Study Sponsor	Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)
EUDRA CT Number	2020-005026-28
Project Code	MP3-pulses-COVID-19
Date	11/12/2020
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MP3-pulses-COVID-19. PULSES OF METHYLPREDNISOLONE VERSUS DEXAMETHASONE RECOVERY REGIMEN IN PATIENTS WITH PNEUMONIA DUE TO SARS-COV-2 CORONAVIRUS INFECTION

STUDY SUMMARY

PROMOTER	Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL
EudraCT NUMBER	2020-005026-28
STUDY CODE	MP3-pulses-COVID-19
TITLE	MP3-pulses COVID-19. PULSES OF METHYLPREDNISOLONE VERSUS DEXAMETHASONE RECOVERY REGIMEN IN PATIENTS WITH PNEUMONIA DUE TO SARS-COV-2 CORONAVIRUS INFECTION.
PHASE OF THE CLINICAL TRIAL	Phase IV
COORDINATING RESEARCHER	Luis Corral Gudino
PARTICIPATING CENTERS	Río Hortega University Hospital (HURH) University Assistance Complex of Salamanca (CAUSA) University Clinical Hospital of Valladolid (HCUV) University Assistance Complex of Burgos University Assistance Complex of León (CAULE)
PRINCIPAL INVESTIGATORS	Luis Corral Gudino (Río Hortega University Hospital) José Ignacio Martín González (University Assistance Complex of Salamanca) Iván Cusácovich Torres (University Clinical Hospital of Valladolid) María López Veloso (University Assistance Complex of Burgos) Alberto Muela Molinero (University Assistance Complex of León)
MANAGEMENT AND MONITORING	The integral management of the project will be carried out by the Biomedical Research Institute of Salamanca.

DRUG IN RESEARCH AND REFERENCE, THERAPEUTIC REGIMEN AND ROUTE OF ADMINISTRATION	**Investigational medicine:** 1) Desamethasona (RECOVERY) 2) Methylprednisolone (BOLUS) **Dose:** RECOVERY branch: Dexamethasone 6 mg/24h - 10 days (alternative Methylprednisolone 30mg/24h) BOLUS: Methylprednisolone 250mg/ 24 hours - 3 days (alternative Dexamethasone 50mg/24h) **Administration:** Intravenous administration. In the case of the RECOVERY branch, the investigator may prescribe oral administration if he considers it necessary from the third day of treatment.
HYPOTHESIS	The use of high doses of bolus glucocorticoids will increase the anti-inflammatory effect without increasing side effects. This will allow a better evolution of patients, reducing the number of deaths and the need for intubation or admission to the Intensive Care Unit.
OBJECTIVES	**Primary:** To compare the effect of high-dose methylprednisolone boluses versus the dexamethasone intermediate dose regimen (RECOVERY trial) in COVID-19 patients with non-critical respiratory failure. **Side:** • To assess the efficacy profile of the use of high-dose glucocorticoids for a short course on mortality in patients with COVID-19 • To assess the efficacy profile of the use of high-dose glucocorticoids for a short course on the evolution to need respiratory support (invasive mechanical ventilation or not) in patients with COVID-19 • To assess the efficacy profile of the use of high-dose glucocorticoids for a short course on the time of admission in patients with COVID-19 • To assess the safety profile of the administration of high doses of glucocorticoids in relation to the presence of added infections, hyperglycemia, psychotic symptoms or other adverse events.
DESIGN	Clinical trial of low level of intervention, phase IV, open-label, randomized, comparison of 2 active treatments.

DISEASE OR DISORDER UNDER STUDY	COVID (coronavirus disease)
POPULATION AND TOTAL NUMBER OF PATIENTS	Sample size: 290 (two groups of 145 patients) Hospitalized patients, diagnosed with certainty of SARS-CoV-2 infection in acute phase (RT-PCR-or antigen positive) who have respiratory failure.
SELECTION CRITERIA	**Inclusion criteria:** 1. Over 18 years old. 2. Hospitalized patient. 3. Diagnosis of SARS-CoV-2 infection confirmed by RT-PCR or antigen. 4. Computed tomography (CT) evidence of lung involvement attributed to COVID infection is presented. Patients in whom CT is not performed should have suspicion of pulmonary involvement by clinically with compatible or suggestive simple radiology. 5. Requires supplemental oxygen by basal saturation ≤ 93% (with ambient O2, 21%) **Exclusion criteria:** 1. The patient's situation is so serious that the doctor responsible thinks he could die in the next 24 hours. 2. Patients require at randomization one of the following 4 ventilatory supports: • High Oxygen Flow Devices • Non-invasive mechanical ventilation • invasive mechanical ventilation • extracorporeal membrane oxygenation (ECMO). 3. The patient is or has been treated in the 2 weeks prior to randomization with glucocorticoids or inflammation-modifying drugs, both conventional (thiopurines, cyclophosphamide, cyclosporine, tracolimus, leflunomide, methotrexate, mycophenolate mofetil / mycophenolic acid, sulfasalazine, hydroxychloroquine or chloroquine) and synthetic or biological directed against therapeutic targets (abatacept, belimumab, CD-20, IL1, IL6, Il12.23, IL-23, Il.17, TNF, integrin α4β7 or JAK inhibitors). 4. The patient is pregnant or breastfeeding 5. The patient has stage 4 or 5 chronic kidney disease (rCC <30 ml/min) 6. Moderate to severe dementia at the discretion of the investigator. 7. Hypersensitivity to any of the active ingredients or to any of the excipients included in its formulation. 8. Untreated systemic infections not caused by COVID-19. 9. Active stomach ulcer or duodenal ulcer.

	10. Recent vaccination with live vaccines. 11. There is another infection or disease that explains the lung disorder 12. Inability of the patient to understand the study or sign the informed consent unless a consent delegated to a legal representative is made. 13. Active participation in another clinical trial in the past 15 days
VISIT PROGRAMME	Selection Visit Randomization Day 4-6 (any day between 4 and 6) Day 12-16 (any day between the 12th and the 16th) Day 28 (window allowed: d24-d30) 3 months (window allowed: ±2weeks) Visit to discharge or premature withdrawal
TRIAL SCHEDULE	Recruitment is planned to begin in December 2020. The overall duration of the study is estimated at approximately 9 months, from the start of the recruitment period (6 months of recruitment) to the last follow-up visit (3 months of follow-up). This study is expected to be completed in September 2021.

1. SIGNATURES APPROVINGTHE PROTOCOL

Protocol Title : USE OF GLUCOCORTICOIDS IN PATIENTS WITH SARS-COV2 CORONAVIRUS INFECTION. Pragmatic essay inserted in real practice during pandemic.

Eudragact number: 2020-005026-28

Protocol code: MP3-pulses-COVID-19

Promoter: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)

Signature of the Promoter:

Representative of the promoter:

María de Lorenzo Santiago (Director of Management - IBSAL)

Signature Date

Signature of the Coordinating Researcher:

Coordinating Investigator of the Study:

Luis Corral Gudino

Signature Date

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE

PROTOCOL TITLE: MP3-pulses COVID-19. PULSES OF METHYLPREDNISOLONE VERSUS DEXAMETHASONE RECOVERY REGIMEN IN PATIENTS WITH PNEUMONIA DUE TO SARS-COV-2 CORONAVIRUS INFECTION

Eudragact number: 2020-005026-28

Protocol code: MP3-pulses-COVID-19

Promoter: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)

PCOS CONFIDENTIALITY AND DECLARATION OF CONFORMITY

I have read the protocol of the previous clinical study and agree that it contains all the information necessary to conduct the study.

I hereby confirm that I have thoroughly read and understood this clinical study protocol, and I agree that my staff and I will conduct the study in accordance with the protocol and comply with its requirements, including ethical and safety considerations.

