0.074 – 1.090)
Days from symptoms onset		
≤8 días	121	0.480 (0.209 – 1.101)
>8 días	79	0.406 (0.120 – 1.370)
≤ 10 días	**164**	**0.437 (0.211 - 0.904) ***
> 10 días	36	0.600 (0.074 – 4.834)

Table S 4: Subgroup of the 32 patients in the low dose group who suffered Clinical Worsening through Day 11.

P.No	First event	Day treatment	Need of MV	Need of ICU	Score level at day 11	Score level at day 14	Death at day 11	Death at day 60
1	Worsening of the patient´s condition	6	No	No	**4**	**4**	No	No
2	NIV/HFO	2	No	Yes	4	3	No	No
3	MV	3	Yes	Yes	6	6	No	No
4	Worsening of the patient´s condition	7	No	No	**4**	**4**	No	No
~~5~~	MV	1	Yes	Yes	6	6	No	No
6	Worsening of the patient´s condition	7	No	No	**4**	**4**	No	No
7	Worsening of the patient´s condition	4	No	No	**4**	**4**	No	Yes
8	Worsening of the patient´s condition	3	No	No	**1**	**1**	No	No
9	Worsening of the patient´s condition	3	No	No	**1**	**1**	No	No
10	Worsening of the patient´s condition	2	Yes	Yes	6	6	No	No
11	Worsening of the patient´s condition	7	No	No	**4**	**4**	No	No
12	Worsening of the patient´s condition	8	No	No	**4**	**4**	No	Yes
13	Worsening of the patient´s condition	3	Yes	Yes	6	6	No	No
14	Worsening of the patient´s condition	3	No	No	**4**	**4**	No	No
15	Worsening of the patient´s condition	2	No	No	5	**4**	No	No
16	Worsening of the patient´s condition	7	No	No	7	7	No	Yes
17	Worsening of the patient´s condition	3	No	No	**4**	**4**	No	No
18	Worsening of the patient´s condition	2	No	No	**1**	**1**	No	No
19	Worsening of the patient´s condition	7	No	No	**1**	**1**	No	No
20	Worsening of the patient´s condition	3	No	No	7	7	Yes	Yes
21	Worsening of the patient´s condition	2	No	No	**1**	**1**	No	No
22	MV	2	Yes	Yes	6	6	No	No
23	MV	5	Yes	Yes	6	6	No	No
24	Death	8	No	No	7	7	Yes	Yes
25	Worsening of the patient´s condition	2	No	Yes	**4**	**1**	No	No
26	Worsening of the patient´s condition	2	Yes	Yes	6	**4**	No	No
27	NIV/HFO	3	Yes	Yes	4	1	No	No
28	MV	6	No	Yes	6	6	No	Yes
29	Worsening of the patient´s condition	5	No	No	**4**	**4**	No	Yes
30	Worsening of the patient´s condition	2	No	No	**1**	**1**	No	No
31	MV	3	Yes	Yes	6	6	No	Yes
32	NIV/HFO	4	No	Yes	4	1	No	No

16 patients in the low dose group did not worsen level greater than 4 at day 11 after starting high doses. On day 14, 7 of those patients had a level lower than 4.

Table S 5: Subgroup of the 16 patients in the high dose group who suffered Clinical Worsening through Day 11.

P.N	First event	Day treatment	Need of MV	Need of ICU	Score level at day 11	Score level at day 14	Death at day 11	Death At day 60
1	Worsening of the patient´s condition	3	Yes	Yes	7	7	Yes	Yes
2	NIV/HFO	1	No	Yes	4	3	No	No
3	MV	4	Yes	Yes	6	6	No	No
4	MV	6	Yes	Yes	4	4	No	No
5	MV	4	Yes	Yes	4	3	No	No
6	Worsening of the patient´s condition	2	No	Yes	4	1	No	No
7	MV	3	Yes	Yes	6	4	No	No
8	MV	5	Yes	Yes	6	6	No	No
9	MV	2	Yes	Yes	6	6	No	No
10	NIV/HFO	3	No	Yes	1	1	No	No
11	Worsening of the patient´s condition	5	Yes	Yes	6	6	No	Yes
12	NIV/HFO	3	No	Yes	4	3	No	No
13	MV	3	Yes	Yes	4	3	No	No
14	Worsening of the patient´s condition	3	No	No	7	7	Yes	Yes
15	MV	2	Yes	Yes	3	1	No	No
16	NIV/HFO	6	No	Yes	5	4	No	No

Figure S1: Kaplan-Meier Analysis of Efficacy Outcomes: clinical worsening.

Shown are Kaplan-Meier curves for the time-to-event analyses of clinical worsening (primary outcome).