I understand that if the Promoter decides to terminate or suspend the study prematurely for any reason, such decision will be communicated to me in writing. On the contrary, if I decide to withdraw from the execution of the study, I will immediately communicate this decision to the Promoter.

I agree not to publish any part of the results of the study conducted under this clinical study protocol without the prior written consent of the Sponsor.

Principal Investigator

Center/Hospital

Compan
y

Date

Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)
University Hospital of Salamanca
Virgen de la Vega Building, 10th floor Pº San Vicente, 55-182. 37007 Salamanca

2. Acronyms

AA: Adverse Event

AAG: Serious Adverse Events

CCR: Creatine clearance

CD: cluster of differentiation

CEIm: Ethical Committee on Research with Medicines

COVID-19: Corona Virus Disease 2019.

CRDe: Electronic data collection notebook

DXA: Dexamethasone

ECG: Electrocardiogram

ECMO: Extra-corporeal membrane oxygenation

VF: Pharmacovigilance

GC: Glucocorticoids

HDC: Hydrocortisone

IL: Interleucine

HOW: Janus cinasa

MP: Methylprednisolone

NHC: Medical history number

WHO: World Health Organization

CRP: C-reactive protein

RA: Adverse reaction

RAI:Unexpected adverse reaction

RAG: Adverse reaction grbird

RAGI: unexpected serious adverse reactions

RT-PCR: Real Time-Polymerase Chain Reaction

Rx: Simple X-ray

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus

CT, Computed Axial Tomography

TNF: Factor de necrosis tumoral.

ICU: Intensive Care Unit

NIV: Non-invasive mechanical ventilation

Table of Contents

3. Overview

1.1. Title, protocol identification number and date.

PROTOCOL TITLE: MP3-pulses-COVID-19. PULSES OF METHYLPREDNISOLONE VERSUS DEXAMETHASONE RECOVERY REGIMEN IN PATIENTS WITH PNEUMONIA DUE TO SARS-COV-2 CORONAVIRUS INFECTION.

Eudragact number: 2020-005026-28

Protocol code: MP3-pulses-COVID-19

1.2. Name and address of the promoter.

Promoter: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)
University Assistance Complex of Salamanca.
Hospital Virgen de la Vega, 10th Floor.
Paseo de San Vicente, 58-182. 37007 Salamanca

1.3. Reference CEIm

Salamanca Health Area.

1.4. Study phase.

Phase IV clinical trial.

1.5. Name and title of the Study Coordinator, address and contact details.

Luis Corral Gudino, graduate specialist in Internal Medicine, Internal Medicine Service, Río Hortega University Hospital. Associate Professor of the degree of Medicine at the University of Valladolid
Río Hortega University Hospital, Calle Dulzaina, 2, 47012 Valladolid.
Phone 983 42 04 00, extension 85801
Email: lcorral@saludcastillayleon.es
corralgudino@yahoo.es

1.6. Participating centers.

1. Río Hortega University Hospital
2. University Assistance Complex of Salamanca
3. University Clinical Hospital of Valladolid

4. University Assistance Complex of Burgos
5. University Assistance Complex of León

4. Introduction and justification of the study

At the end of December 2019, cases of viral pneumonia caused by previously unknown people in the city of Wuhan China began to be described. A few weeks later, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated for the first time, and the disease was referred to as COVID-19. Since then the virus has been spreading and causing a global epidemic that has overwhelmed global health systems and for which there is still no established cure.

During the first phase of the pandemic, different therapeutic approaches were used, mainly aimed at preventing both the viral phase (the virus entering cells or replicating) and a second phase of severe inflammation. This second phase is characterized by a marked elevation of acute phase reactants and the development of adult respiratory distress syndrome. To stop this second phase, different immunomodulatory treatments have been tested, including glucocorticoids.

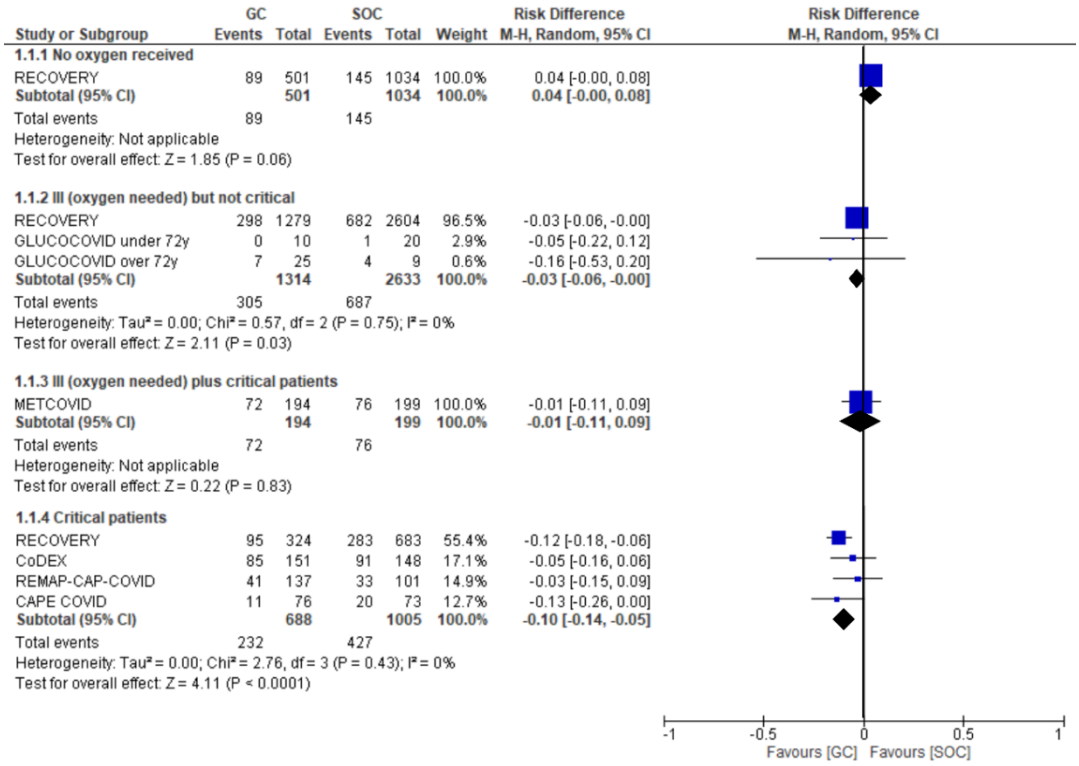
The RECOVERY[1] study has demonstrated the usefulness of an intermediate regimen of dexamethasone in critically ill patients with SARS-CoV-2 infection and less markedly in patients who need oxygen but are not in critical condition. Another 3 studies in critically ill patients (CoDEX[2], CAPE-COVID[3], REMAP-CAP-COVID[4]) have confirmed these results. In severe but non-critical patients, GLUCOCOVID[5] demonstrated improvement in a combined endpoint (death, ICU admission, mechanical ventilation) with an intermediate dose of glucocorticoids (GC). The METCOVID[6] study, however, has not refuted these data with a 5-day course of methylprednisolone at intermediate-high doses (see Figure 1 and Table 1).
On the other hand, uncontrolled observational studies have shown possible improvement with the use of higher doses of GC during a short cycle instead of the intermediate dose [7–9].

The pathophysiological explanation for this possible improved higher dose response would be activation of the non-genomic GC activation pathway. GCs exert their action in two ways, genomics and non-genomics. The mechanisms of this second way are not fully defined [10,11]. The genomic pathway is responsible for the classic immunomodulatory and anti-inflammatory action of GCs and the main side effects, glycemic, lipid and bone. The non-genomic pathway is mediated by the interaction of GCs with a specific membrane receptor that is particularly expressed in inflammatory cells. This pathway begins to be activated with boluses, but not with intermediate doses. Activation of this pathway could justify improved bowling response.

Table 1. GC randomized clinical trials guidelines in COVID.

I am a student	Agenda	Equivalent in prednisone day	Days
RECOVERY	Dexamethasone 6 mg/24h	DXA 6 mg = 30 mg	10 days
METCOVID	Methylprednisolone 0.5 mg/kg/12h	Patient type 70 kg MP 70 mg = 87,5 mg	5 days
GLUCOCOVID	Methylprednisolone 40 mg/12h x 3 days and then 20 mg/12h x 3 days	MP 80 mg = 100 mg	6 days
CoDEX	Dexamethasone 20 mg/24h x 5 days Dexamethasone 10 mg/24h x 5 days	DXA 20 mg= 125 mg DXA 10 mg= 62,5 mg	10 days
REMP-CAP C	Hydrocortisone 50-100mg/6h x 7 days	HDC 200 mg = 50 mg	7 days
CAPE COVID	Hydrocortisone 200 mg/24h x7 days, then 100 mg/24h x4 days, Then 50 mg/24hh x 3 days.	HDC 200 mg = 50 mg	14 days (8 if good evolution)

Figure 1. Results of the different studies published with CG in covid-19



5. Objective and Purpose of the Test

5.1. Hypothesis of the study.

The use of high doses of bolus glucocorticoids will increase the anti-inflammatory effect without increasing side effects. This will allow a better evolution of patients, reducing the number of deaths and the need for intubation or admission to the Intensive Care Unit.

5.2. Main objective.

To compare the effect of high-dose methylprednisolone boluses versus the dexamethasone intermediate-dose regimen (RECOVERY trial) in non-critical COVID-19 patients with respiratory failure.

5.3. Secondary objectives:

- To assess the efficacy profile of the use of high-dose glucocorticoids for a short course on mortality in patients with COVID-19.

- To assess the efficacy profile of the use of high doses of glucocorticoids for a short cycle on the evolution to need respiratory support (invasive mechanical ventilation or not) in patients with COVID-19.
- To assess the efficacy profile of the use of high-dose glucocorticoids for a short course on the time of admission in patients with COVID-19.
- To assess the safety profile of the administration of high doses of glucocorticoids in relation to the presence of added infections, hyperglycemia, psychotic symptoms or other adverse events.

6. Trial Design

Low-intervention clinical trial, phase IV, open-label, randomized, comparison of 2 active treatments.

[Justification for the low level of intervention: paragraph 8.3 of this Protocol and Annex 2]

6.1. Selection and Randomization

Action	Responsible
1. Inclusion of the patient in the study	The doctor who attends the patient is the one who decides the need to prescribe corticosteroids and informs the patient to propose their inclusion in the study
2. Patient randomization	It will be carried out centrally through the electronic data collection notebook (CRDe). Eligible subjects will be randomly assigned 1:1 to the two treatment groups.
3. Implementation of treatment.	Once the patient is randomized, the doctor will prescribe the treatment as usual, which will be prepared and dispensed in each center according to the usual practice of the same.

Since randomization is centralized and through the CRDe, the treatment list of patients is not accessible to researchers, so they do not know a priori what may be the treatment arm assigned to each patient**.**

7. Selection and Withdrawal of Subjects

7.1. Criteria for inclusion of subjects

Patients must meet ALL of the following criteria to be included in the study:

1) Over 18 years old
2) Inpatient
3) Diagnosis of SARS-CoV-2 infection confirmed by RT-PCR or antigen.
4) Computed tomography (CT) evidence of lung involvement attributed to COVID infection is presented. Patients in whom CT is not performed should have suspicion of pulmonary involvement by clinically with compatible or suggestive simple radiology.
5) Requires supplemental oxygen by basal saturation ≤ 93% (with ambient O2, 21%)

7.2. Criteria for excluding subjects.

Patients who present ANY of the following criteria may not be selected to participate in this study:

1) The patient's situation is so serious that the doctor responsible thinks he could die in the next 24 hours.
2) Patients require at randomization one of the following 4 ventilatory supports:
    a) High oxygen flow devices.
    b) VNon-invasive mechanical entilation.
    c) Invasive mechanical ventilation.
    d) extracorporeal membrane oxygenation (ECMO).

3) The patient is or has been on treatmentin the s 2 weeks s prior to randomization with glucocorticoids or inflammation-modifying drugs, both conventional (thiopurines, cyclophosphamide, cyclosporine, tracolimus, leflunomide, methotrexate, mycophenolate mofetil / mycophenolic acid, sulfasalazine, hydroxychloroquine or chloroquine) and synthetic or biological directed against therapeutic targets (abatacept, belimumab, CD-20, IL1, IL6, Il12.23, IL-23, Il.17, TNF, integrin α4β7 or Janus kinase inhibitors JAK). Patients who are only on maintenance therapy with corticosteroid doses less than or equal to 7.5 mg of prednisone or equivalent per day will not be excluded.

4) The patient is pregnant or nursing.

5) The patient has stage 4 or 5 chronic kidney disease (rCC <30 ml/min).

6) Moderate to severe dementia at the discretion of the investigator.

7) Hypersensitivity to any of the active ingredients or to any of the excipients included in its formulation.

8) Untreated systemic infections not caused by COVID-19.

9) Stomach ulcer the ulcer duodenal active.

10) Recent vaccination with live vaccines.

11) There is another infection or disease that explains the lung disorder

12) Inability of the patient to understand the study or sign the informed consent unless a consent delegated to a legal representative is made.

13) Active participation in another clinical trial in the past 15 days.

7.3. Criteria for withdrawal of subjects.

- Voluntary patient abandonment: patients have the right to withdraw from the study at any time and for any reason, being able to express it personally or through their representative.

- By medical criteria (safety and efficacy):

  – that it is necessary to adopt new treatments due to the presence of serious adverse events that may be related to the use of corticosteroids such as severe infection of bacterial origin, etc.

- the deterioration of this is severe and it is considered necessary to replace the administered corticosteroid or initiate additional immunosuppressants or immunodulators.
- That there is scientific evidence that supports the administration of new treatments that change the prognosis of patients and force them to modify the standard treatment of these.

- For non-compliance or violation of the rules contained in the protocol: when the patient no longer complies with the rules or procedures established in this protocol or there is loss of follow-up.

All patients who, regardless of the cause and stage of the study in which they are, prematurely and permanently discontinue treatment or follow-up, should complete the premature withdrawal visit, which will take place within 24-48 hours of becoming aware of withdrawal.

7.4. Premature discontinuation of the Study.

This study may be temporarily interrupted or terminated prematurely if in the opinion of the sponsor there is sufficient reasonable cause. The investigator will receive written notice that the terminating party documents the reason for the suspension of the study.

The circumstances justifying the suspension of the present study include, but are not limited to:

(a)Identification of unforeseen, substantial or unacceptable risks to patients.

(b)Inability to enroll an acceptable number of patients.

(c)Insufficient compliance with the requirements of the protocol.

d) Plans for modification, suspension or discontinuity of the development of the study drug.

e) Administrative reasons that the promoter could not solve with the health authorities.

f) The study is interrupted if scientific evidence appears to support the administration of new treatments that change the prognosis of patients and force them to modify the standard treatment of these.

A safety rule to stop the trial is to find significant differences in efficacy endpoint or adverse event variables in interim analyses. The significance level established for stopping the test is $p<0.01$ for safety and $p<0.001$ for efficiency(Haybittle-Peto limit) [13].