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	5,992	1	,014

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Clinical worsening

Nº at risk	D_0	D_3	D_6	D_9	D_{11}
Low dose	102	84	76	70	70
High dose	98	88	82	82	82

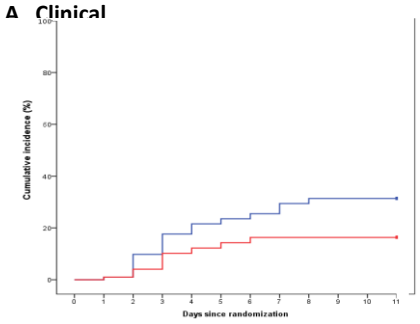

Figure S2: Kaplan-Meier Analysis of Efficacy Outcomes: recovery.

Shown are Kaplan-Meier curves for the time-to-event analyses of recovery, defined as the first day after enrollment, on which a patient attained category 1, 2, or 3 on the 7-point ordinal scale (scores range from 1 to 7, with higher scores indicating worse clinical condition.

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	,000	1	,991

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Recovery

Nº at risk	D_0	D_4	D_8	D_{12}	D_{16}	D_{20}	D_{24}	D_{28}
Low dose	102	86	41	23	17	13	10	10
High dose	98	78	45	26	17	13	10	9

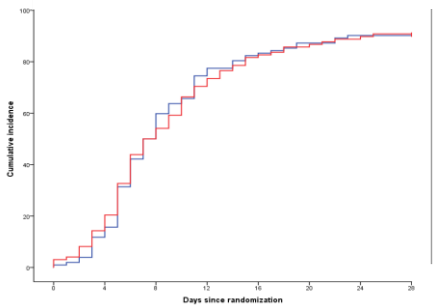

Figure S3: Kaplan-Meier Analysis of Efficacy Outcomes: hospital discharge.

Shown are Kaplan-Meier curves for the time-to-event analyses of hospital discharge.

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	,400	1	,527

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Hospital discharge

Nº at risk	D_0	D_4	D_8	D_{12}	D_{16}	D_{20}	D_{24}	D_{28}
Low dose	102	95	53	30	21	17	14	12
High dose	98	94	55	33	21	17	14	13

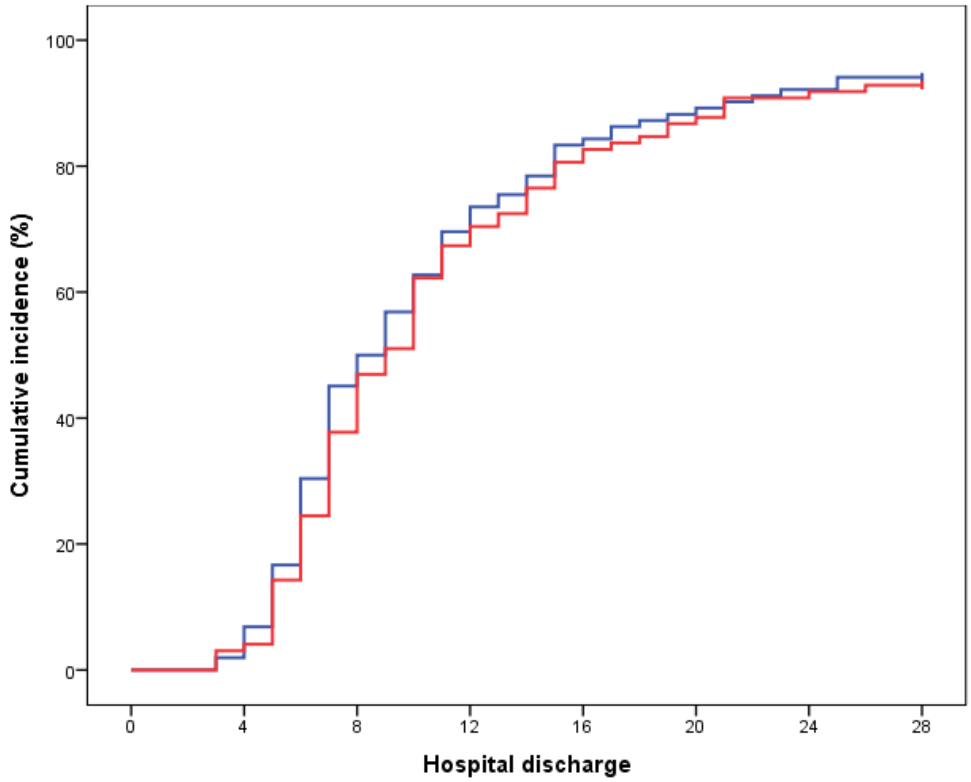

Figure S4: Kaplan-Meier Analysis of Efficacy Outcomes: death.

Shown are Kaplan-Meier curves for the time-to-event analyses of death

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	,003	1	,956

Prueba de igualdad de distribuciones de supervivencia para diferentes niveles de Dosis de Dexametasona.

Death at 28

Nº at risk	**D_0**	**D_4**	**D_8**	**D_{12}**	**D_{16}**	**D_{20}**	**D_{24}**	**D_{28}**
Low dose	102	102	102	99	97	96	96	96
High dose	98	98	98	95	95	92	92	92