If the trial ends early or is suspended for any reason, the investigator shall promptly inform the trial subjects, ensuring appropriate treatment and follow-up of the trial and, where required by applicable law, inform the regulatory authority.

If the investigator terminates or suspends a trial without the prior agreement of the sponsor, he or she shall promptly inform the institution, and the investigator/institution shall promptly inform the sponsor and the CEIm and provide them with written justification for the cause of such termination or suspension.

If the sponsor terminates or suspends a trial, the investigator must inform the Institution where the trial is conducted and the investigator/institution must promptly inform the CEIm by providing written justification of the reasons for the termination or suspension.

If the Ethics Committee (CEIm) terminates or withdraws the favourable opinion of a trial, the investigator shall inform the institution and the investigator/institution shall promptly inform the sponsor of this fact and provide written justification as to the cause of such termination or suspension.

8. Description of the treatment.

8.1. Characteristics of the Research Product

Methylprednisolone boluses are currently a common treatment in diseases with a serious component of infamation such as lupus nephritis. That is why its application in the inflammation phase of COVID could be useful, since these patients have a severe inflammatory profile. The response to intermediate doses of dexamethasone suggests a possible effect of treatment with higher doses.

The risks of corticosteroid treatment at the bolus dose in the short term are similar to those of administration of intermediate doses, with an increased risk of bacterial superinfection, baseline glycemic decompensation, or risk of psychosis or arousal. Use in cycles of a few days has no long-term side effects such as hypertension, dyslipidemia or osteoporosis.

The chosen pattern is the same as that used in acute inflammatory diseases, such as lupus nephritis. In case of lack of stock, it could be decided to use other glucocorticoid preparations in doses equivalent to that of methyl-prednisolone, according to the following table:

Table 2. Guidelines equivalences to methylprednisolone in different studiess.

Active substance	Agenda	Equivalence in methyl-prednisoitin the	Equivalence in prednisona
Dexamethasone	6 mg/24h	30 mg/24h	37,5mg/24h

Metilprednisolona	250mg/24h	N/A	312,5 mg/24h
Hidrocortisona	50-100mg/6h	20-40 mg/12h	25-50 mg/12h

Reference: doses calculated according to "Steroid Conversion Calculator", accessible in https://www.mdcalc.com/steroid-conversion-calculator#evidence

Patients with a confirmed diagnosis of SARS-CoV-2 who have pulmonary involvement and are at risk of developing adult respiratory distress syndrome will be included.

There are studies that have evaluated observationally the treatment with GC boluses in this pathology in which there seems to be a beneficial effect when compared with the usual treatment (Callejas-Rubio, Rodríguez-Baño, Ruiz-Irastorza).

8.2. Treatment groups and selected doses.

Patients continue with the treatment that is considered standard in their center and associate glucocorticoids in 2 possible regimens (group membership is done randomly)

1) RECOVERY guideline. Intravenous administration of 6mg of dexamethasone every 24h for 10 days. It can be given both orally and intravenously at the same dose

2) BOWLING GUIDELINE. Intravenous administration of 250mg of methylprednisolone every 24 hours for 3 days.

The standard treatment in each group is as described, but given the pandemic situation and the risk of stock depletion, in the case of the RECOVERY regimen the use of methylprednisolone 30 mg could be assessed as an alternative to dexamethasone 6 mg, as well as in the case of the bolus regimen, the use of dexamethasone 50 mg could be assessed as an alternative in case of stock depletion.

Method of administration

Once the patient has been included in the study, it is recorded in the data collection notebook and randomization is performed. Once the treatment group is known, the doctor prescribes the treatment according to the usual procedure in the center according to the protocol.

The pharmacy of the center prepares the medication according to the medical schedule, for intravenous administration in the case of methylprednisolone or intravenous or oral according to the medical criteria for dexamethasone.

8.3. Justification character low level of intervention.

The investigational products are marketed drugs and will be used according to the guidelines of the SmPC, so that the study cannot be classified as a low level of intervention. In addition, procedures outside of standard practice that were not performed on thesepatients outside the study will not be performed. (Annex 2)

On the other hand, on 18 September 2020, the AEMPS published, with reference MUH 28/2020, that the Committee for Medicinal Products for Human Use (CHMP) P has concluded that, for the treatment of patients with COVID-19, dexamethasone can be administered orally or administered as an injection or infusion (drip) intravenously. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days. In this way, the use of dexamethasone as a new indication in patients with COVID-19 is possible.

8.4. Concomitant treatments

8.3.1. Concomitant treatment allowed (Standard Treatment)

Although this is a pragmatic study in real practice and some degree of heterogeneity is accepted in standard treatment, minimum requirements are considered to be able to include patients in the study. Thus, as standard treatment is accepted:

a) Supplemental oxygen. For use in patients with hypoxemia. The target for oxygen therapy should not exceed 92% in patients at risk of respiratory failure with hypercapnia and 96% in all other patients.

b) Antibiotic treatment. Standard treatment protocols should not recommend the administration of empirical antibiotic treatment on a routine basis. Its administration should only be recommended when risk of bacterial pneumonia is considered as co-infection. The antibiotic regimen will correspond to the usual treatment guide of the center.

c) Prophylaxis or thromboembolism treatment with low molecular weight heparins. Thrombotic prophylaxis is recommended in all admitted patients and the use of therapeutic doses in patients with confirmed thromboembolic disease. The use of extended prophylaxis guidelines could be assessed according to the recommendations of the Spanish society of thrombosis and hemostasis.

d) Remdesivir. The use of remdesivir is accepted if it is done according to the recommendations of the Ministry of Health.

e) Other antiviral drugs or drugs that block viral activity. The protocols should not incorporate the following drugs: Hydroxychloroquine or chloroquine, lopinavir-ritonarvir.

f) Serum therapy. The use of serum therapy is allowed in those indications defined in the protocols.

g) Other concomitant medications without antiviral or immunosuppressive effect (eg: antihypertensives, analgesics, lipid-lowering agents, antiplatelet agents,...). There is no limitation to the use of these drugs.

8.3.2. Concomitant treatments prohibited.

Other immunosuppressants. The concomitant use of other immunosuppressants is NOT allowed in the first 48 hours of evolution. If immunosuppressants are prescribed during the study, patients in whom they are initiated with the third or subsequent dose of CG should be maintained. The use of these drugs in these patients will be considered as an event.

9. Development of the study.

9.1. Study schedule.

Recruitment is planned to begin in December 2020.

The overall duration of the study is estimated at approximately 9 months, from the start of the recruitment period (6 months of recruitment) to the last follow-up visit (3 months of follow-up). This study is expected to be completed in September 2021.

9.2. Calendar of visits.

Processes to be carried out	SCR	Day 4-6	Day 12-16	Day 28	3 months	Premature withdrawal
Informed consent	X					
Inclusion criteria	X					
Randomization	X					
Medical history comorbidities	X					
Physical examination	X	X	X	X	X*	X*
COVID Clinical Evaluation	X	X	X	X	X	X
WHO scale of 10 categories	X	X	X	X	X*	X*
Concomitant medication	X	X	X	X	X	X
Biochemistry and blood count	X	X	X	X	X*	X*
Adverse events	X	X	X	X	X	X
Rx the TC	X		X		X*	X*
ECG	X					

* Only in case of being a face-to-face visit.

9.3. Description of the visits and the procedures to be carried out in each visit.

9.3.1. Study visits

- Selection/Randomization.
- Day 4-6 (any day between 4 and 6).
- Day 12-16 (any day between the 12th and the 16th).
- Day 28 (window allowed: day 24 to day 30).
- 3 months (window allowed: ±2weeks). This visit can be made in person or by telephone at medical discretion, depending on the patient's condition and the usual practice of the center.
- Visit to discharge or premature withdrawal. This visit can be done in person or by telephone.

9.3.2. Study Procedures

- **Chronopathology of COVID-19 infection.** During the screening visit, the date of onset of symptoms and the date of the first confirmatory diagnostic test

will be collected. In addition, if the diagnostic RT-PCR was not performed in the last 10 days, it will be necessary to repeat it and confirm the positivity.

- **Medical history comorbidities** (including hypertension, diabetes mellitus, dyslipidemia, heart failure, ischemic heart disease, stroke, chronic obstructive pulmonary disease, bronchial asthma, hypopnea sleep apnea syndrome, hypoventilation, chronic kidney disease, chronic liver disease, neoplasia, transplant, human immunodeficiency virus infection, autoimmune disease, dementia, smoker)

- **Clinical evaluation of COVID**, assessment of own symptoms, date of onset of symptoms and evolution of them.

- **WHO scale** of 10 categories (Annex 1).

- **Physical examination** (includes general assessment of the patient, degree of hydration, nutrition, vital signs and respiratory situation, cardiopulmonary ascultation, abdominal examination and a neurological assessment of alertness).

- **Concomitant medication** registration (start and end date, active substance and dose).

- **Biochemistry and blood count** (determination of blood count, coagulation with D-dimer, biochemistry including creatinine, ions, AST, ALT, BT, BD, LDH, PCR, ferritin, blood gases and IL-6).

- **Adverse events**, medication-related or non-medication-related.

- **Chest X-ray (X-ray) or Computed Tomography (CT)** (Brixia scale – Annex 1).

- **Electrocardiogram (ECG), according to** the usual practice of the center.

- Both the 3-month follow-up visit and the premature withdrawal visit can be done in person or by telephone. If the visit is carried out in person, in addition to the assessment of the COVID clinic, the registration of concomitant medication and the registry of adverse events, the following procedures would be carried out:

    - WHO scale of 10 categories (Annex 1).
    - Physical examination.
    - Biochemistry and blood count.

- Chest X-ray (X-ray) or Computed Tomography (CT) (Brixia[12] scale – Annex 1).

10. Study variables and parameters

10.1. Variable Principal:

• Death after 28 days

10.2. Secondary Variables

- Admission to the Intensive Care Unit at 28 days
- Need for noninvasive mechanical ventilation or high-flow oxygen at 28 days.
- Need for mechanical ventilation and intubation at 28 days.
- Use of other immunosuppressive drugs.
- Time to discharge (days of hospitalization from start of treatment)
- Baseline at 3 months of treatment according to the WHO 10-category scale .

10.3. Security variables

- Nosocomial infection (superadded infection developed at least 3 days after administration of the first dose of steroids) with microbiological confirmation by culture. When there is no microbiological confirmation, the diagnosis is established at the discretion of the physician.
- Hyperglycemia in non-diabetic patients or decompensation of diabetes mellitus in previously controlled patients. To define this event, the presence of at least one glycemic value greater than 180 mg/dl in the laboratory at any point of evolution or a value greater than 150 mg/dl in fasting capillary glycemia during the days that the patient receives treatment with glucocorticoids is established.

- Episodes of psychosis defined as the presence of euphoria, behavioral changes, aggressiveness, alteration of thought with disorganization of this or presence of hallucinations or delusions.

- Any other treatment-related adverse reaction that, in medical judgment, isrelevant to the safety of the drug under study.

11. Statistical considerations

11.1. Estimation of sample size.

Initial estimates:

28-day mortality in patients requiring oxygen who received intermediate-dose glucocorticoids	Mortality at 21-28 days in patients requiring oxygen and receiving boluses of glucocorticoids (observational studies, indirect evidence)
GLUCOCOVID data 17% RECOVERY data 23.3% METCOVID data 37%	Data Granada 8% SAM-COVID data: 10% Crossing Data: 9.1%
Estimate: 23%	Estimate: 10%

The following values apply: alpha error 5%, beta error 20%.

Estimated sample size: two groups of 145 patients (290 in total)

11.2. Data Management

11.2.1. Electronic Data Collection Notebook (CRDe)

The data collected will be recorded in an electronic Data Collection Notebook (CRDe), whose veracity will be validated by the designated monitors. In the CRD, each patient will be identified by an alphanumeric code that identifies the patient. At all times, the data protection provisions of Organic Law 3/2018 on the Protection of Personal Data and guarantee of digital rights will be respected.

11.2.2. Identification

Each patient receives an identification number when randomized. Only the pharmacy and principal investigator at each facility know the correspondence between the study identification number and the patient's medical record number (NHC).

It corresponds to the principal investigator of each center, who will be responsible for maintaining the list with the allocation of patients and their medical history number.

11.2.3. Record in medical records

Participation in the study will be included in the evolution of the clinical history of each center. All study data shall be recorded in the study so that all data collected in the CRDe can be verified. The data will be obtained from the personal interview with the patient and access to their complete medical history.

In the event that the patient does not attend any of the planned visits, the researcher will contact him by telephone to confirm that this absence is not due to a conscious abandonment of the follow-up. If you do not contact him, you will access the local or regional digital medical record to know if there have been events related to the study that have been evaluated in another health center.

11.3. Statistical analysis

The categorical variables will be presented as frequency and percentage and the continuous variables as mean and standard deviation.

Death after 28 days, intubation or admission to the ICU will be presented as proportions. The difference in proportions will be estimated with a 95% confidence interval.

An analysis per protocol will be performed, considering those patients who have received at least 2 doses of the assigned drug. In addition, an intention-to-treat analysis will be carried out.

In the event that there is a depletion of stock and any of the guidelines are replaced by one of the alternatives proposed in point 8.2, no adjustment would be made in the analysis since the equivalence of dose and dosage between the original dose and the substitution is established.

For the analysis of the main outcome, death at 28 days, survival analysis will be performed and the Hazard ratio of the Cox regression, with the log-rank statistic, will be used to estimate the mortality relationship.

An alpha error of 5% is set.

In case there was a lack of balance in the age of the patients between the groups, **age-adjusted analyses** would be performed, establishing 2 groups: < 70 years and ≥ 70 years.

Two interim efficacy and safety analyses are established with 100 and 200 patients

2 analyses of the results are established according to:

a) Time of evolution (<7 days from the onset of symptoms, ≥ 7 days from the onset of symptoms).

b) Presence of a state of high inflammation. The patient is considered to have a high degree of inflammation when he meets any of the following laboratory criteria:

- Ferritin greater than or equal to 1000 mg/dl
- IL-6 greater than or equal to 20 pg/ml
- PCR mayor o igual a 150 mg/l
- D-dimer greater than or equal to 1000 mg/dl

Finally, since no age criterion is established to exclude older patients, a sensitivity analysis will be performed, leaving out those patients who had orders of no intubation or non-invasive mechanical ventilation prior to being included in the study.

For statistical analysis, the IBM SPSS statistics, version 21 program will be used.

11.4. Responsibilities

- Coordination between the different groups for data management tasks is the responsibility of the promoter.
- Only authorised and adequately trained persons shall have access to the electronic data collection system.
- Data controllers shall ensure access to the system to all authorised persons.
- The promoter shall be responsible for the consistency of the eCRD data against the source data.

- Verification of eCRD data and source data will be the responsibility of the study monitor or, failing that, of the sponsor.

12. Security Assessment.

12.1. Definitions.

- **Adverse Event (AA):** An adverse event is any unwanted medical reaction experienced by the patient at any time during the course of the study, whether or not considered related to the study treatment. This definition includes the development of a new disease and the exacerbation of pre-existing disorders other than the indication under study.

- **Adverse Reaction (AR):** An RA is any harmful and unintended reaction to an investigational drug, regardless of the dose administered.

- **Serious Adverse Event (SAA) and Serious Adverse Reaction (RAG):** AEs or RAs are considered serious if, at any dose, may result in death, threaten the life of the subject, require hospitalization of the patient or prolong an existing hospitalization, cause permanent or significant disability or disability, or result in a congenital anomaly or malformation. Suspicions of medically important AA or RA are also considered serious, even if they do not meet the above criteria, including important medical events that require intervention to prevent one of the consequences described above from occurring. In addition, all suspected transmission of an infectious agent through a medicinal product shall be reported as serious.

  The concept "threatening the life of the subject" in the definition refers to the fact that, in the opinion of the researcher, the patient at the time of AA or RA is at real risk of death; it does not mean that AA/RA hypothetically could have caused death if it had been more intense.

  The concept of "requiring hospitalization" will exclude both hospitalizations planned for scheduled treatments and those that have been planned or anticipated before the study begins in relation to a pre-existing medical condition.

- **Unexpected Adverse Reaction (RAI):** Any RA whose nature, intensity or consequences do not correspond to the reference safety information.

- **Unexpected Serious Adverse Reaction (RAGI):** AGR (previously defined), the nature, severity or consequences of which do not correspond to the reference safety information.

12.2. Causality Criteria

- **Related OA:** The temporal relationship of AA to the medication under study indicates a possible causal relationship and cannot be explained by factors such as the patient's clinical status, therapeutic interventions.

- **Unrelated OA:** The temporal relationship of AA with study medication indicates an unlikely causal relationship, or other factors (medication or concomitant conditions), other therapeutic interventions provide a satisfactory explanation for AA.

12.3. Reference Security Information

In this study the reference safety information (SRI) will be the information available in the corresponding Summary of Product Characteristics of the drugs under study:

1. RECOVERY guideline. Intravenous administration of 6mg of dexamethasone every 24h for 10 days. It can be given both orally and intravenously at the same dose.

2. BOWLING GUIDELINE. Intravenous administration of 250mg of methylprednisolone every 24 hours for 3 days.

12.4. Security variables and parameters

The assessment of the safety of the drugs under study will be carried out through clinical examination (physical, analytical and / or radiological) and by collecting serious adverse effects and those that may be directly related to the medication under study, such as:

- Nosocomial infection (superadded infection developed at least 3 days after administration of the first dose of steroids) with microbiological confirmation by

culture. When there is no microbiological confirmation, the diagnosis is established at the discretion of the physician.

- Hyperglycemia in non-diabetic patients or decompensation of diabetes mellitus in previously controlled patients. To define this event, the presence of at least one glycemic value greater than 180 mg/dl in the laboratory at any point of evolution or a value greater than 150 mg/dl in fasting capillary glycemia during the days that the patient receives treatment with glucocorticoids is established.

- Episodes of psychosis defined as the presence of euphoria, behavioral changes, aggressiveness, alteration of thought with disorganization of this or presence of hallucinations or delusions.

- Any other treatment-related adverse reactions that, in their medical judgment, are relevant to the safety of the study drug.

12.5. Information on Adverse Events

All adverse events shall be recorded in the data collection log. For each adverse event, the start and resolution dates, intensity, duration and consequence on study treatment (e.g. discontinuation) will be recorded. The severity of the adverse event and its relationship to the study will be assessed according to specific guidelines. Any action taken or results obtained (e.g. hospitalisation, withdrawal of treatment, etc.) will also be recorded.

The investigator or a collaborator will question and/or examine the subject in relation to the incidence of adverse events.

Adverse events will be collected once the subject has been recruited. If a subject suffers an adverse event after signing the informed consent document (inclusion), but before assigning the treatment (recruitment), the event will NOT be recorded unless the researcher considers that it has a causal relationship with some procedure of the protocol.

Over the course of the study, the facility staff will again note any changes that occur in the disorder and nature of the possible adverse events.

12.6. Assessment of the intensity of adverse events and their relationship to treatment

The following definitions shall be applied to assess the intensity of adverse events:

- Mild: the sign, symptom or event is known, but it is easily tolerated.
- Moderate: there is enough discomfort to interfere with usual activity and may warrant intervention.
- Severe: it is disabling and produces inability to perform usual activities or significantly affects the clinical state and warrants intervention.
- Life-threatening: immediate risk of death.
- Death

12.7. Assessment of the imputability of adverse events and serious adverse events with the study treatment: Imputability criteria.

The sponsor will classify adverse events, based on their causal relationship with the drug, according to the Karch and Lasagna Algorithm (1977), as:

- **Definitive:** there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the RA described for the drug, improves with its suppression, reappears after its readministration and cannot be explained by alternative causes.
- **Probable:** there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the ARs described for the drug, improves after discontinuation of treatment and cannot be explained by other alternatives.
- **Possible:** there is a reasonable time sequence between the administration of the drug and the appearance of AA. This event coincides with the RA described for the drug but can be explained by alternative causes.
- **Conditional or Unlikely:** there is a reasonable temporal sequence between the administration of the drug and the appearance of AA. This event does not coincide with the RA described for the drug and can be explained by alternative causes.
- **Unrelated:** there is no reasonable time sequence between the administration of the drug and the appearance of AA. This event does not coincide with the RA described for the drug and can be explained by alternative causes.

For expedited notification purposes, the definitive, probable and possible categories of Karch and Lasagna's (1977) algorithm will be considered as related and the conditional or improbable category of said algorithm as unrelated.

The determination of the possible relationship with the treatment of the study is the responsibility of the principal investigator of the research center or the person designated by it and, once notified, will be reviewed by the sponsor of the study and / or person to whom it delegates.

12.8. Monitoring of adverse events

Subjects with adverse events should be monitored using appropriate clinical assessments and laboratory tests as indicated by the investigator. All adverse events should be followed until satisfactory resolution or stabilization. All measures taken and the results of the monitoring should be recorded in the relevant section of the data collection booklet. If laboratory abnormalities are clinically significant and cause clinical symptoms or meet the criteria for serious adverse event, the diagnosis shall be reported as such a serious adverse event.

12.9. AAG Notification, Expedited Notification, and Pregnancy Notification

Although the safety data collected in the corresponding Summary of Product Characteristics of the investigational drugs indicate their tolerance profile, the limited data on the doses used in this study make us take measures to control the safety of the product. Therefore, any adverse event that meets the severity criteria defined throughout the study follow-up will be collected and reported.

12.10. Reporting of Serious Adverse Events

The principal investigator or collaborator shall report to the Pharmacovigilance Department FV-UICEC-HUC, all serious adverse events (as defined below), whether or not considered treatment-related or expected, within **24 hours** (one working day), of their knowledge and through the corresponding notification form. Serious adverse events occurring should be reported at any time after the patient is included in the study (defined as the time the subject signs informed consent) and up to 30 days after the subject concludes or leaves the study. A subject is considered complete: after the conclusion of the last visit or contact (e.g., telephone contact with the investigator or a collaborator),

as indicated in the protocol assessment schedule, or after the last dose of study medication, whichever is later. Withdrawal is defined as the date on which a subject and/or investigator determines that the subject can no longer meet the study requirements at any subsequent visits and assessments.

The reporting investigator will complete and sign the AAG notification form for the study that will be faxed or emailed to:

PhD Patricia Rodríguez Fortúnez

Head of Pharmacovigilance UICEC of the University Hospital of the Canary Islands (HUC)

Telephone: 922 678 117 Fax: 922 677 284

Email: patricia.rodriguez@scren.es

PV staff will review the form received and, if appropriate, request additional information from the investigator. The investigator will provide information to the sponsor or to whoever assumes the tasks delegated by the sponsor (FV-UICEC-HUC Unit) whenever requested and, in any case, when his initial assessment changes in terms of severity or causality. The reporting of follow-up information shall follow the notification procedure described above.

The staff of FV-UICEC-HUC shall keep a detailed record of all AAGs or of special interest communicated to them by investigators.

In the event of a medication error or the investigational medicinal product is used outside the provisions of the protocol during the development of the study, the investigator will notify the FV-UICEC-HUC within 24 hours of becoming aware of it. The circuit for notification and form will be the same as for AAGs.

AEs that meet the severity criteria described in the definitions section will be considered serious. Clinically significant events that do not result in death, are life-threatening or require hospitalization may be considered serious adverse pharmacological experiences when, based on appropriate medical judgment, they may endanger the individual or require medical or surgical intervention to prevent one of the outcomes listed in this

definition. Examples of such medical events are allergic bronchospasm requiring intensive treatment, at home or in an emergency unit, blood dyscrasias or seizures that do not result in hospitalization, or development of dependence or substance abuse.

It is also necessary to report changes to laboratory tests that are considered clinically relevant, unless otherwise indicated in this section of the protocol.

12.10.1. Expedited notification of RAGIs

The FV-UICEC-HUC department is responsible for notifying the AEMPS and the Autonomous Communities where the test is carried out, all the RAGI that are collected in the study, following the procedure indicated in the current legislation.

The maximum period for reporting an individual case of suspected RAGI will be 15 calendar days from the moment the sponsor became aware of it. When the suspicion of RAGI has caused the death of the patient, or endangered his life, the sponsor will send the information within 7 calendar days from the moment he becomes aware of it. You will complete this information, if possible, within 8 days.

This information should include an assessment of the significance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

Likewise, the competent body of each of the Autonomous Communities where the test is carried out must be notified of the suspicions of RAGI that occurred in the health centers of their Community. In both cases, the RAGI notification form will be used for this purpose.

12.10.2. Expedited notification of other relevant security information

The FV-UICEC-HUC department shall notify as soon as possible and no later than 15 days after becoming aware of it any information that could modify the benefit/risk ratio of the investigational medicinal product (for example: increase in the percentage of occurrence of expected RAGs, RAGIs occurring after the end of a clinical trial, new developments related to the conduct of the trial or the development of the investigational medicinal product, any recommendations of the data monitoring committee relevant to the safety of the subjects, etc.).

12.10.3. Pregnancy Notification

In the event that any pregnancy occurs during the development of the study, the investigator will notify the sponsor or whoever assumes the tasks delegated by the sponsor within 24 hours of his knowledge. The pregnancy will also be monitored to document its outcome and the health status of the newborn. If the outcome of pregnancy meets criteria for SAA or if the newborn has a serious event, the procedures described for reporting SAA will be followed. Notification will be made using AAG's specific notification form which will be faxed or emailed to the same contact who will receive AAG notifications.

12.11. Periodic safety report

The annual safety reports that will include the RAGIs and AAGs collected in the study since the patient is randomized, will be sent by FV-UICEC of the University Hospital of the Canary Islands to the AEMPS (Clinical Trials Area of the General Subdirectorate of Medicines for Human Use), to the corresponding Autonomous Communities and to the CEIm, within the deadlines established in current legislation.

The submission of the annual safety report and other safety reports by the sponsor shall, in any case, comply with the criteria and procedure specified in Articles 43, 45 and 53 of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014.

12.12. Report to researchers

The sponsor will present to investigators safety information that could impact the safety of patients enrolled in the study as soon as possible. In addition, the researcher will be informed throughout the study about any safety aspects, including protocol modifications due to safety reasons.

12.13. Discontinuation of study drugs due to adverse events

Certain events or conditions may necessitate temporary or permanent discontinuation of study medication. Patients presenting with such events or conditions will remain "in the study" and will be followed until the end of the study. Any patient who temporarily discontinues study medication should restart it as soon as possible. Study guidelines will be

discontinued and replaced by out-of-study guidelines with continued follow-up in patients. If the administered drug is permanently discontinued, subsequent therapy is at the discretion of the investigator.

- **Temporal Discontinuation:** Criteria for Temporal Discontinuation of Study Drugs: The development of toxicity that, depending on its nature and severity, requires temporary discontinuation of study medication until toxicity resolves as indicated in the toxicity management section above, as well as the development of another medical condition that discourages administration of the study drug. The decision to temporarily discontinue study medication in this situation will be left to the discretion of the investigator. The period during which the patient is not taking the study medication will be as short as possible.

- **Permanent Discontinuation:** Criteria for Permanent Discontinuation of Study Drugs: The development of toxicity that requires permanent discontinuation of any study drug, refusal of the patient to continue treatment, when in the opinion of the investigator continuing study therapy is not the best option for the patient and completion of the study.

13. Quality Control and Assurance

In order to ensure data quality, the sponsor shall:

- Provide quality instruction and training to research staff prior to the start of the study. Training topics include, but are not limited to: PCB certificates, AA reports, details of the study and its procedures, study documentation, informed consent, and patient recruitment.

- Perform regular monitoring in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP). The data will be evaluated with respect to compliance with the protocol and accuracy in relation to the source documents. Monitors will verify that the clinical trial is conducted, that data is generated, documented and reported in compliance with protocol, good clinical practice and any applicable local regulatory requirements.

Direct access to the data will be granted to the principal investigators, monitors, members of the evaluating CEIm and the AEMPS, as well as to the authorities that are necessary, in order to allow monitoring and surveillance related to the study, audits and inspections. At each center, they will be able to review the study records and compare them directly with the source documents, they could discuss how to conduct the study with the investigator, and verify that the facilities remain acceptable. Audit reports will be treated confidentially

14. Ethical and legal aspects.

The trial will be conducted in accordance with the recommendations for clinical trials and drug evaluation in man, contained in the Declaration of Helsinki of 1964, revised in Tokyo, Venice, Hong Kong, South Africa, Edinburgh, Washington, Tokyo and Seoul (2008) and in the Document of instructions of the Spanish Agency of Medicines and Health Products for the conduct of clinical trials in Spain (Version 9 of July 27, 2018). The researcher will carry out the study in compliance with the ethical principles of the Declaration of Helsinki.

The study/trial must adhere to the protocol, which guarantees compliance with Good Clinical Practices, described in the ICH Harmonized Tripartite Guidelines of Good Clinical Practices.

This study/trial will be submitted for evaluation by a Research Ethics Committee with medicines and will be notified to the Spanish Agency for Medicines and Health Products (AEMPS).

14.1. Patient Information and Informed Consent Sheet (HIP-CI)

The investigator will explain to each patient (witness or legal representative) the nature of the study and the purposes, procedures, estimated duration, possible risks and benefits of their participation in the study / trial and possible inconveniences that this may cause. All patients will be informed of the voluntary nature of their participation and that they may withdraw at any time, without affecting their future medical care or their relationship with the doctor responsible for their treatment.

The patient will have sufficient time to read and understand the explanations included in the patient information sheet before giving informed consent. No patient may be included in the study before having obtained informed consent in the manner indicated in accordance with the standards of good clinical practice.

The patient will not be tested or treated by the study before informed consent is obtained.

14.2. Audit and monitoring.

Regulatory authorities, the CEIm, and the sponsor or a designated representative may request access to all original documents, patient data collection notebooks, and other study documentation to conduct an on-site audit or inspection. The researcher must ensure direct access to these documents and collaborate at all times in carrying out these activities. In

such procedures, due protection of private personal identification data will be attended to in accordance with the data protection law.

The objective of this audit is to systematically evaluate all activities and documentation related to the trial in order to determine if these activities have been carried out and if the data have been analyzed and reported in accordance with the protocol, Good Clinical Practice Standards, International Conference on Harmonization (ICH) Guidelines and legal requirements.

Monitoring.

Before starting the study, at the start visit of each center or at a meeting of researchers, a representative of the Sponsor will review the protocol and the data collection notebooks with the researchers and other personnel involved in the study. During the study, the monitor will regularly visit the center, to compare the data collected in the CRD with the source documents, check adherence to the protocol and the Standards of Good Clinical Practice. The investigator and trial personnel should be available to assist the monitor during these visits.

No data revealing the identity of patients should leave the participating center.

14.3. Failure to comply with protocol.

Serious breaches of the authorised protocol should be reported to the sponsor without undue delay and at the latest within three calendar days from the date on which it became aware of the non-compliance. The sponsor will communicate it to the Spanish Agency of Medicines and Health Products and the CEIm. For these purposes, a serious non-compliance is one that may significantly compromise the safety and rights of the subjects or the reliability and robustness of the data obtained in the clinical trial.

Where immediate deviation from the protocol is required to avoid immediate risks to patients, the investigator shall contact the sponsor, circumstances permitting, to discuss planned action. Any deviation from the protocol should be documented in detail in the CRD and in the original documentation.

15. Data Management and Archiving of Records

The confidentiality of individual patient data will be respected at all times. The original data will be kept in the corresponding Service and only the researchers of the study / trial or the inspectors will have access to them, in case of inspection by the Spanish Health Authorities.

Patients in the study/trial will be identified by a patient code. The investigator will inform patients that the data obtained during the study/trial will be stored and analyzed electronically, in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and on the free movement of such data and on Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights.

The researcher is the only person who can and should know the origin of the data obtained and who can associate them with the patient.

The personal data (full name, address, place of work, NIF) of the researchers will be recorded in a computerized file, with the sole purpose of facilitating the organizational and logistical aspects necessary for the development of the study / trial.

In compliance with the regulations described above, the data file will be treated confidentially and researchers may exercise their rights of access, rectification, cancellation and opposition with respect to the registered personal data, if they request it by writing to the Data Protection Officer of the promoter in protecciondedatos@ibsal.es.

16. Financing and Insurance

This is a non-commercial study. The trial will be funded by the sponsor and will be carried out with the means and staff of the sponsor himself.

Sure.

Because the clinical trial has been requested as a low-intervention clinical trial, the sponsor takes advantage of the insurance coverage established by RD 1090/2015, of December 4, for this type of trial.

17. Difficulties and limitations of the study

The main problem is the very nature of the pandemic due to SARS-CoV-2 infection, which has already surprised the health authorities in its evolution in several stages. This makes it very difficult to establish a fixed and stable recruitment line.

Another limitation of the study is due to the pragmatic nature of this, since it could happen that it was necessary to add some treatment or remove it from the standard of treatment given the speed with which the knowledge of the disease evolves.

18. Publication Policy

Regardless of the results of the study, the sponsor agrees to present them to the medical community through scientific publications, congresses or other means.

Any formal presentation or publication of the results of the study shall be considered a joint publication of the investigator(s) and the sponsor.

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ANNEX 1: Scales of measurement

A. Serious situation. WHO Proposal[14]

Patient status	Descriptor	Scale
	Not infected. No virus detected	0
Ambulant. Mild illness	Asymptomatic, independent, virus detected	1
	Symptomatic, independent	2
	Symptomatic, needs help	3
Hospitalized. Moderate disease	Hospitalized. Does not require Oxygen	4
	Hospitalized. Precise oxygen either by nasal glasses, or by conventional mask	5
Hospitalized. Severe illness	High-flow oxygen or noninvasive mechanical ventilation	6
	Mechanical intubation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200	7
	Mechanical intubation, vasopressors, or pO2/FIO2 <150 (SpO2/FiO2 <200)	8
	Mechanical intubation, pO2/FiO2 <150 + vasopressors, dialysis, or ECMO	9
Deceased	Deceased	10

B. Severity scale Rx Brixia Score (0 to 18 points)[12].

Lung area	Normal	Interstitial infiltrate	Interstitial and alveolar infiltrate with predominance of the former	Interstitial and alveolar infiltrate with predominance of the second
Top right	0	1	2	3
Middle right	0	1	2	3
Lower right	0	1	2	3
Top left	0	1	2	3
Middle left	0	1	2	3
Bottom left	0	1	2	3
Total				

ANNEX 2: Justification for the low-level nature of intervention.

It is requested that the CEIm evaluator of the trial rate it as:

Clinical trial of low level of intervention according to the provisions of RD 1090/2015 and European Regulation No. 536/2014 for the following conditions:

1. The use of the investigational medicinal product is evidence-based and supported by published scientific data on the safety and efficacy of such medicinal products in one of the Member States concerned.

    1.1.1. The use of corticosteroids in COVID-19 pneumonia is validated mainly according to the results of the RECOVERY clinical trials (ISRCTN50189673) conducted by the British National Health System (NHS), as well as the meta-analysis conducted by the World Health Organization (doi:10.1001/jama.2020.17023).

2. The complementary diagnostic or follow-up procedures entail an additional risk or burden for the safety of the subjects that is minimal compared to that of routine clinical practice in one of the Member States involved, since they are the usual ones carried out in the Prevention Services Involved.

3. Low-intervention clinical trials are often crucial to evaluate standard treatments and diagnoses and optimize the use of medicines, thereby contributing to a high level of public health:

    3.1. There is currently no effective solution for the treatment of COVID pneumonia, because despite the improvement in prognosis with the use of the RECVOERY dexamethasone regimen, the case fatality rate is still 23% in non-critical patients.

    3.2. Although there is the possibility of application of dexamethasone in intermediate doses, it seems logical that an alternative can be offered with higher doses of corticosteroids from which patients with COVID pneumonia can be benefited.

Additional information:

Clinical trials assessing the usefulness of intermediate doses in patients with COVID-19 pneumonia

- RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized patients with Covid-19 - Preliminary Report. N Engl J Med. Published online July 17, 2020. doi:10.1056/NEJMoa2021436
- Tomazini B, Maia I, Cavalcanti A, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. JAMA. doi:10.1001/jama.2020.17021
- Dequin P, Heming N, Meziani F, et al. Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. doi:10.1001/jama.2020.16761
- Angus D, Derde L, Al-Beidh F, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. doi:10.1001/jama.2020.17022
- Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. GLUCOCOVID: A Controlled Trial of Methylprednisolone in Adults Hospitalized with COVID-19 Pneumonia. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.06.17.20133579
- Prado-Jeronimo CM, Farias MEL, Val FFA, et al. Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial. Clin Infect Dis. Published online August 12, 2020. doi:10.1093/cid/ciaa1177

Meta-analyses assessing the usefulness of corticosteroids in patients with COVID-19 pneumonia

- The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. A Meta-analysis. JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

Observational studies assessing the usefulness of high doses of corticosteroids in COVID-19 pneumonia

- Callejas Rubio JL, Luna Del Castillo J de D, de la Hera Fernández J, Guirao Arrabal E, Colmenero Ruiz M, Ortego Centeno N. Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection. Med Clin (Engl Ed). 2020;155(4):159-161. doi:10.1016/j.medcle.2020.07.002
- Rodríguez-Baño J, Pachón J, Carratalà J, et al. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state: a multicentre cohort study (SAM-COVID-19). Clin Microbiol Infect. Published online August 27, 2020. doi:10.1016/j.cmi.2020.08.010
- Ruiz-Irastorza G, Pijoan J-I, Bereciartua E, et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data. PLoS ONE. 2020;15(9):e0239401. doi:10.1371/journal.pone.0239401